Natural History and Long-Term Outcomes of Ablated Atrial Fibrillation

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Background—Atrial fibrillation (AF) ablation is increasingly used in clinical practice. We aimed to study the natural history and long-term outcomes of ablated AF.

Methods and Results—We followed 831 patients after pulmonary vein isolation (PVI) performed in 2005. We documented clinical outcomes using our prospective AF registry with most recent update on this group of patients in October 2009. In the first year after ablation, 23.8% had early recurrence. Over long-term follow-up (55 months), only 8.9% had late arrhythmia recurrence defined as occurring beyond the first year after ablation. Repeat ablations in patients with late recurrence revealed conduction recovery in at least 1 of the previously isolated PVs in all of them and right-sided triggers with isoproterenol testing in 55.6%. At last follow-up, clinical improvement was 89.9% (79.4% arrhythmia-free off antiarrhythmic drugs and 10.5% with AF controlled with antiarrhythmic drugs). Only 4.6% continued to have drug-resistant AF. It was possible to safely discontinue anticoagulation in a substantial proportion of patients with no recurrence in the year after ablation (CHADS score ≤2, stroke incidence of 0.06% per year). The procedure-related complication rate was very low.

Conclusions—Pulmonary vein isolation is safe and efficacious for long-term maintenance of sinus rhythm and control of symptoms in patients with drug-resistant AF. It obviates the need for antiarrhythmic drugs, negative dromotropic agents, and anticoagulants in a substantial proportion of patients. (Circ Arrhythm Electrophysiol. 2011;4:271-278.)

Key Words: atrial fibrillation • ablation • long-term outcomes

Atrial fibrillation (AF), the most common cardiac arrhythmia, is associated with increased morbidity and mortality.1–3 Pharmacological therapy is considered as first-line strategy for the management of AF.4 However, in clinical practice, anticoagulation is frequently suboptimal, and antiarrhythmic drugs (AAD) are often ineffective and have serious adverse effects.3,5–7

Clinical Perspective on p 278

Pulmonary vein isolation (PVI) by catheter-based radiofrequency ablation has become an effective treatment for drug-refractory AF, with cumulative evidence suggesting that ablation may be safer and more effective than pharmacotherapy8–15 in improving hospitalization rates11,12 and quality of life.10,12 However, ablation remains a second-line intervention for the management of AF, with limited long-term outcome data16–21 and safety concerns.22 The role of ablation for long-term maintenance of sinus rhythm in patients with drug-resistant AF has not been established. This is important clinically, with data suggesting that maintenance of sinus rhythm is associated with improved survival rates,23,24 a beneficial effect that may be offset by the adverse effects of AAD in patients treated medically. PVI has the potential to restore sinus rhythm, eliminating the need for AADs and potentially for long-term anticoagulation. However, data are limited regarding late recurrence of AF beyond 1 year after ablation.

We aimed to study the natural history of ablated AF, in particular, the efficacy of PVI for long-term maintenance of sinus rhythm and control of symptoms in patients with drug-resistant AF.

Methods

Study Population and Follow-Up
All 831 patients who underwent PVI for drug-resistant AF in 2005 at our institution were included in the study. Patients with arrhythmia recurrences were divided into an early recurrence group, with recurrences occurring within 12 months of ablation,
and a late recurrence group, with recurrences occurring beyond 1 year after ablation. Atrial arrhythmias occurring during the first 2 months after PVI were not counted as recurrences because they do not necessarily imply failure of the procedure.25,26 This was considered a blanking period.

After ablation, patients were given an event recorder to monitor for arrhythmias during the first 3 months and recorded on a weekly basis and whenever symptomatic. Additional event recorder monitoring was obtained beyond the 3-month period if patients had atrial tachyarrhythmia within the first 3 months or had symptoms consistent with arrhythmia. Patients had 24-hour Holter recordings done at 3 months, 6 months, and every 6 months thereafter. Follow-up visits were scheduled at 3, 6, and 12 months after ablation and yearly thereafter when possible. More frequent follow-ups were scheduled for patients who had symptoms, arrhythmia recurrence, or complications from the procedure. All patients had a transthoracic echocardiogram within 3 months before ablation, an echocardiogram, and a cardiac computerized tomography scan assessing for possible PV stenosis at 3 months after ablation. Mild, moderate, and severe PV stenosis was defined as <50%, 50% to 70%, or >70% narrowing in 1 of the PVs.

Arrhythmia recurrence was identified when patients reported symptoms consistent with arrhythmia and/or when an atrial tachyarrhythmia, lasting ≥30 seconds, was captured on a 12-lead ECG, event recording, or Holter monitor recording. In the absence of such documentation, patients were analyzed as arrhythmia-free. AADs were used in the first 2 months after ablation and were then stopped unless continued arrhythmia mandated their use, in which case patients were considered with arrhythmia recurrence. Amiodarone was never used after ablation. All success rates were determined off AAD.27 For patients with no documented recurrence in the first year after ablation, those with low risk for thromboembolic events (CHADS score ≤2) were considered for discontinuation of warfarin.

All patients were required to have in-person follow-up visits at 3, 6, and 12 months. Beyond the year after ablation, patients referred for ablation from distant regions were medically released for follow-up with their local electrophysiologists, but every effort was made to update our clinical records with their progress. In our practice at the Cleveland Clinic, all clinical documentation, including telephone encounters, or other forms of communication with the patients or their referring physicians, such as letters, is documented electronically. Our AF registry includes clinical data collected before ablation, ablation procedures, and data from subsequent follow-up visits scheduled at 3, 6, and 12 months and then yearly after ablation in addition to all unscheduled visits, telephone encounters, and communication with referring physicians. Our AF registry is regularly updated using the electronic clinical record and by means of telephone encounters (most recently, in October 2009 for this group of patients, with 94.5% response rate), assessing for symptoms, recurrences, strokes, and medication use including AADs and warfarin.

### Ablation Protocol

Our PVI and periprocedural anticoagulation protocols have been described in detail.28 Briefly, all AADs were stopped 4 to 5 half-lives before ablation, with the exception of amiodarone, which was stopped a minimum of 4 to 5 months before the procedure. A transesophageal echocardiogram was obtained for patients presenting in AF if they had a subtherapeutic international normalized ratio within 3 weeks before ablation. A 10F phased-array intravascular ultrasound catheter (Siemens AG Inc, Malvern, PA) was placed in the right atrium to assist with performing transseptal punctures, to guide catheter location and manipulation within the left atrium, and to monitor for cardiac complications during ablation. All PV antra were isolated in all patients under intracardiac echocardiographic (ICE) guidance. Electric isolation was confirmed with absence of PV potentials along the antrum by use of a circular mapping catheter. In all patients, the superior vena cava (SVC) was mapped, and potentials were ablated when there was no phrenic nerve stimulation. In redo ablations for arrhythmia recurrence, drug testing with isoproterenol with up to 20 mg/min for 10 minutes was performed to uncover any potential non-PV triggers.

### Table 1. Demographic and Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study Population</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>831 (100%)</td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>644 (77.5%)</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>94.5 ± 19.4</td>
<td></td>
</tr>
<tr>
<td>Nonparoxysmal AF</td>
<td>256 (30.8%)</td>
<td></td>
</tr>
<tr>
<td>Symptoms at baseline</td>
<td>831 (100%)</td>
<td></td>
</tr>
<tr>
<td>Drug-resistant AF</td>
<td>831 (100%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>296 (35.6%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>67 (8.1%)</td>
<td></td>
</tr>
<tr>
<td>Coronary disease</td>
<td>118 (14.2%)</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>53.0 ± 9.8</td>
<td></td>
</tr>
<tr>
<td>Left atrial size, cm²</td>
<td>23.9 ± 8.1</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.93 ± 0.21</td>
<td></td>
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<tr>
<td>HbA1C</td>
<td>5.8 ± 2.7</td>
<td></td>
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<tr>
<td>BNP, pg/mL</td>
<td>88.4</td>
<td></td>
</tr>
<tr>
<td>Ultrasensitive CRP, mg/L</td>
<td>3.3</td>
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</table>

LVEF indicates left ventricular ejection fraction.

### Statistical Analysis

Results are presented as percentages for categorical variables and mean±SD for continuous variables. The χ² or Fisher exact test was used as appropriate to compare categorical variables between the groups. Kaplan–Meier survival curves were used to present arrhythmia-free survival during follow-up. Univariate Cox proportional hazards analyses were used to assess for factors associated with early (including all patients) or very late arrhythmia recurrence (including only patients who remained arrhythmia-free at 1-year follow-up) after a single ablation. Covariate-adjusted Cox proportional hazards models were then used to assess for independent predictors of early and very late arrhythmia recurrence after a single ablation. All factors found to have a statistically significant relationship with arrhythmia recurrence in univariate analyses were included in the multivariable Cox model. A 2-sided probability value of <0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (version 14.0, SPSS Inc, Chicago, IL).

### Results

In 2005, 831 patients underwent AF ablation (256 with nonparoxysmal AF [non-PAF], 30.8%; 93 with longstanding persistent AF, 11.2%). All were symptomatic and referred for ablation after failure of at least 2 class I or III AAD, plus a negative dromotropic agent. Patients’ clinical characteristics are summarized in Table 1. All patients underwent isolation of all 4 PVs in addition to SVC in the majority (79.3%). They were followed for a median follow-up of 55 months (range, 12 to 58 months; interquartile range, 54 to 56 months) after the initial procedure. Outcome data at 12, 24, 36, 48, and 54 months after ablation for our population was collected on 100%, 94.2%, 92.9%, 82.3%, and 79.7% of patients, respectively. In-person follow-up visits in our electrophysiology clinics were completed by 81.1%, 60.3%, 43.4%, and 21.9% of our patients at 12, 24, 36, and 48 months, respectively. During the blanking period, 322 patients (38.7%) had documented arrhythmia; most of these occurred during the first month (256 patients, 79.5%). At 12 months after PVI, 633 patients were arrhythmia-free off AAD (76.2%), whereas 198 patients had recurrence of their arrhythmia (23.8%). Over long-term follow-up, very late arrhythmia recurrence beyond...
the year after ablation in the absence of recurrences within 1 year after ablation occurred in 74 patients (8.9%). Follow-up and outcome data are summarized in Figure 1.

Predictors and Characteristics of Arrhythmia Recurrence After a Single Ablation

In univariate analysis, factors found to be associated with early arrhythmia recurrences after a single ablation were male sex (hazard ratio [HR], 1.21; 95% confidence interval [CI], 1.03 to 1.34; P<0.04), older age (HR, 1.03; 95% CI, 1.01 to 1.05; P=0.002), higher body mass index (HR, 1.04; 95% CI, 1.02 to 1.07; P=0.004), non-PAF at baseline (HR, 1.86; 95% CI, 1.47 to 2.35; P<0.001), hypertension (HR, 1.11; 95% CI, 1.03 to 1.29; P=0.04), lower left ventricular ejection fraction (HR, 1.03; 95% CI, 1.01 to 1.06; P<0.001), larger left atrial size (HR, 1.02; 95% CI, 1.01 to 1.06; P<0.001), higher ultrasensitive C-reactive protein (CRP) (HR for +1 log ultrasensitive CRP change, 1.72; 95% CI, 1.13 to 2.41; P=0.01) and higher B-type natriuretic peptide (BNP) levels (HR for +1 log BNP change, 5.13; 95% CI, 3.78 to 5.82; P<0.001).

In patients without arrhythmia recurrence in the first year after initial ablation, factors found to be associated with late arrhythmia recurrences in univariate analysis were older age (HR, 1.02; 95% CI, 1.01 to 1.03; P=0.04), non-PAF at baseline (HR, 1.24; 95% CI, 1.13 to 1.36; P=0.02), and larger atrial size (HR, 1.01; 95% CI, 1.01 to 1.06; P=0.03).

The results of univariate Cox proportional hazards analysis to identify factors associated with early or late arrhythmia recurrences after a single ablation are summarized in Table 2.

The occurrence of arrhythmia in the first 2 months after ablation was not found to be associated with late recurrences (HR, 1.23; 95% CI, 0.84 to 1.41; P=0.18).

In multivariable analysis, independent predictors for early arrhythmia recurrence after a single ablation were older age (HR, 1.02; 95% CI, 1.01 to 1.03; P=0.005), higher body mass index (HR, 1.02; 95% CI, 1.01 to 1.05; P=0.04), non-PAF at baseline (HR, 1.81; 95% CI, 1.57 to 2.46; P<0.001), lower left ventricular EF (HR, 1.02; 95% CI, 1.01 to 1.05; P<0.001), larger left atrial size (HR, 1.07; 95% CI, 1.04 to 1.09; P<0.001), higher CRP levels (HR for +1 log ultrasensitive CRP, 1.59; 95% CI, 1.11 to 1.96; P=0.02), and higher BNP levels (HR for +1 log BNP, 4.26; 95% CI, 3.98 to 4.79; P<0.001). In patients without recurrences in the first year after ablation, factors found to predict very late arrhythmia recurrences were non-PAF at baseline (HR, 1.21; 95% CI, 1.11 to 1.34; P=0.03) and larger left atrial size (HR, 1.02; 95% CI, 1.01 to 1.07; P=0.02).

The results of multivariable Cox proportional hazards analysis to identify independent predictors of early or late arrhythmia recurrences after a single ablation are summarized in Table 3.

More patients with non-PAF had early (89 of 256 versus 109 of 575; 34.8% versus 19.0%; P<0.0001) and late recurrences (29 of 256 versus 45 of 575; 11.3% versus 7.8%; P<0.0001) than patients with PAF at baseline. In patients with very late recurrence, there were documented recurrences as AF in 59 patients (79.7%), atrial flutter (AFL) in 20 patients (27.0%), and atrial tachycardia in 3 patients (4.1%). Some patients had both AF and AFL. In the early recurrence group, the documented recurrences were AF in 164 patients (82.8%), AFL in 95 patients (48.0%), and atrial tachycardia
in 11 patients (5.6%). Of these arrhythmia types, only AFL was significantly different between the groups ($P=0.002$), occurring more commonly in the early recurrence group.

**Repeat PVI and Outcomes**

In the late recurrence group (74 patients), 27 patients (36.5%) underwent repeat ablations. Their arrhythmia at first ablation was PAF in 18 (66.7%) patients and non-PAF in 9 patients (33.3%). Their recurrent arrhythmias were AF in 16 (59.3%), AFL in 8 (29.6%), AF/AFL in 2 (7.4%), and atrial tachycardia/AFL in 1 (3.7%). During repeat procedures, PV mapping revealed conduction recovery in at least 1 of the previously isolated veins in all of them. Sixteen patients (59.3%) had SVC reconnection, and this was reisolated. With isoproterenol challenge, right-sided premature atrial complexes initiating AF were identified and ablated in 15 patients (55.6%). No triggers from the coronary sinus were identified.

Over a median follow-up of 17 months after repeat ablation, 20 (74.1%) remained arrhythmia-free off AAD and 7 (25.9%) had arrhythmia controlled with AAD.

In the early recurrence group (198 patients), 161 patients (81.3%) underwent repeat ablations, revealing PV recovery in all of them, and right-sided electric foci in 67 patients (41.6%). Over a median follow-up of 14 months after repeat ablations, 127 patients (78.9%) remained arrhythmia-free but 34 patients had recurrence (21.1%, 22 [64.7%] controlled with antiarrhythmic medications).

At last follow up, 660 of 831 patients were arrhythmia-free off AAD therapy after a total of 1019 ablations, averaging 1.2±0.4 ablations per patient (79.4%, 513 after a single ablation in 643 patients, 147 after 2 ablations in 188 patients with repeat ablations performed between August 2005 and June 2008). One hundred twenty-five patients (15.0%, 41 with more than 1 ablation) continued to have atrial arrhythmia.

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**Table 2. Results of Univariate Cox Proportional Hazards Analysis to Identify Factors Associated With Arrhythmia Recurrences After a Single Ablation**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early Recurrence*</th>
<th>Late Recurrence†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P Value</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.21</td>
<td>0.04</td>
</tr>
<tr>
<td>Age, +1 y</td>
<td>1.03</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI, +1 kg/m²</td>
<td>1.04</td>
<td>0.004</td>
</tr>
<tr>
<td>Nonparoxysmal AF</td>
<td>1.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.11</td>
<td>0.04</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>0.96</td>
<td>0.69</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>0.91</td>
<td>0.34</td>
</tr>
<tr>
<td>Ejection fraction, −1%</td>
<td>1.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrial size, +1 cm²</td>
<td>1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Natural log of ultrasensitive CRP, +1 log</td>
<td>1.72</td>
<td>0.01</td>
</tr>
<tr>
<td>Natural log of BNP, +1 log</td>
<td>5.13</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.

*Defined as recurrence in the first year after ablation (all patients included in the model).
†Defined as recurrence beyond 1 year after ablation in the absence of early recurrences (only patients arrhythmia-free at 1 year included in the model).

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**Table 3. Results of Multivariable Cox Proportional Hazards Analysis to Identify Independent Predictors of Arrhythmia Recurrences After a Single Ablation**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early Recurrence*</th>
<th>Late Recurrence†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P Value</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.87</td>
<td>0.3</td>
</tr>
<tr>
<td>Age, +1 y</td>
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<td>0.005</td>
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<tr>
<td>BMI, +1 kg/m²</td>
<td>1.02</td>
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<tr>
<td>Nonparoxysmal AF</td>
<td>1.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.94</td>
<td>0.49</td>
</tr>
<tr>
<td>Ejection fraction, −1%</td>
<td>1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrial size, +1 cm²</td>
<td>1.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Natural log of ultrasensitive CRP, +1 log</td>
<td>1.59</td>
<td>0.02</td>
</tr>
<tr>
<td>Natural log of BNP, +1 log</td>
<td>4.26</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.

*Defined as recurrence in the first year after ablation (all patients included in the model).
†Defined as recurrence beyond 1 year after ablation in the absence of early recurrences (only patients arrhythmia-free at 1 year included in the model).
controlled with AAD in 87 of them (69.6%). Only 38 patients (4.6%) continued to have drug-resistant AF and were treated with rate control with negative dromotropic agents.

Kaplan–Meier curves for arrhythmia-free survival after single or repeat ablations are outlined in Figure 2. The time to event was defined as the interval between time of ablation and time of first documented recurrence after the procedure.

**Procedure-Related Complications**

A total of 1019 ablations were performed in 831 patients in this cohort (643 patients with a single ablation and 188 patients with 2 ablations). The incidence of procedure-related complications (Table 4) was low and occurred in 20 patients (2.4%). Three strokes (0.29%), which were all suspected during ablation, were confirmed with computed tomography angiograms; patients received thrombolytic therapy and had no long-term neurological deficits. Three patients had hematomas requiring intervention. Two patients (0.2%) had cardiac tamponade, and 1 of them required surgery for repair of a left atrial dome perforation. On computed tomography scans performed 3 months after ablation, 6 patients (0.6%) were found to have PV stenosis (all asymptomatic, 3 with mild stenosis, 3 with moderate stenosis), but no intervention was required in any of them. No procedure-related death occurred.

**Table 4. Procedure-Related Complications**

<table>
<thead>
<tr>
<th>Complications</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriovenous fistula</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Tamponade</td>
<td>2 (0.20%)</td>
</tr>
<tr>
<td>Ischemic stroke, reversible</td>
<td>3 (0.29%)</td>
</tr>
<tr>
<td>Hematomas, required intervention</td>
<td>3 (0.29%)</td>
</tr>
<tr>
<td>Hematomas, no intervention needed</td>
<td>4 (0.39%)</td>
</tr>
<tr>
<td>Pericardial effusion, asymptomatic</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Pulmonary vein stenosis, asymptomatic</td>
<td>6 (0.59%)</td>
</tr>
<tr>
<td><strong>Total number of procedures</strong></td>
<td><strong>1019</strong></td>
</tr>
</tbody>
</table>

**Figure 2.** Kaplan–Meier curves for arrhythmia-free survival after AF ablation. **A,** Early recurrences (in the first year) after a single ablation. **B,** All recurrences (early and late) after a single ablation. **C,** Late recurrences in patients with no early recurrences after a single ablation. **D,** All recurrences after last ablation (831 patients underwent 1019 ablations).

**Long-Term Anticoagulation in Patients With Successful Ablation**

Of 587 patients with no arrhythmia recurrence in the year after ablation, warfarin was stopped in 449 patients (76.5%) with CHADS score of 0. Of those, 207 patients (46.1%) had a CHADS score of 0; 191 (42.5%) had a CHADS score of 1; and 51 (11.4%) had a CHADS score of 2. Of all 587 patients, 164 had a CHADS score of 2, but only 51 of those were considered for discontinuation of warfarin (31.1%). Warfarin was not stopped in any patients with a stroke history were considered for warfarin cessation were younger (56.3±10.0 versus 61.9±8.8 years, *P*<0.0001) and were less likely to have non-PAF (19.6 versus 35.3%, *P*<0.0001) or diabetes mellitus at baseline (4.9 versus 9.9%, *P*=0.04). No patients with a stroke history were considered for warfarin
cessation. Over a median follow-up of 44 months (range, 35 to 46), only 1 patient (0.06% per year) had an ischemic stroke with minimal residual deficit. A 70-year-old woman with hypertension, PAF, and left atrial scarring was off warfarin with no documented late recurrence. At last follow-up, 388 patients (66.1%) were off warfarin (386 with no recurrence after a single ablation and 20 with no recurrence after repeat ablation).

Discussion
To our knowledge, this is the largest study to date with long-term outcomes of AF ablation. In a patient population of >800 patients followed for >4.5 years, the efficacy of PVI for long-term maintenance of sinus rhythm in patients with drug-resistant AF was 79.4% and was associated with a low incidence of procedure-related complications. Of 831 patients, 660 patients (79.4%) were arrhythmia-free off AADs over long-term follow-up. Moreover, 87 patients (10.5%) had their arrhythmia controlled with AAD that have previously failed. The incidence of late arrhythmia recurrence beyond 12 months after ablation was 8.9%. In the absence of arrhythmia recurrence in the year after PVI, warfarin was safely discontinued in a substantial proportion of patients with CHADS score of ≤2. With cumulative evidence regarding the efficacy and safety of PVI,12–15,22,26,28 the current study highlights its efficacy for long-term maintenance of sinus rhythm and control of symptoms with high success rates. Only a small number of patients remained in AF unresponsive to AAD. Repeat ablations were successful in both early and late recurrence patients.

Our data are concordant with a recent report by Ouyang et al.,16 in which PVI resulted in stable sinus rhythm in the majority of 161 patients with PAF undergoing ablation over long-term follow-up, and a previous study by Medi et al.17 in which it was found that among PAF patients who maintain sinus rhythm in the year after ablation, a minority had late AF recurrence. In contrast to these studies, our population included both PAF and non-PAF. Few other reports in the literature suggest that late recurrences are fairly common,18–20 particularly in patients undergoing ablation for persistent AF and those with underlying cardiovascular diseases.19,20 In our study, having non-PAF and enlarged left atria predicted recurrences in patients who remained arrhythmia-free in the year after ablation. These observations are of clinical relevance when considering patients for warfarin cessation after successful ablation.

Ablation for Symptomatic Drug-Resistant AF
In clinical practice, control of symptoms is a major therapeutic goal in the management of AF.26 This can be achieved with either a rate control or a rhythm control strategy. However, AADs are often ineffective and may have serious side effects,23 and many patients unresponsive to AADs remain symptomatic despite rate control.

Our study showed that PVI is efficacious for long-term control of symptoms and eliminated the need for AAD and negative dromotropic agents in a large proportion of patients. Furthermore, it restored and maintained sinus rhythm off AAD in almost 80% of our patients. This is clinically relevant, with studies suggesting that maintenance of sinus rhythm is better than rate control and is associated with better survival rates.23,24

Mechanisms Underlying Recurrences
Our results on early recurrence are concordant with the data in the literature.27,30–32 Independent predictors for arrhythmia recurrences were found to be older age, non-PAF at baseline, lower left ventricular ejection fraction, and larger atria. Importantly higher body mass index, elevated BNP, and elevated CRP levels were found to independently predict early recurrences but not late recurrences, suggesting that obesity, a higher burden of inflammation,33 and increased cardiac chamber wall stress34 may contribute to early recurrence rather than late recurrence.

In fact, the cases with very late recurrences are still the most challenging.35–38 In our study, most late recurrences were due to AF, whereas approximately half of the patients with early recurrence had AFL. We postulate that a significant subset of early recurrence was due to iatrogenic arrhythmia secondary to gaps in ablation lines and/or tissue recovery. On repeat ablation, all patients with late recurrence had reconnection of at least 1 previously isolated PV antrum. Of interest, there was also reconnection of the SVC right atrial junction in about 60% of patients in this group. With isoproterenol challenge, additional right atrial triggers of AF were identified in more than half of these patients.

In patients with no documented recurrences in the first year, larger left atrial size and/or having non-PAF at baseline were found to be independent predictors of recurrences over the long-term follow-up. These factors independently predicted early recurrences as well. Therefore, patients with enlarged atria and/or non-PAF with no recurrence within the first year appear to be at increased risk of late recurrence. The persistence of a cardiac substrate that is potentially arrhythmogenic can predispose to late recurrence.39 In such patients, drug testing at the time of initial ablation may be warranted to uncover potential non-PV and SVC triggers to optimize outcomes.

Anticoagulation After Successful PVI
Over a follow-up of >3.5 years, the occurrence of stroke off warfarin in patients with no arrhythmia recurrence in the year after PVI was low (0.06% per year). Our data, while suggesting that warfarin can be stopped in select patients with no arrhythmia recurrence and is concordant with a recently published report,40 does not provide definitive answers regarding this issue. The decision to stop warfarin should be made on a case-by-case basis, accounting for CHADS score, type of arrhythmia at baseline, previous stroke history, and most importantly, considering the intensity of arrhythmia monitoring during the year after ablation, which is a major factor in this selection process. In all, further studies will help better stratify patients for warfarin cessation and its optimal timing, especially in patients with higher CHADS scores.

Study Limitations
It is possible that our study underestimates the rates of arrhythmia recurrences and may have missed patients with asymptomatic recurrences. Also, in the absence of arrhythmia documentation in the first 3 months after ablation, the event-monitor recording period was not extended, which may have missed more events in this particular group of patients and is a potential source for a misclassification bias. In fact,
our study has the inherent limitations of registries at tertiary care centers. It is known that in such settings, follow-up is difficult, especially when patients are from another city, state, or country. Patients must endure hardship and cost of travel in addition to cost of lodging, if needed. With the current economic conditions, follow-up will become an even bigger problem. However, from the onset of our AF program, we have applied every effort to ensure that our patients are followed up to get meaningful outcomes data. Most of our patients in this study had an in-person follow-up up to 12 months after ablation. All had Holter recordings done at 3 months, 6 months, and every 6 months after ablation either at the Cleveland Clinic or locally with their treating doctors and had the Holter tracings faxed and entered into our registry. All communication with our patients or their local physicians in any form is documented in the electronic medical record. As mentioned earlier, our AF registry is regularly updated, using the electronic clinical record and by means of telephone encounters (most recently in October 2009 for this group of patients, with 94.5% response rate), assessing for symptoms, recurrences, redo ablation at another facility, strokes, and medication use, including AADs and warfarin. In reality, one cannot guarantee 100% follow-up. Even if all patients were implanted with loop recorders, this will not be sufficient because these typically lasted between 18 months and 3 years during the study period. Also data regarding redo ablation, stroke, and so forth would not be gathered.

Despite our concerted efforts to collect as much follow-up data as possible, 46 patients were lost to long-term follow-up (5.5%). We performed a sensitivity analysis to assess for the effect of the missing data on overall results. We assumed the worst-case scenario, in which all 46 patients had late recurrence and none of them was responding to AAD. In this scenario, the overall results at 4.5 years would be 660 of 831 patients arrhythmia-free off AAD (79.4%), 87 of 831 patients with arrhythmia controlled on AAD (10.5%), and 84 of 831 patients with drug-resistant AF (10.1%). Under this scenario, clinical success with sinus rhythm or arrhythmia control with AAD would be 89.9%.

Furthermore, our data on safety of AF ablation is from a referral center with a large volume of AF ablation procedures performed under ICE guidance and may not necessarily reflect the actual complication rates in the general practice of PVI.

**Conclusion**

PVI is safe and efficacious for long-term maintenance of sinus rhythm and control of symptoms in patients with drug-resistant AF. It allowed the discontinuation of AADs, negative dromotropic agents, and anticoagulants in a substantial proportion of patients undergoing ablation.

**Disclosures**

Dr Saliba receives speaking honoraria from Biosense Webster. Dr Martin acts on the advisory board for Medtronic. Dr Dressing receives speaking honoraria from Medtronic, Boston Scientific, Cardionet, St Jude Medical, and Biotronik. Dr Callahan receives speaking honoraria from Biotronik and Boston Scientific. Dr Kanj receives speaking honoraria from Biosense Webster. Dr Lindsay is a consultant for Biosense Webster. Dr Natale receives speaking honoraria from St Jude Medical, Biosense Webster, Medtronic, and Boston Scientific and research grants from St Jude Medical. Dr Wazni receives speaking honoraria from St Jude Medical.

**References**


Pulmonary vein isolation (PVI) by catheter-based radiofrequency ablation has become an effective treatment for drug-refractory atrial fibrillation (AF). However, most of the outcome data in the literature do not have long-term follow-up. In the current study, we report our experience with long-term outcomes of AF ablation. In a patient population of >800 patients followed for >4.5 years, the efficacy of PVI for long-term maintenance of sinus rhythm in patients with drug-resistant AF was 79.4% and was associated with a low incidence of procedure-related complications. Additionally, 10.5% had their arrhythmia controlled with antiarrhythmic drugs that had previously failed. The incidence of late arrhythmia recurrence beyond 12 months after ablation was 8.9%. With cumulative evidence regarding the efficacy and safety of PVI, the current study highlights its efficacy for long-term maintenance of sinus rhythm and control of symptoms with high success rates.

CLINICAL PERSPECTIVE

Pulmonary vein isolation (PVI) by catheter-based radiofrequency ablation has become an effective treatment for drug-refractory atrial fibrillation (AF). However, most of the outcome data in the literature do not have long-term follow-up. In the current study, we report our experience with long-term outcomes of AF ablation. In a patient population of >800 patients followed for >4.5 years, the efficacy of PVI for long-term maintenance of sinus rhythm in patients with drug-resistant AF was 79.4% and was associated with a low incidence of procedure-related complications. Additionally, 10.5% had their arrhythmia controlled with antiarrhythmic drugs that had previously failed. The incidence of late arrhythmia recurrence beyond 12 months after ablation was 8.9%. With cumulative evidence regarding the efficacy and safety of PVI, the current study highlights its efficacy for long-term maintenance of sinus rhythm and control of symptoms with high success rates.


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