Pulmonary Vein Isolation for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation: a Meta-Analysis of Randomized Controlled Trials

Running Title: Piccini – PVI Meta-Analysis

Jonathan P. Piccini M.D., M.H.S., Renato D. Lopes, M.D., Ph.D., M.H.S, Melissa H. Kong, M.D., Vic Hasselblad, Ph.D., Kevin Jackson, M.D., Sana M. Al-Khatib, M.D., M.H.S.

Division of Cardiology, Duke Clinical Research Institute, Duke University Medical Center, Durham, NC


Address for correspondence:
Sana M. Al-Khatib, MD, MHS
Duke Clinical Research Institute
PO Box, 17969
Durham, NC 27715
Telephone: 919-668-8649
Fax: 919-668-7058
e-mail: alkha001@mc.duke.edu
Abstract

**Background:** Catheter ablation is an established, yet evolving non-pharmacologic intervention for the maintenance of sinus rhythm in patients with atrial fibrillation (AF). The efficacy and safety of pulmonary vein isolation (PVI) compared with medical therapy remain in question.

**Methods and Results:** We conducted a meta-analysis of all randomized controlled trials comparing PVI and medical therapy for the maintenance of sinus rhythm. The primary endpoint in this analysis was freedom from recurrent AF at 12 months. The relative efficacy of PVI was estimated using random-effects modeling according to the intention-to-treat. We identified six trials that randomized a total of 693 patients with AF to PVI or control. PVI was associated with markedly increased odds of freedom from AF at 12 months of follow-up (n=266/344 [77%] vs n=102/346 [29%]; OR 9.74 [95%CI 3.98-23.87]). When we excluded the one trial that only enrolled patients with persistent AF (Q-statistic 2.485; p=0.647 after exclusion), PVI was associated with even greater odds of AF-free survival (15.78 [95% CI 10.07 -24.73]). PVI was associated with a decreased hospitalization for cardiovascular causes (14 vs. 93 per 100 person-years; Rate Ratio 0.15 [95% CI 0.10-0.23]). Among those randomized to PVI, 17% required a repeat PVI ablation before 12 months. The rate of major complications was 2.6% (n=9/344) in the catheter ablation group.

**Conclusion:** Compared with a non-ablation treatment strategy, PVI results in dramatically increased freedom from AF at one year. While the procedure can be associated with major complications, the risk of these complications is comparable to other interventional procedures.

**Key words:** catheter ablation, pulmonary vein isolation, atrial fibrillation, meta-analysis, clinical trials
Introduction

Atrial fibrillation (AF) is the most common sustained clinical arrhythmia, affecting 1% of the general population and up to 10% of people over 80 years of age. AF is associated with significant morbidity including a five-fold increased risk of stroke as well as debilitating symptoms and impaired quality of life. Catheter ablation is an established, yet evolving non-pharmacologic intervention for the maintenance of sinus rhythm. Despite the proliferation of catheter ablation for the treatment of AF, medical therapy remains the standard approach to patients with AF. Unfortunately, medical therapy is of limited efficacy as 50% of patients on medical therapy develop recurrent AF within 1 year.

While there are multiple randomized clinical trials of pulmonary vein isolation (PVI) versus medical therapy, because of the small sample size and differences in ablation technique, the relative efficacy and safety of PVI compared with antiarrhythmic drug therapy alone for the maintenance of sinus rhythm in patients with AF remain in question. The goal of this meta-analysis was to determine if PVI is more efficacious than medical therapy alone and whether its safety profile is comparable to other invasive procedures.

Methods

Study Search

We searched MEDLINE (January 1, 1993 to December 12, 2008), the Cochrane Controlled Trials Register and the National Institute of Health clinicaltrials.gov database of federally and privately supported clinical trials for...
reports of randomized controlled trials of catheter-based PVI for the maintenance of sinus rhythm in patients with AF. MEDLINE was searched with the following medical subject heading (MeSH) terms: “catheter ablation” AND atrial fibrillation AND randomized controlled trial [Publication Type].” The MEDLINE query was limited to studies involving adults only (≥ 19 years), written in English, and published in the past 15 years. The bibliographies of the final selection of full-length publications and two expert consensus statements were manually searched for additional citations.

Eligibility and Data Abstraction

Studies in which patients were randomized to catheter ablation versus control or antiarrhythmic drug therapy were included in the analysis. Additional inclusion criteria were: randomization to PVI / left atrial ablation, follow-up ≥ 12 months, and full-length peer-reviewed publication. Studies were excluded if catheter ablation was used in both treatment arms (i.e. no non-ablation comparator arm), if the follow-up period was less than 12 months, if the control arm had less than 10 patients, if surgical ablation was included, if only patients with atrial flutter were included, and if patients in a previously reported publication (e.g. substudy) were included in the analysis.

Citations were reviewed and data were abstracted independently in a standardized fashion by two of the investigators (J.P.P. and R.D.L.). The MEDLINE query results included those reports identified by the other search methods (clinicaltrials.gov, Cochrane database, and the aforementioned bibliographies). Abstracted data included eligibility criteria, study population
demographics, baseline characteristics, study design (including the treatment and control arms), follow up, and outcomes. The primary endpoint was freedom from AF at 12 months. All recurrences after the blanking periods were considered regardless of antiarrhythmic drug status. Secondary pre-specified outcomes of interest included incidence of repeat PVI or cross-over to ablation therapy, hospitalization for cardiovascular causes, thromboembolic events (including stroke/transient ischemic attacks), pulmonary vein stenosis, esophageal injury, and all-cause mortality. All outcomes were analyzed according to the intention-to-treat principle. Shown in Figure 1 is the study selection process, according to the QUOROM guidelines.7

Statistical Analysis

The patient was chosen as the individual unit of analysis (as opposed to person years). The effects of PVI on the primary and secondary outcomes were determined with random-effects modeling using the DerSimonian and Laird method. The measure of treatment effect for the primary endpoint was reported by odds ratios (OR) with 95% confidence intervals (CI). The measure of treatment effect for cardiovascular hospitalizations (count data) was modeled with DerSimonian and Laird random-effects modeling and was reported with rate ratios using hospitalizations per patient-years of exposure. We assumed independence of risks for hospitalization between study subjects. We assessed heterogeneity between studies using Cochrane’s Q statistic and the I² index.8,9 Statistical testing was two-tailed, and statistical significance was declared at p <
0.05. All analyses were conducted using the Comprehensive Meta-Analysis program (Biostat, Englewood, NJ).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Search Results

We identified 102 abstracts that were reviewed for inclusion and exclusion criteria (Figure 1). Among this group of abstracts, 96 were excluded for the following reasons: studies comparing 2 catheter ablation or surgical techniques without a medical therapy only arm (n=39); trials of imaging or mapping techniques (n=9); observational studies (including reviews, design papers, and editorials, n=14); studies of medical therapy only (e.g. rate-versus rhythm-control, n=10); trials of pacing strategies or atrioventricular nodal ablation (n=17); studies of supraventricular tachycardia or atrial flutter only (n=7). The full manuscripts for the remaining 6 studies were retrieved for detailed review, and after full manuscript review, all 6 were included for analysis.

Trial Characteristics and Study Quality

As shown in Table 1, we identified 6 randomized controlled trials of PVI for inclusion that enrolled a total of 693 patients.10-15 Two trials were conducted at one center, while the rest of the trials were multi-center.10,12 Three trials were supported by industry13-15, 1 was funded through a charitable foundation11, 1 trial was funded internally10, and 1 trial did not provide information on the funding mechanism.12 Three trials (including two pilot studies) did not report power...
calculations, the 3 studies that did were all powered \((\beta - 1) \geq 90\%\).\textsuperscript{11-13}

These 3 trials met their a priori sample size determination. Krittayaphong, et. al.\textsuperscript{10}, Stabile, et. al.\textsuperscript{13}, and Wazni, et. al.\textsuperscript{14} enrolled patients with paroxysmal and persistent AF, whereas Oral, et. al.\textsuperscript{11} enrolled only patients with persistent AF. Two trials, Pappone, et. al.\textsuperscript{12} and Jais, et. al.\textsuperscript{15} enrolled only patients with paroxysmal AF.\textsuperscript{12} All 6 trials randomized patients to PVI versus a non-ablation treatment strategy; however, there was variation in the non-ablation/control arms. Most trials compared PVI with antiarrhythmic drug therapy, including only amiodarone in 2 trials\textsuperscript{10,13}, and any class I or class III Vaughan-Williams agent in 2 trials.\textsuperscript{12,14} The A4 study (Jais, et. al.) left single or combination drug therapy to the discretion of the treating physician.\textsuperscript{15} In the trial enrolling patients with persistent AF only, patients were randomized to PVI or cardioversion followed by 3 months of amiodarone therapy in both arms.\textsuperscript{11} While anticoagulation recommendations in each trial were highly variable, the majority of the trial protocols recommended anticoagulation following PVI for at least one month.\textsuperscript{11,12,14,15}

We assessed heterogeneity between studies using Cochrane’s Q statistic and the \(I^2\) index. When we examined the treatment effect across the 6 studies, there was evidence of heterogeneity (Cochrane’s Q=25.516; \(p<0.001\) and \(I^2 =80.4\)). However, after excluding the study that enrolled patients with persistent AF only that randomized to PVI or cardioversion and included 3 months of antiarrhythmic drug therapy in both arms\textsuperscript{11}, there was no evidence of heterogeneity (Cochrane’s Q=2.485; \(p =0.647\) and \(I^2 <0.001\)).
Baseline Patient Characteristics

Baseline patient characteristics are provided in Table 2. Of the 693 patients included in this meta-analysis, 486 (70%) had paroxysmal AF. In the 5 studies that reported sex, 27% (n=167/623) of the patients were female. The mean age was 55 years. The mean left atrial diameter among patients randomized to ablation in the 5 trials was 42 ± 3 mm. The mean left ventricular ejection fraction in all randomized patients was 60 ± 4%. Among the 3 trials reporting pre-enrollment antiarrhythmic drug failure, the mean number of prior ineffective antiarrhythmic drugs before enrollment was two. By definition, patients enrolled in 1 trial had never received antiarrhythmic drug therapy before enrollment. In 1 trial, patients were mandated to have failed at least one antiarrhythmic drug before enrollment. Most trials did not report baseline beta-blocker status.

Catheter Ablation Technique

Circumferential PVI was the catheter ablation technique of choice in 5 of the trials, and 1 trial used segmental PVI. In 2 trials the ablation endpoint was anatomic PVI only. In 2 trials the ablation endpoint was based upon reductions in electrogram amplitude, including low peak-to-peak bipolar pulmonary vein potentials <0.1 mV inside the radiofrequency lesions, or an 80% reduction in the amplitude of the pulmonary vein potentials. Electrical isolation of the pulmonary veins was the ablation endpoint in two trials and was defined as the absence of pulmonary vein potentials or dissociation of the pulmonary veins from the left atrium. Four of the 5 trials utilized
electroanatomical mapping per protocol and 1 used intracardiac
echocardiography for imaging guidance. Four trials employed a mitral isthmus
line and 4 created a linear tricuspid isthmus lesion. Among the 4 trials that reported procedure times, the total procedure duration ranged from 81 ± 31 to 357.4 ± 47.6 minutes. The mean fluoroscopy time was 64 ± 48 minutes.

**Electrocardiographic Monitoring and Follow Up**

Patients were followed for one year after enrollment in all 6 trials. Similarly, all trials employed a blanking period. Three of the six trials used a blanking period of 3 months (range 1 to 3 months). As shown in Table 3, electrocardiographic monitoring during follow up varied, although most trials used event recorders (n=4) and Holter monitors (n=5). Four trials recorded follow up echocardiographic data.

**Efficacy of Pulmonary Vein Isolation**

The primary endpoint in all 6 trials was freedom from AF at 12 months of follow-up. PVI was associated with markedly increased odds of maintaining sinus rhythm (77 vs 29%; OR 9.74 [95%CI 3.98-23.87]). Due to significant heterogeneity (Cochrane’s Q p<0.001) we excluded the 1 trial that only enrolled patients with persistent AF. In the remaining 5 trials (Figure 2) that predominantly evaluated patients with paroxysmal AF (Cochrane’s Q p=0.647), PVI was associated with even greater odds of AF-free survival (15.78 [95% CI 10.07 -24.73]). When we examined freedom from AF with PVI in each randomized trial, there was evidence of improved freedom from AF with time.
(p<0.001 by the Cochran-Armitage trend test), such that the largest treatment effect was observed in the most recent study (OR 23.25 [8.51-63.57]). With respect to freedom from both AF and antiarrhythmic drug therapy, only two trials reported the number of subjects free from AF without antiarrhythmic medications at 12 months. In those trials, 86% (n=131/152) of those randomized to PVI were free from AF without an antiarrhythmic therapy at 12 months.

The primary endpoint in our analysis was freedom from AF at 12 months. We also attempted to examine freedom from recurrent symptomatic AF; however, these data were not reported in any of the trials. Three trials reported symptom burden data. Only Oral, et al. provided symptom burden specific to those patients with recurrent AF. They noted a 5 point reduction (17 ± 4 vs 12 ± 4) in the AF Severity Score.

In the 3 trials that reported hospitalization, PVI was associated with a decreased hospitalization for cardiovascular causes (14 vs. 93 per 100 person-years. Rate Ratio 0.15 [95% CI 0.10-0.23], p<0.001; Figure 3). Among the 4 trials that reported repeat PVI data (at 12 months), 17% of patients who were randomized to PVI required a repeat PVI ablation procedure (Figure 4). On the other hand, in trials where crossover from a non-catheter ablation strategy to PVI was allowed, 51% crossed over and underwent catheter ablation.

Both LA diameter and LVEF after ablation were pre-specified variables of interest in our analysis. However, Given the significant differences in how these data were reported, it was not possible to derive an unbiased summary measure of the treatment effect, nor compare the findings from one study to another.
Complications of Catheter Ablation

The rate of major complications was 2.6% (n=9/344) in the catheter ablation group (tamponade n=2, symptomatic pulmonary vein stenosis n=1, pericardial effusion n=2, phrenic nerve paralysis n=1, thromboembolic events n=3). Thromboembolic events were more common in patients randomized to catheter ablation than medical therapy (n=3 vs. n=1). There were only 3 reported cases of pulmonary vein stenosis. One case was symptomatic (major pulmonary stenosis) and required dilation and stenting (crossover patient).\(^{15}\) Two cases of asymptomatic pulmonary stenosis occurred in the single trial that used a segmental PVI technique (one mild, one moderate).\(^{14}\) However, only one trial reported routine assessment of the pulmonary veins post-ablation (spiral CT at 3 months).\(^{14}\) No patient, in any of the trials, developed atrioesophageal fistula.

Among the patients randomized to antiarrhythmic drug therapy, the rate of reported adverse events associated with antiarrhythmic drug therapy was 8% (n=29/346). There were 3 cases of proarrhythmia with flecainide; 9 cases of thyroid dysfunction secondary to amiodarone; 11 cases of sexual impairment due to sotalol; 1 gastroenterologic adverse event, 2 corneal microdeposits; 2 abnormal liver function tests; and 1 case of sinus node dysfunction due to amiodarone.\(^{10, 12}\)

Publication Bias

In order to evaluate the impact of potential publication bias, we plotted study precision (1/standard error) against the log odds ratio for the treatment effect (freedom from AF). Evaluation of the funnel plot demonstrated no
publication bias among the five studies included in the determination of treatment effect.

Discussion

There are three main findings in this meta-analysis. First, the efficacy of PVI for the maintenance of sinus rhythm is 75% at one-year, more than two-fold greater than that of antiarrhythmic drug therapy. Second, PVI is associated with a two-third reduction in hospitalization for cardiovascular causes. Finally, PVI appears to carry a small risk of major procedural complications.

Efficacy of Pulmonary Vein Isolation

Two meta-analyses of catheter ablation for AF have been published, however, these meta-analyses excluded trials evaluating patients with persistent AF, did not formally evaluate treatment effect on cardiovascular hospitalizations, included little to no information on catheter ablation techniques or procedural safety and did not include more recent trials. We conducted the present meta-analysis to provide a comprehensive and up-to-date assessment of the treatment effect, risks, and benefits of catheter ablation compared with medical therapy only for AF.

In the present ACC/AHA/HRS guidelines, catheter ablation is a class IIa recommendation as an alternative to pharmacologic treatment to prevent recurrent AF in those with symptoms and little to no left atrial enlargement. At one year, up to 50% of patients on antiarrhythmic medication for the maintenance of sinus rhythm develop recurrent AF. In this meta-analysis,
77% of those randomized to catheter ablation were free from AF at one year (despite an aggressive rhythm analysis protocol). When we excluded the 1 trial that enrolled only patients with persistent AF, PVI was associated with even greater odds of AF-free survival. Approximately 1 in 6 patients randomized to PVI required a second ablation procedure during study follow-up. While relatively infrequent in this meta-analysis, observational data suggest that repeat ablation is required in 20 to 40% of patients.\textsuperscript{21, 22} The lower incidence of repeat ablation in this meta-analysis compared with the observational studies likely reflects the experience of these referral centers and the limited follow-up (12 months) in the trials. Among patients randomized to medical therapy, over half crossed-over to catheter ablation – highlighting the limitations of antiarrhythmic drug therapy. Given the superior efficacy of PVI documented in 6 randomized controlled trials and the limitations of antiarrhythmic drug therapy (including proarrhythmia and increased mortality)\textsuperscript{23, 24} one might argue that PVI should be elevated to a class I recommendation for the prevention of recurrent AF. However, these trials have been limited by relatively short follow-up without data on long-term safety and efficacy. The international, multicenter, randomized Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial will provide critically important long-term follow up data for “hard” endpoints after catheter ablation, including stroke and all-cause mortality (NCT00911508).

Patients with AF frequently require rehospitalization.\textsuperscript{25} Similar to other chronic medical conditions, hospitalization is one of the most important determinants of health care costs in patients with AF.\textsuperscript{26} Not only was PVI more
efficacious at maintaining sinus rhythm, but it was also associated with a 2/3 reduction in hospitalization for cardiovascular causes. Formal cost-effectiveness analyses should be incorporated into future trials of catheter ablation for AF.

Safety of Pulmonary Vein Isolation

An international survey of catheter ablation for AF reported a major complication rate of 6%.27 Included in this figure was nearly a 1% incidence of stroke or TIA and a 1.2% incidence of cardiac tamponade. This world-wide survey included data from 181 electrophysiology labs. In the present analysis, PVI was associated with a 3% rate of major complications and a stroke rate of less than 1%. This lower complication rate likely reflects the expertise of the centers participating in these trials and the continued evolution of the procedure and its safety. A 3% major complication rate is comparable to that observed with high risk percutaneous coronary intervention, however, it is not negligible.28 On the other hand, the risks of antiarrhythmic drug therapy are numerous and frequent. Most notably, antiarrhythmic drug therapy carries the risk of proarrhythmia and sudden cardiac death. Nearly 1 in 4 patients randomized to medical therapy in this analysis developed an adverse event related to their antiarrhythmic drug therapy. Unfortunately, most trials did not report the rate of freedom from antiarrhythmic drug therapy in those patients randomized to PVI.

Limitations

While this study examined almost 700 patients from six randomized controlled trials, as with any meta-analysis, it is subject to several potential biases. First, our analysis was restricted to randomized controlled trials. While
randomized controlled trials minimize bias and are the gold-standard for
determination of experimental effect, they may not be reflective of patients
treated in general clinical practice at centers with less experience with complex
catheter ablation techniques. Additionally, our meta-analysis incorporates trials
that employed different methods of PVI, different ablation endpoints, and different
methods of monitoring for recurrent AF in follow-up. While these variations reflect
current clinical practice, they make explicit application of the efficacy and safety
estimates challenging. Finally, it is important to note that follow up in these trials
was limited to 12 months. Therefore, this meta-analysis cannot address long-
term outcomes after pulmonary vein isolation.

Clinical implications

Our meta-analysis demonstrates that PVI is an efficacious treatment for
maintenance of sinus rhythm in patients with paroxysmal AF when compared
with medical therapy. While there are known risks associated with the procedure,
the incidence of these complications seems to be comparable to other
percutaneous, catheter-based interventions. Finally, PVI appears to be
associated with a substantially decreased risk of hospitalization. It is important to
note that this meta-analysis does not evaluate PVI as a first-line treatment for
symptomatic AF and that our findings may not apply to older patients, patients
with multiple comorbidities, patients with congestive heart failure due to systolic
or diastolic dysfunction, or patients with significant left atrial enlargement as
these patients were not included in the randomized clinical trials combined in this
meta-analysis. Several ongoing randomized studies comparing catheter ablation
with medical therapy for AF might provide important insights on these topics including information about efficacy of this procedure in patients not included in the published clinical trials and long-term efficacy and safety of this procedure and perhaps lead to a more tailored recommendation for PVI in future guidelines.

**Conclusions**

Compared with a non-ablation treatment strategy, PVI results in significantly increased freedom from AF at one year. Catheter ablation seems to be associated with significantly decreased hospitalization for cardiovascular causes. While the procedure can be associated with major complications, including stroke, cardiac perforation, and pulmonary vein stenosis, these events appear to be rare. Large, multicenter, randomized trials are still needed to assess longer-term safety and efficacy of PVI for the maintenance of sinus rhythm.

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REFERENCES


Table 1. Randomized trials of pulmonary vein isolation for the maintenance of sinus rhythm

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>No of patients</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Circumferential vs Segmental Ablation</th>
<th>Endpoint</th>
<th>Additional Ablation Lines</th>
<th>Control Arm</th>
<th>Primary Endpoint</th>
<th>Follow-up (mo)</th>
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<tbody>
<tr>
<td>Krittayaphong, et. al. 10</td>
<td>2003</td>
<td>30</td>
<td>• Symptomatic AF &gt; 6 months&lt;br&gt;• Refractory to ≥ 1 AAD (including a class IA or III agent)&lt;br&gt;• Amiodarone naive&lt;br&gt;• Monthly symptomatic AF ≥ 3 months</td>
<td>• Transient AF&lt;br&gt;• Bleeding disorder&lt;br&gt;• Thyroid disease&lt;br&gt;• Prior stroke&lt;br&gt;• Life expectancy &lt; 1 year&lt;br&gt;• Valvular heart disease&lt;br&gt;• Age &lt; 18 or &gt; 75&lt;br&gt;• History of atrial flutter or atrial flutter ablation&lt;br&gt;• Prior open heart surgery&lt;br&gt;• Prior AAD therapy&lt;br&gt;• Contraindication to anticoagulation</td>
<td>Circumferential Anatomic isolation</td>
<td>Freedom from AF at 12 months</td>
<td>Amiodarone with cardioversion for persistent AF</td>
<td>Freedom from AF at 12 months</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Wazni, et. al. 14</td>
<td>2005</td>
<td>70</td>
<td>• Monthly symptomatic AF ≥ 3 months</td>
<td></td>
<td>Segmental Electrical isolation</td>
<td>None reported.</td>
<td>MD selection of recommended AAD (flecainide, propafenone, sotalol). Amiodarone only after 2 AAD failures</td>
<td>Freedom from AF at 12 months</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Stabile, et. al. 13</td>
<td>2005</td>
<td>137</td>
<td>• Paroxysmal or persistent AF&lt;br&gt;• Intolerant to or failure of ≥ 2 AADs</td>
<td>• Age &lt; 18 or &gt; 80&lt;br&gt;• Permanent AF&lt;br&gt;• AF due to a reversible cause&lt;br&gt;• Recurrent AF triggered by a uniform supraventricular arrhythmia&lt;br&gt;• Wolf-Parkinson-White syndrome&lt;br&gt;• Intracardiac thrombus&lt;br&gt;• NYHA III or IV with LVEF ≤ 35%&lt;br&gt;• LA diameter &gt; 60 mm&lt;br&gt;• Unstable angina or MI in prior 3 monts&lt;br&gt;• Cardiac surgery in prior 6 months</td>
<td>Circumferential Anatomic isolation</td>
<td>Freedom from atrial arrhythmia s at 12 months</td>
<td>Amiodarone</td>
<td>Freedom from atrial arrhythmia s at 12 months</td>
<td>12</td>
<td></td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>N</td>
<td>Conditions</td>
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</tbody>
</table>
| Oral, et al. | 2006 | 146 | - Chronic AF without SR for > 6 months  
- Recurrence within one week of cardioversion  
- Age < 18 or > 70  
- LA diameter > 55 mm  
- Contraindication to amiodarone or anticoagulation  
- Mechanical prosthetic heart valve  
- Prior stroke  
- LA thrombus  
- Prior surgical or catheter ablation of AF |
| Pappone, et al. | 2006 | 198 | - Paroxysmal AF > 6 months and >2 episodes/month  
- Creatinine < 1.5 mg/dL  
- Age < 18 or > 70  
- LA diameter > 65 mm  
- Intra-atrial thrombus  
- LVEF < 35%  
- NYHA class II or greater  
- Prior AAD therapy with amiodarone, flecainide, and/or sotalol  
- Contraindication to beta-blockade  
- Rheumatic mitral valve disease  
- Unstable angina or MI within 6 months  
- Wolf-Parkinson-White syndrome  
- Renal or hepatic failure  
- Pacemaker or ICD  
- Contraindication to AAD therapy or anticoagulation  
- Requirement for AAD therapy for a non-AF |

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Procedure</th>
</tr>
</thead>
</table>
| Oral, et al. | Circumferential Anatomic isolation  
(1) Posterior LA (roof) line, (2) Mitral isthmus line |
| Pappone, et al. | Circumferential Anatomic isolation  
(1) Mitral isthmus line, (2) Cavotricuspid isthmus line |

| | Freedom from AF/flutter at 12 months |
| | Freedom from atrial tachyarrhythmia at 12 months |

<p>| | 12 months |
| | 12 months |</p>
<table>
<thead>
<tr>
<th>Jais, et al.</th>
<th>2008</th>
<th>112</th>
<th>Symptomatic paroxysmal AF ≥ 6 months</th>
<th>Prior stroke</th>
<th>Prior catheter or surgical ablation for AF</th>
<th>Contraindications to &gt; 2 AAD</th>
<th>Contraindication to anticoagulation</th>
<th>Prior AF ablation</th>
<th>Pregnancy</th>
<th>Freedom from AF at 12 months</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 episodes of AF within 1 month</td>
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</table>

AF = atrial fibrillation; AAD = antiarrhythmic drug; RA = right atrium; SVC = superior vena cava; IVC = inferior vena cava; ICD = implantable cardioverter defibrillator; LA = left atrium; LVEF = left ventricular ejection fraction; MD = physician; MI = myocardial infarction; NYHA = New York Heart Association; SR = sinus rhythm.

**Circumferential Electrical Isolation**
(1) Additional LA lines at operators’ discretion, (2) Cavotricuspid isthmus line

AAD therapy at the discretion of the investigator

Freedom from AF at 12 months
Table 2. Patient characteristics in randomized trials of pulmonary vein isolation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mean age (yrs)</th>
<th>Female (%)</th>
<th>Paroxysmal AF (%)</th>
<th>Persistent AF (%)</th>
<th>Mean EF (%)</th>
<th>Mean LA diameter (mm)</th>
<th>Mean # prior ineffective AADs</th>
<th>Beta-blockers (%)</th>
</tr>
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<tbody>
<tr>
<td>Krittayaphong, et. al.¹⁰</td>
<td>52</td>
<td>37</td>
<td>67</td>
<td>33</td>
<td>63</td>
<td>39</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Wazni, et. al.¹⁴</td>
<td>54</td>
<td>NR</td>
<td>96</td>
<td>4</td>
<td>54</td>
<td>42</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>Stabile, et. al.¹³</td>
<td>62</td>
<td>41</td>
<td>67</td>
<td>33</td>
<td>59</td>
<td>46</td>
<td>NR</td>
<td>10</td>
</tr>
<tr>
<td>Oral, et. al.¹¹</td>
<td>57</td>
<td>12</td>
<td>0</td>
<td>100</td>
<td>56</td>
<td>45</td>
<td>2</td>
<td>NR</td>
</tr>
<tr>
<td>Pappone, et. al.¹²</td>
<td>56</td>
<td>33</td>
<td>100</td>
<td>0</td>
<td>61</td>
<td>39</td>
<td>2</td>
<td>NR</td>
</tr>
<tr>
<td>Jais, et. al.¹⁵</td>
<td>51</td>
<td>16</td>
<td>100</td>
<td>0</td>
<td>64</td>
<td>40</td>
<td>≥ 1</td>
<td>NR</td>
</tr>
</tbody>
</table>
Table 3. Electrocardiographic monitoring and follow up.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Blanking period</th>
<th>12-lead ECG</th>
<th>24-hour Holter recording</th>
<th>Event monitor</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krittayaphong, et. al.</td>
<td>3 months</td>
<td>1,3,6,12 months</td>
<td>1,3,6,12 months</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Wazni, et. al.</td>
<td>2 months</td>
<td>NR</td>
<td>Discharge, 3, 6, &amp;12 months</td>
<td>2-3 times daily for 1 month during months 1 and 3; Additional recording after 3 months if symptomatic</td>
<td>CT at 3, 6, 12 months (PVI arm only)</td>
</tr>
<tr>
<td>Stabile, et. al.</td>
<td>1 month</td>
<td>1,4,7,10,13 months &amp; symptom directed</td>
<td>1,4,7,10,13 months</td>
<td>Daily transmission for 30 seconds and with symptoms x 3 months</td>
<td>Echo at 1,4,7,10,13 months</td>
</tr>
<tr>
<td>Oral, et. al.</td>
<td>3 months</td>
<td>3, 6,12 months</td>
<td>NR</td>
<td>5 days per week for 3 minutes and with symptoms</td>
<td>Echo at 3, 6,12 months</td>
</tr>
<tr>
<td>Pappone, et. al.</td>
<td>6 weeks</td>
<td>3,6,12 months</td>
<td>3,6,12 months (48 hour monitor)</td>
<td>1-3 times daily and with symptoms</td>
<td>Echo at 3, 6, 12 months</td>
</tr>
<tr>
<td>Jais, et. al.</td>
<td>3 months</td>
<td>3,6,12 months</td>
<td>3,6,12 months</td>
<td>NR</td>
<td>Echo after each ablation and at 12 months</td>
</tr>
</tbody>
</table>
Figure Legends

Figure 1. QUOROM algorithm

Figure 2. Odds ratios (ablation versus control) for freedom from atrial fibrillation at 12 months

Figure 3. Rate ratios (ablation versus control) for hospitalization for cardiovascular causes per patient-years.

Figure 4. Incidence of repeat pulmonary vein isolation or crossover in the first year of follow up.* The vertical bars show the percent of patients who underwent repeat PVI or crossed over to catheter ablation in each study.

*Krittayaphong, et al. did not report repeat PVI or crossover data. In Wazni, et al., the protocol discouraged crossover to PVI during the trial, however, 4 out of 32 patients underwent repeat PVI after the 12 month study.
MEDLINE, Cochrane Controlled Trials Register, & clinicaltrials.gov searched for “catheter ablation” AND “atrial fibrillation” AND “randomized controlled trial”

102 abstracts reviewed for inclusion & exclusion criteria

96 abstracts excluded:
- comparison of catheter ablation or surgical techniques without a medical therapy only arm (n=39)
- trials of imaging or mapping techniques (n=9)
- observational studies (n=14)
- medical therapy only (n=10)
- pacing strategies or atrioventricular nodal ablation (n=17)
- studies of supraventricular tachycardia or atrial flutter only (n=7)

6 full papers extracted for detailed review & all included in analysis
The bar chart shows the percentage of repeat PVI in the ablation arm and crossover to PVI in the control arm across different studies.

- **Repeat PVI in ablation arm (%):**
  - Stabile, et al.: 0%
  - Oral, et al.: 52%
  - Pappone, et al.: 77%
  - Jais, et al.: 63%
  - Combined: 57%

- **Crossover to PVI in control arm (%):**
  - Stabile, et al.: 6%
  - Oral, et al.: 26%
  - Pappone, et al.: 42%
  - Jais, et al.: 43%
  - Combined: 17%
Pulmonary Vein Isolation for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation: a Meta-Analysis of Randomized Controlled Trials
Jonathan P. Piccini, Renato D. Lopes, Melissa H. Kong, Vic Hasselblad, Kevin Jackson and Sana M. Al-Khatib

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