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

Jonathan P. Piccini, MD, MHS; Renato D. Lopes, MD, PhD, MHS; Melissa H. Kong, MD; Vic Hasselblad, PhD; Kevin Jackson, MD; Sana M. Al-Khatib, MD, MHS

Background—Catheter ablation is an established yet evolving nonpharmacologic 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 end point in this analysis was freedom from recurrent AF at 12 months. The relative efficacy of PVI was estimated using random-effects modeling according to intention to treat. We identified 6 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%] versus n = 102/346 [29%]; odds ratio, 9.74; 95% CI, 3.98 to 23.87). When we excluded the 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 to 24.73). PVI was associated with a decreased hospitalization for cardiovascular causes (14 versus 93 per 100 person-years; rate ratio, 0.15; 95% CI, 0.10 to 0.23). Among those randomly assigned 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.

Conclusions—Compared with a nonablation treatment strategy, PVI results in dramatically increased freedom from AF at 1 year. Although the procedure can be associated with major complications, the risk of these complications is comparable to other interventional procedures. (Circ Arrhythm Electrophysiol. 2009;2:626-633.)

Key Words: catheter ablation ■ pulmonary vein isolation ■ atrial fibrillation ■ meta-analysis ■ clinical trials

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 5-fold increased risk of stroke as well as debilitating symptoms and impaired quality of life. Catheter ablation is an established yet evolving nonpharmacologic 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 because 50% of patients receiving medical therapy have recurrent AF within 1 year.

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Although there are multiple randomized, controlled 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 whether 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 2 expert consensus statements were manually searched for additional citations.

Eligibility and Data Abstraction
Studies in which patients were randomly assigned to catheter ablation versus control or antiarrhythmic drug therapy were included.

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From the Division of Cardiology, Duke Clinical Research Institute, Duke University Medical Center, Durham, NC.
Correspondence to Sana M. Al-Khatib, MD, MHS, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715. E-mail alkhato01@gmail.com
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in the analysis. Additional inclusion criteria were random assignment 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 (ie, no nonablation comparator arm), if the follow-up period was <12 months, if the control arm had <10 patients, if surgical ablation was included, if only patients with atrial flutter were included, and if patients in a previously reported publication (eg, substudy) were included in the analysis.

Citations were reviewed and data were abstracted independently in a standardized fashion by 2 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 end point was freedom from AF at 12 months. All recurrences after the blanking periods were considered regardless of antiarrhythmic drug status. Secondary prespecified outcomes of interest included incidence of repeat PVI or crossover 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 end point was reported by odds ratios (ORs) with 95% CIs. 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 the Cochrane Q statistic and the I² index.8,9 Statistical testing was 2-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 (eg, rate versus rhythm control, n=10); trials of pacing strategies or atrioventricular nodal ablation (n=17); and 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 1 center, whereas the rest of the trials were multicenter.10,12 Three trials were supported by industry,13–15 1 was funded through a charitable foundation,11 1 trial was funded internally,10 and 1 trial did not provide information on the funding mechanism.12 Three trials (including 2 pilot studies) did not report power calculations, the 3 studies that did were all powered (β-1) ≥90%.11–13 These 3 trials met their a priori sample size determination. Krittayaphong et al,10 Stabile et al,13 and Wazni et al14 enrolled patients with paroxysmal and persistent AF, whereas Oral et al11 enrolled only patients with persistent AF. Two trials, Pappone et al12 and Jais et al,15 enrolled only patients with paroxysmal AF.12 All 6 trials randomly assigned patients to PVI versus a nonablation treatment strategy; however, there was variation in the nonablation/control arms. Most trials compared PVI with antiarrhythmic drug therapy, including only amiodarone in 2 trials,10,13 and any class I or class III Vaughan-
Williams agent in 2 trials.12,14 The A4 study (Jais et al) left single or combination drug therapy to the discretion of the treating physician.15 In the trial enrolling patients with persistent AF only, patients were randomly assigned to PVI or cardioversion followed by 3 months of amiodarone therapy in both arms.11 Although anticoagulation recommendations in each trial were highly variable, the majority of the trial protocols recommended anticoagulation after PVI for at least 1 month.11,12,14,15

### Table 1. Randomized Trials of PVI 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 End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krittayaphong et al10</td>
<td>2003</td>
<td>30</td>
<td>Symptomatic AF &gt;6 mo Refractory to ≥AAD (including a class Ia or III agent) Amiodarone naive</td>
<td>Transient AF Bleeding disorder Thyroid disease Prior stroke Life expectancy &lt;1 y Valvular heart disease</td>
<td>Circumferential Anatomic isolation</td>
</tr>
<tr>
<td>Wazni et al14</td>
<td>2005</td>
<td>70</td>
<td>Monthly symptomatic AF ≥3 mo</td>
<td>Age &lt;18 or &gt;75 History of atrial flutter or atrial flutter ablation Prior open heart surgery Prior AAD therapy Contraindication to anticoagulation</td>
<td>Segmental Electrical isolation</td>
</tr>
<tr>
<td>Stabile et al13</td>
<td>2005</td>
<td>137</td>
<td>Paroxysmal or persistent AF Intolerant to or failure of ≥2 AADs</td>
<td>Age &lt;18 or &gt;80 Permanent AF AF due to a reversible cause Recurrent AF triggered by a uniform supraventricular arrhythmia Wolf-Parkinson-White syndrome Intracardiac thrombus NYHA III or IV with LVEF ≤35% LA diameter &gt;60 mm Unstable angina or MI in prior 3 mo Cardiac surgery in prior 6 mo Renal or hepatic failure Pacemaker or ICD</td>
<td>Circumferential Anatomic isolation</td>
</tr>
<tr>
<td>Oral et al11</td>
<td>2006</td>
<td>146</td>
<td>Chronic AF without SR for &gt;6 mo Recurrence within 1 wk of cardioversion</td>
<td>Age &lt;18 or &gt;70 LA diameter &gt;55 mm Contraindication to amiodarone or anticoagulation Mechanical prosthetic heart valve Prior stroke LA thrombus Prior surgical or catheter ablation of AF</td>
<td>Circumferential Anatomic isolation</td>
</tr>
<tr>
<td>Pappone et al12</td>
<td>2006</td>
<td>198</td>
<td>Paroxysmal AF &gt;6 mo and ≥2 episodes/mo Creatinine &lt;1.5 mg/dl</td>
<td>Age &lt;18 or &gt;70 LA diameter &gt;65 mm Intraatrial thrombus LVEF &lt;35% NYHA class II or greater Prior AAD therapy with amiodarone, flecainide, and/or sotalol Contraindication to β-blockade Rheumatic mitral valve disease Unstable angina or MI within 6 mo 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 arrhythmia Prior stroke Prior catheter or surgical ablation for AF</td>
<td>Circumferential Anatomic isolation</td>
</tr>
<tr>
<td>Jais et al15</td>
<td>2008</td>
<td>112</td>
<td>Symptomatic paroxysmal AF ≥6 mo 2 episodes of AF within 1 mo</td>
<td>Contraindications to &gt;2 AAD Contraindication to anticoagulation Prior AF ablation Pregnancy</td>
<td>Circumferential Electrical isolation</td>
</tr>
</tbody>
</table>

AAD indicates 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.
We assessed heterogeneity between studies using the Cochrane Q statistic and the $I^2$ index. When we examined the treatment effect across the 6 studies, there was evidence of heterogeneity (Cochrane $Q=25.516; P<0.001$ and $I^2=80.4$).

However, after excluding the study that enrolled patients with persistent AF only randomly assigned to PVI or cardioversion and included 3 months of antiarrhythmic drug therapy in both arms,\textsuperscript{11} there was no evidence of heterogeneity (Cochrane $Q=2.485; P=0.647$ 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 randomly assigned to ablation in the 5 trials was $42\pm3$ mm. The mean left ventricular ejection fraction in all randomly assigned patients was $60\pm4\%$. Among the 3 trials reporting preenrollment antiarrhythmic drug failure, the mean number of prior ineffective antiarrhythmic drugs before enrollment was 2.\textsuperscript{11,12,15} By definition, patients enrolled in 1 trial had never received antiarrhythmic drug therapy before enrollment.\textsuperscript{14} In 1 trial, patients were mandated to have failed at least 1 antiarrhythmic drug before enrollment.\textsuperscript{10} Most trials did not report baseline β-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.\textsuperscript{14} In 2 trials, the ablation end point was anatomic PVI only.\textsuperscript{10,12} In 2 trials, the ablation end point was based on reductions in electrogram amplitude, including low peak-to-peak bipolar pulmonary vein potentials <0.1 mV inside the radiofrequency lesions,\textsuperscript{13} or an 80% reduction in the amplitude of the pulmonary vein potentials.\textsuperscript{11} Electric isolation of the pulmonary veins was the ablation end point in 2 trials and was defined as the absence of pulmonary vein potentials or dissociation of the pulmonary veins from the left atrium.\textsuperscript{14,15} Four\textsuperscript{10–13} of the 5 trials used electroanatomic mapping per protocol and 1 used intracardiac echocardiography for imaging guidance.\textsuperscript{14} Four trials used a mitral isthmus line\textsuperscript{10–11} and 4 created a linear tricuspid isthmus lesion.\textsuperscript{10,12,13,15} Among the 4 trials that reported procedure times, the total procedure duration ranged from $81\pm31$ to $357.4\pm47.6$ minutes.\textsuperscript{10,12,13,15} The mean fluoroscopy time was $64\pm48$ minutes.\textsuperscript{10,13,15}

### ECG Monitoring and Follow-Up

Patients were followed for 1 year after enrollment in all 6 trials. Similarly, all trials used a blanking period. Three of the 6 trials used a blanking period of 3 months (range, 1 to 3 months).\textsuperscript{10,11,15} As shown in Table 3, ECG monitoring during follow-up varied, although most trials used event recorders (n = 4)\textsuperscript{11–14} and Holter monitors (n = 5).\textsuperscript{10,12–15} Four trials recorded follow-up echocardiographic data.\textsuperscript{11–13,15}

### Efficacy of PVI

The primary end point 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 versus 29%; OR, 9.74; 95% CI, 3.98 to 23.87). Due to significant heterogeneity (Cochrane $Q P<0.001$) 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.

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### Table 1. Continued

<table>
<thead>
<tr>
<th>Additional Ablation Lines</th>
<th>Control Arm</th>
<th>Primary End Point</th>
<th>Follow-Up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Mitral isthmus line, (2) cavotricuspid isthmus line, (3) mid-RA line, (4) SVC to IVC line</td>
<td>Amiodarone with cardioversion for persistent AF</td>
<td>Freedom from AF at 12 mo</td>
<td>12</td>
</tr>
<tr>
<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 mo</td>
<td>12</td>
</tr>
<tr>
<td>(1) Mitral isthmus line, (2) cavotricuspid isthmus line</td>
<td>Amiodarone</td>
<td>Freedom from atrial arrhythmias at 12 mo</td>
<td>12</td>
</tr>
<tr>
<td>(1) Posterior LA (roof) line, (2) mitral isthmus line</td>
<td>In both arms: Amiodarone ×6 wk then cardioversion Amiodarone discontinued after 3 mo</td>
<td>Freedom from AF/ flutter at 12 mo</td>
<td>12</td>
</tr>
<tr>
<td>(1) Mitral isthmus line, (2) cavotricuspid isthmus line</td>
<td>Randomized to 1 of 3 AADs: flecainide, sotalol, amiodarone</td>
<td>Freedom from atrial tachyarrhythmia at 12 mo</td>
<td>12</td>
</tr>
<tr>
<td>(1) Additional LA lines at operator discretion, (2) cavotricuspid isthmus line</td>
<td>AAD therapy at the discretion of the investigator</td>
<td>Freedom from AF at 12 mo</td>
<td>12</td>
</tr>
</tbody>
</table>
(Cochrane Q $P=0.647$), PVI was associated with even greater odds of AF-free survival (15.78; 95% CI, 10.07 to 24.73). When we examined freedom from AF with PVI in each randomized trial, there was evidence of improved freedom from AF with freedom from AF (OR, 23.25; 8.51 to 63.57). With respect to freedom from AF, the largest treatment effect was observed in the most recent trial, there was evidence of improved freedom from AF with freedom from AF with PVI in each randomized trial, allowing, 51% crossed over and underwent catheter ablation. The crossover from a noncatheter ablation strategy to PVI was required a repeat PVI ablation procedure (Figure 4). On the other hand, in trials in which were randomly assigned to PVI, 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 caused by sotalol; 1 gastroenterological adverse event, 2 corneal microdeposits; 2 abnormal liver function tests; and 1 case of sinus node dysfunction caused by amiodarone.

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 who were randomly assigned to PVI were free from AF without an antiarrhythmic therapy at 12 months.

The primary end point 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 versus 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 versus 93 per 100 person-years; rate ratio, 0.15; 95% CI, 0.10 to 0.23; $P<0.001$; Figure 3). Among the 4 trials that reported repeat PVI data (at 12 months), 17% of patients who were randomly assigned to PVI required a repeat PVI ablation procedure (Figure 4). On the other hand, in trials in which the number of subjects free from AF without antiarrhythmic therapy at 12 months. We also attempted to examine freedom from AF after ablation were prespecified 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.

### Table 2. Patient Characteristics in Randomized Trials of PVI

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mean Age, y</th>
<th>Female, %</th>
<th>Paroxysmal AF, %</th>
<th>Persistent AF, %</th>
<th>Mean EF, %</th>
<th>Mean LA Diameter, mm</th>
<th>Mean No. of Prior Ineffective AADs</th>
<th>β-Blockers, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krittayaphong et al</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</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</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</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</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</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>

EF indicates ejection fraction; LA, left atrial; AADs antiarrhythmic drugs.

### Table 3. ECG Monitoring and Follow-Up

<table>
<thead>
<tr>
<th>Trial</th>
<th>Blanking Period</th>
<th>12-Lead ECG</th>
<th>24-h Holter Recording</th>
<th>Event Monitor</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krittayaphong et al</td>
<td>3 mo</td>
<td>1, 3, 6, 12 mo</td>
<td>1, 3, 6, 12 mo</td>
<td>NR</td>
<td>CT at 3, 6, 12 mo</td>
</tr>
<tr>
<td>Wazni et al</td>
<td>2 mo</td>
<td>NR</td>
<td>Discharge, 3, 6, and 12 mo</td>
<td>2 to 3 times daily for 1 mo during mos1 and; additional recording after 3 mo if symptomatic</td>
<td>CT at 3, 6, 12 mo (PVI arm only)</td>
</tr>
<tr>
<td>Stabile et al</td>
<td>1 mo</td>
<td>1, 4, 7, 10, 13 mo and symptom directed</td>
<td>1, 4, 7, 10, 13 mo</td>
<td>Daily transmission for 30 s and with symptoms ×3 mo</td>
<td>Echo at 1, 4, 7, 10, 13 mo TEE at 4 mo (PVI arm only)</td>
</tr>
<tr>
<td>Oral et al</td>
<td>3 mo</td>
<td>3, 6, 12 mo</td>
<td>NR</td>
<td>5 d per week for 3 min and with symptoms</td>
<td>Echo at 3, 6,12 mo</td>
</tr>
<tr>
<td>Pappone et al</td>
<td>6 wk</td>
<td>3, 6, 12 mo</td>
<td>3, 6, 12 mo (48-h monitor)</td>
<td>1 to 3 times daily and with symptoms</td>
<td>Echo at 3, 6, 12 mo</td>
</tr>
<tr>
<td>Jais et al</td>
<td>3 mo</td>
<td>3, 6, 12 mo</td>
<td>3, 6, 12 mo</td>
<td>NR</td>
<td>Echo after each ablation and at 12 mo</td>
</tr>
</tbody>
</table>
Publication Bias
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 5 studies included in the determination of treatment effect.

Discussion
There are 3 main findings in this meta-analysis. First, the efficacy of PVI for the maintenance of sinus rhythm is 75% at 1 year, more than 2-fold greater than that of antiarrhythmic drug therapy. Second, PVI is associated with a two-thirds reduction in hospitalization for cardiovascular causes. Finally, PVI appears to carry a small risk of major procedural complications.

Efficacy of PVI
Two meta-analyses of catheter ablation for AF have been published\(^{16,17}\); 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.\(^{11,15}\) 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 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines, catheter ablation is a class IIA recommendation as an alternative to pharmacological treatment to prevent recurrent AF in those with symptoms and little to no left atrial enlargement.\(^{18}\) At 1 year, up to 50% of patients on antiarrhythmic medication for the maintenance of sinus rhythm develop recurrent AF.\(^{19,20}\) In this meta-analysis, 77% of those randomly assigned to catheter ablation were free from AF at 1 year (despite an aggressive rhythm analysis protocol). When we excluded the trial that enrolled only patients with persistent AF, PVI was associated with even greater odds of AF-free survival. Approximately 1 in 6 patients randomly assigned to PVI required a second ablation procedure during study follow-up. Although relatively infrequent in this meta-analysis, observational data suggest that repeat ablation is required in 20% to 40% of patients.\(^{21,22}\) The lower incidence of repeat ablation in this meta-analysis compared with the observational studies probably reflects the experience of these referral centers and the limited follow-up (12 months) in the trials. Among patients randomly assigned to medical therapy, more than 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)\(^{23,24}\)

Figure 2. ORs (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 PVI or crossover in the first year of follow-up. Vertical bars show the percentage 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 of 32 patients underwent repeat PVI after the 12-month study.
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” end points after catheter ablation, including stroke and all-cause mortality (NCT00911508).

Patients with AF frequently require rehospitalization.25 Similar to other chronic medical conditions, hospitalization is one of the most important determinants of health care costs in patients with AF.26 Not only was PVI more efficacious at maintaining sinus rhythm, but it was also associated with a two-thirds 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 transient ischemic attack and a 1.2% incidence of cardiac tamponade. This worldwide 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 <1%. This lower complication rate probably 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 randomly assigned to medical therapy in this analysis had 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 randomly assigned to PVI.

Limitations
Although this study examined almost 700 patients from 6 randomized, controlled trials, as with any meta-analysis, it is subject to several potential biases. First, our analysis was restricted to randomized, controlled trials. Although 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 used different methods of PVI, different ablation end points, and different methods of monitoring for recurrent AF in follow-up. Although 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. Although 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 caused by systolic or diastolic dysfunction, or patients with significant left atrial enlargement because these patients were not included in the randomized, clinical trials combined in this meta-analysis. Several ongoing randomized trials of PVI should provide important insights on these topics, including ablation in different patient populations and long-term safety and efficacy data. Accordingly, future trial data may lead to a more tailored recommendation for PVI in future guidelines.

Conclusion
Compared with a nonablation treatment strategy, PVI results in significantly increased freedom from AF at 1 year. Catheter ablation appears to be associated with significantly decreased hospitalization for cardiovascular causes. Although 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.

Disclosures
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References


CLINICAL PERSPECTIVE

Catheter ablation is an established yet evolving nonpharmacologic intervention for the maintenance of sinus rhythm in patients with atrial fibrillation. To quantify the efficacy and safety of pulmonary vein isolation (PVI) compared with medical therapy, we conducted a meta-analysis of all randomized, controlled trials of PVI versus medical therapy only for the maintenance of sinus rhythm. Based on 6 trials that randomly assigned a total of 693 patients with atrial fibrillation to PVI or control, PVI was associated with markedly increased odds of freedom from atrial fibrillation at 12 months of follow-up (77% versus 29%; odds ratio, 9.74; 95% CI, 3.98 to 23.87). PVI was also associated with decreased hospitalization for cardiovascular causes (14 versus 93 per 100 person-years; rate ratio, 0.15; 95% CI, 0.10 to 0.23). Among those randomly assigned to PVI, 17% required a repeat PVI ablation before 12 months. The rate of major complications was 2.6% (n=9344) in the catheter ablation group. Compared with a nonablation treatment strategy, PVI resulted in dramatically increased freedom from atrial fibrillation at 1 year. Although the procedure can be associated with major complications, the risk of these complications is comparable to other interventional procedures. 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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Jonathan P. Piccini, Renato D. Lopes, Melissa H. Kong, Vic Hasselblad, Kevin Jackson and Sana M. Al-Khatib

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