Radiofrequency Ablation vs Antiarrhythmic Drugs as First-line Treatment of Symptomatic Atrial Fibrillation
A Randomized Trial

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Context  Treatment with antiarrhythmic drugs and anticoagulation is considered first-line therapy in patients with symptomatic atrial fibrillation (AF). Pulmonary vein isolation (PVI) with radiofrequency ablation may cure AF, obviating the need for antiarrhythmic drugs and anticoagulation.

Objective  To determine whether PVI is feasible as first-line therapy for treating patients with symptomatic AF.

Design, Setting, and Participants  A multicenter prospective randomized study conducted from December 31, 2001, to July 1, 2002, of 70 patients aged 18 to 75 years who experienced monthly symptomatic AF episodes for at least 3 months and had not been treated with antiarrhythmic drugs.

Intervention  Patients were randomized to receive either PVI using radiofrequency ablation (n=33) or antiarrhythmic drug treatment (n=37), with a 1-year follow-up.

Main Outcome Measures  Recurrence of AF, hospitalization, and quality of life assessment.

Results  Two patients in the antiarrhythmic drug treatment group and 1 patient in the PVI group were lost to follow-up. At the end of 1-year follow-up, 22 (63%) of 35 patients who received antiarrhythmic drugs had at least 1 recurrence of symptomatic AF compared with 4 (13%) of 32 patients who received PVI (P<.001). Hospitalization during 1-year follow-up occurred in 19 (54%) of 35 patients in the antiarrhythmic drug group compared with 3 (9%) of 32 in the PVI group (P<.001). In the antiarrhythmic drug group, the mean (SD) number of AF episodes decreased from 12 (7) to 6 (4), after initiating therapy (P=.01). At 6-month follow-up, the improvement in quality of life of patients in the PVI group was significantly better than the improvement in the antiarrhythmic drug group in 5 subclasses of the Short-Form 36 health survey. There were no thromboembolic events in either group. Asymptomatic mild or moderate pulmonary vein stenosis was documented in 2 (6%) of 32 patients in the PVI group.

Conclusion  Pulmonary vein isolation appears to be a feasible first-line approach for treating patients with symptomatic AF. Larger studies are needed to confirm its safety and efficacy.

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liminary data from our and other laboratories suggest that pulmonary vein isolation (PVI) may cure AF, obviating the need for antiarrhythmic drugs and anticoagulation in many patients. However, ablative therapy is usually considered only after drugs have failed because catheter ablation is an invasive procedure with attendant potential risks, including procedural stroke and pulmonary vein stenosis.

Recently presented data from a study involving patients who had previously not responded to antiarrhythmic drug therapy suggests that patients who received catheter-based AF ablation had significantly less AF during follow-up than those who received further antiarrhythmic drug therapy. In contrast with this study, which used PVI as second-line therapy after antiarrhythmic drug therapy had failed, our study was designed to determine if PVI is a feasible option as first-line therapy for treating patients with symptomatic AF.

METHODS

We conducted a multicenter prospective randomized pilot study. At the time our study was initiated, there were no consistent data about the success rates of PVI in the medical literature. Therefore, enrollment for our trial was open for 6 months regardless of the sample size obtained during that period.

Patients were eligible to enter the study if they had experienced monthly symptomatic AF episodes for at least 3 months. Exclusion criteria were age younger than 18 years and older than 75 years, previous history of atrial flutter or AF ablation, previous history of open-heart surgery, previous treatment with antiarrhythmic drugs, and contraindication to long-term anticoagulation treatment. Each patient signed a written informed consent after approval by the institutional ethics and review board committees at each of the corresponding hospitals.

Randomization was computer generated at the Cleveland Clinic Foundation, Cleveland, Ohio, but actual enrollment occurred at the following centers: San Giovanni, Rotondo, Italy (n=21); Mestre, Venice, Italy (n=23); and Coburg, Coburg, Germany (n=26). Patients were randomized to receive either antiarrhythmic drug therapy or PVI for treatment of AF. Patients were not randomized to a rate-control strategy because, at the time the study was initiated, a rate-control strategy had not been shown to be as effective as a rhythm-control strategy. Physicians providing patient care were advised to keep patients in the same treatment group during the 1-year follow-up period. All patients underwent 3 preenrollment 24-hour Holter monitoring studies.

The primary end point of the study was any recurrence of symptomatic AF or asymptomatic AF lasting longer than 15 seconds during Holter or event monitoring in the 1-year follow-up period. Secondary end points included hospitalization rate during the 1-year follow-up and quality of life as assessed using the Medical Outcomes Study 36-item Short-Form health survey (Short-Form 36). Quality of life was measured at enrollment and at the 6-month follow-up visit.

Antiarrhythmic Drug Treatment

The physician providing patient care chose the drug used in the antiarrhythmic drug study group. Each study center was advised to use the maximum tolerable dose of each antiarrhythmic drug. An effort was made to use amiodarone only after the patient failed at least 2 antiarrhythmic drugs. The initiation of class I antiarrhythmic agents was conducted on an outpatient basis, while class III agents were administered in-hospital. The recommended medical regimen consisted of oral flecainide (100-150 mg) twice daily, propafenone (225-300 mg) 3 times daily, and sotalol (120-160 mg) twice daily. For patients not already receiving warfarin, anticoagulation with warfarin was initiated and maintained throughout the study in all patients enrolled in the antiarrhythmic drug group with a target international normalized ratio of 2 to 3.

Pulmonary Vein Isolation

Patients were brought to the electrophyslogic laboratory in a fasting, nonsedated state. A multipolar mapping catheter was placed into the coronary sinus via the right internal jugular vein to record right atrial and coronary sinus electrograms. The ablation catheter and circular mapping catheter were placed via the right femoral vein to the left atrium using a double transseptal puncture technique. In addition, PVI was performed by using phased-array intracardiac echocardiographic monitoring with an intracardiac echocardiographic catheter introduced to the right atrium via the left femoral vein. Intracardiac echocardiography was used to ensure circular mapping catheter positioning, appropriate site of energy delivery, and to guide energy titration by monitoring microbubble formation. When a scattered microbubble pattern was observed, energy was titrated down in 5-W increments until microbubble generation subsided. Energy delivery was terminated immediately when a brisk shower of dense microbubbles was observed. Radiofrequency energy was delivered by using an 8-mm tip ablation catheter (Biosense Webster, Baldwin Park, Calif, and EP Technologies, Sunnyvale, Calif). Intravenous heparin was administered to achieve an activated clotting time of 350 to 400 seconds.

Radiofrequency ablation was performed whenever pulmonary vein potentials were recorded around the pulmonary vein antra. The end point of ablation was complete electrical disconnection of the pulmonary vein antrum from the left atrium. This was considered achieved when no pulmonary vein potentials could be recorded along the antrum or inside the vein by the circular mapping catheter, or if there was electrical dissociation of the pulmonary vein from the left atrium. At the end of the procedure, all 4 pulmonary venous antra were extensively re-mapped with the circular mapping catheter to check for any persisting pulmonary vein potentials and, if necessary, further ablation was performed to eliminate these potentials. All 4 pulmonary ve
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pulmonary Vein Isolation Group (n=33)</th>
<th>Antiarrhythmic Drug Group (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>53 (8)</td>
<td>54 (8)</td>
</tr>
<tr>
<td>Left atrial size, mean (SD), cm</td>
<td>4.1 (0.8)</td>
<td>4.2 (0.7)</td>
</tr>
<tr>
<td>Duration of atrial fibrillation, mean (SD), mo</td>
<td>5 (2.0)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>32 (97)</td>
<td>35 (96)</td>
</tr>
<tr>
<td>Persistent</td>
<td>1 (3)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Structural heart disease and hypertension</td>
<td>8 (25)</td>
<td>10 (28)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, mean (SD), %</td>
<td>53 (5)</td>
<td>54 (6)</td>
</tr>
<tr>
<td>Use of β-blocker therapy</td>
<td>19 (57)</td>
<td>23 (62)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) unless otherwise specified.

Figure 1. Flow of Patients With Atrial Fibrillation

- 233 Patients Screened
- 163 Excluded
  - 132 Did Not Meet Criteria
  - 31 Refused
- 70 Randomized
- 33 Assigned to Receive Pulmonary Vein Isolation
- 37 Assigned to Receive Antiarrhythmic Drug Therapy
- 1 Lost to Follow-up
- 2 Lost to Follow-up
- 32 Included in Primary Analysis
- 35 Included in Primary Analysis

Follow-up

Follow-up was scheduled at 1, 3, 6, and 12 months. A loop event-recorder, which was worn for 1 month, was used in all patients to monitor events during the first month and was repeated at 3 months. During the monitoring period, patients were asked to record when they experienced symptoms and 2 to 3 times daily, even if they were asymptomatic. Additional event-recorder monitoring was obtained after the 3-month period for patients with recurrence of symptoms. Patients were also monitored with a 24-hour Holter recording before discharge, and at 3, 6, and 12 months postenrollment. In addition, patients were called by telephone on a monthly basis. All patients in the PVI group had a spiral computed tomographic scan after 3 months. This was repeated at 6 and 12 months, if there was evidence of any degree of pulmonary venous narrowing.

Statistical Analysis

All continuous variables are expressed as mean (SD) and were compared using Student t test. Differences among groups of continuous variables were determined by analysis of variance. Categorical variables were compared by χ² analysis or Fisher exact test. SPSS version 11.0 (SPSS Inc, Chicago, Ill) was used for the statistical analysis. Results with P<.05 were considered statistically significant.

For the 2-month period after enrollment, AF recurrence and hospitalizations in both treatment groups were reported separately. This 2-month period was used to account for AF recurrences and hospitalizations that occurred during antiarrhythmic drug titration and to account for the fact that AF recurrence early after PVI may be transient and does not necessarily imply failure of PVI19; therefore, these data are reported separately to minimize bias against the antiarrhythmic drug group of the study. However, for descriptive purposes, we also present a Kaplan-Meier curve of AF-free survival that includes all events and data during these 2 months.

RESULTS

Study Population

From December 31, 2001, to July 1, 2002, 70 patients were enrolled. Baseline characteristics of the study population are shown in Table 1 and Figure 1. Patients were randomized to receive either PVI (n=33) or antiarrhythmic drug treatment (n=37). The mean duration of AF symptoms and left ventricular ejection fraction in both groups were comparable. In the group treated with PVI, 32 patients had paroxysmal AF and 1 had persistent AF, whereas in the group treated with antiarrhythmic drugs, 35 patients had paroxysmal AF and 2 had persistent AF. At baseline, the 2 treatment groups were similar with respect to left atrial size, prevalence of structural heart disease and hypertension, use of β-blocker therapy, and quality of life as assessed by the Short-Form 36 health survey.

Events During the Initial 2 Months of Follow-up

During the initial 2 months of follow-up, 20 patients in the antiarrhythmic drug group had recurrence of AF, which resulted in 26 hospitalizations for direct current cardioversion and medication adjustment. In the PVI group, 9 patients had AF recurrence. There were no hospitalizations in the PVI group during this period. No thromboembolic events occurred in either group.

Follow-up After 2 Months

Three patients (2 in the antiarrhythmic drug group and 1 in the PVI group) did not present for follow-up and were
excluded from the primary analysis. These 3 patients were still alive based on vital statistics information available at the time of preparation of this article. There were no repeat ablation procedures throughout the 1-year period. The 1-year follow-up results are shown in Table 2 and Table 3. After excluding events in the first 2 months after enrollment, 22 (63%) of 35 patients who received antiarrhythmic drugs had at least 1 recurrence of symptomatic AF during the 1-year follow-up period compared with 4 (13%) of 32 in the PVI group (P < .001) (Table 2). Asymptomatic AF was documented in 16% of the antiarrhythmic drug group and in 2% of the PVI group (Table 3). There were no significant differences between patients who had recurrence and those who did not with respect to age (mean [SD], 53 [8] vs 54 [7] years, P = .40), left atrial size (4.1 [0.3] vs 4.2 [0.2] cm, P = .40), duration of AF (5.4 [1.4] vs 5.1 [1.3] months, P = .50), structural heart disease, left ventricular ejection fraction (54.4 [1.7] vs 53.2 [0.5], P = .50), and use of β-blockers (59% vs 61%, P = .80). Three patients received the initial antiarrhythmic drugs only; in 6 patients, the dose of the antiarrhythmic drugs was increased; and in the remaining 16, the initial drug was changed to an alternative drug. When combining the effect of the first and second antiarrhythmic drugs, symptomatic AF recurred in 16% of the antiarrhythmic drug group.

The initial antiarrhythmic drug used was flecainide in 27 patients (77%) and sotalol in 8 patients (23%). Of the 27 patients who received flecainide, 20 experienced recurrence of symptomatic AF. Of those patients, the dosage was increased in 5 patients and changed to a second antiarrhythmic drug in 15 patients. Two of the 8 patients who received sotalol as the initial antiarrhythmic drug experienced recurrence of AF; amiodarone was then initiated for 1 patient and the dose was increased in the second patient. Continuation of β-blocker therapy was left to the physician providing care and was continued in 43% of the PVI group and 52% of the antiarrhythmic drug group. A calcium channel antagonist was not used in the PVI group, but was administered to 28% of patients in the antiarrhythmic drug group.

Hospitalization during follow-up occurred in 19 (54%) of 35 patients randomized to the antiarrhythmic drug treatment compared with 3 (9%) of 32 patients randomized to PVI (P < .001). In the PVI group, the mean (SD) number of nonsustained AF episodes recorded per Holter monitoring decreased from 13 (6) episodes pre-PVI to 1 (2) episodes after the ablation procedure (P = .002). In the antiarrhythmic drug group, the number of AF episodes decreased from 12 (7) to 6 (4) (P = .01), after initiating the therapy (Table 3). Figure 2 is a Kaplan-Meier curve presenting AF recurrences in both groups.

Quality of Life Assessment

At 6-month follow-up, the improvement in quality of life of patients in the PVI group was significantly better than the improvement in quality of life in the antiarrhythmic drug group in 5 subclasses of the Short-Form 36 health survey (Table 4).

Complications

There were no thromboembolic events, defined as transient ischemic events, stroke, deep vein thrombosis, or pulmonary embolism, in either treatment group. Bleeding rates were similar in both groups. Incidence of documented bradycardia was higher in the antiarrhythmic drug group (3 [8.6%]

Table 2. One-Year Follow-up Results by Treatment Group

<table>
<thead>
<tr>
<th>Complication</th>
<th>Pulmonary Vein Isolation Group (n = 32)</th>
<th>Antiarrhythmic Drug Group (n = 35)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic atrial fibrillation recurrence</td>
<td>4 (13)</td>
<td>22 (63)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>3 (9)</td>
<td>19 (54)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2 (6.3)</td>
<td>1 (2.9)</td>
<td>.60</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>3 (8.6)</td>
<td>.20</td>
</tr>
<tr>
<td>Pulmonary vein stenosis†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (3)</td>
<td>0</td>
<td>.50</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (3)</td>
<td>0</td>
<td>.50</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
*Defined as transient ischemic events, stroke, deep vein thrombosis, or pulmonary embolism.
†Mild pulmonary vein stenosis is defined as less than 50%; moderate, 50% to 70%; and severe, more than 70%.

Table 3. Atrial Fibrillation Event Recordings

<table>
<thead>
<tr>
<th>Pulmonary Vein Isolation (n = 4)</th>
<th>Antiarrhythmic Drugs (n = 22)</th>
<th>Corrected Difference in Mean Change (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Initiation</td>
<td>Study Completion</td>
<td>No. (%) of Patients</td>
<td></td>
</tr>
<tr>
<td>Duration of episodes, mean (SD), s</td>
<td>480 (30)</td>
<td>520 (40)</td>
<td>10 (−7 to 27)</td>
</tr>
<tr>
<td>Ventricular rate, mean (SD), beats/min</td>
<td>138 (26)</td>
<td>126 (35)</td>
<td>22 (16 to 28)</td>
</tr>
<tr>
<td>No. of episodes, mean (SD)</td>
<td>13 (6)</td>
<td>12 (7)</td>
<td>−6 (−13 to 1)</td>
</tr>
<tr>
<td>Time patients are in asymptomatic episodes of AF, %</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; CI, confidence interval.
of 35 patients vs none in the PVI group). Asymptomatic moderate (50%-70%) pulmonary vein stenosis was documented in 1 (3%) of 32 patients in the PVI group affecting only 1 vein; no patient developed severe (>70%) pulmonary vein stenosis.

**Follow-up After 1 Year**

After the 1-year follow-up dictated by the study protocol, 4 patients who had recurrence of AF in the PVI group underwent a second procedure. Three of these patients have remained AF free and are not taking antiarrhythmic drugs and 1 patient is in sinus rhythm with antiarrhythmic drug therapy. In the antiarrhythmic drug group, 3 of the patients with recurrence developed chronic AF. Additionally, 18 patients in the antiarrhythmic drug group underwent PVI for AF recurrence. Of these patients, 15 are AF free and are not taking antiarrhythmic drugs and 3 are in sinus rhythm with antiarrhythmic drug therapy.

**Missing Data**

One-year follow-up data were complete for all study participants except for the 3 patients who did not return for follow-up. To assess the possible effect of these missing data, we performed a sensitivity analysis assuming a worst-case scenario in which 1 patient in the PVI group was assumed to have AF recurrence and 2 patients in the antiarrhythmic drug group were assumed to have remained AF free. In this case, the AF recurrence rate in the PVI group would have occurred in 5 (15%) of 33 patients and in the antiarrhythmic drug group, 22 (59%) of 37 patients, which is still significant (P<.001). Under a similar worst-case scenario for hospitalization, there is little difference from the primary analysis.

**COMMENT**

This is the first randomized study to our knowledge demonstrating that a strategy of using first-line PVI for symptomatic AF is associated with improved clinical outcomes compared with initial antiarrhythmic drug therapy. Pulmonary vein isolation was associated with less AF recurrence, improved quality of life, and a lower hospitalization rate during follow-up after the initial 2 months of follow-up. During the initial 2 months of follow-up, there were more recurrences in AF in both groups compared with the results reported at 1 year. However, events were higher in the antiarrhythmic drug group in this period. The initial 2 month period was used to account for AF recurrences and hospitalizations that occur during antiarrhythmic drug titration and to account for the fact that AF recurrence early after PVI may be transient and does not necessarily imply failure of PVI.19

Recent randomized trials2,8 have shown that a strategy of rate control is
comparable with a strategy of rhythm control using antiarrhythmic drugs in treating many patients with AF. We did not include a rate-control group because our study was initiated at a time when the results of these trials were unknown. Even so, the degree to which the results of these trials can be applied to our patient population is unclear. Our study population mainly consisted of younger patients with highly symptomatic AF. This population was underrepresented in recent trials, which included mostly elderly patients with recurrent persistent AF. Elderly patients tend to be less symptomatic than younger patients with paroxysmal AF; therefore, a strategy limited to rate control in younger patients with symptomatic AF may not be as effective in controlling symptoms. In addition, the benefits of restoring sinus rhythm may be greater in younger patients because doing so may prevent progressive atrial remodeling that leads to chronic AF.

The results of the rate-control vs rhythm-control trials might lead to the conclusion that sinus-rhythm restoration is of comparable efficacy with allowing patients to remain in AF with a controlled ventricular rate. Such a conclusion is unwarranted. These studies only showed that a strategy of rhythm control using antiarrhythmic drugs was comparable with a strategy of rate control. A limitation of all these trials is that the rhythm-control strategy was not efficacious. For example, in 1 trial, only 39% of patients randomized to the antiarrhythmic drug group were in sinus rhythm at the end of the study. Furthermore, in an analysis of 1 study that evaluated predictors of mortality, sinus rhythm was associated with a 47% reduction in the risk of death, whereas use of antiarrhythmic drug therapy was associated with a 49% increase in mortality. This suggests that the neutral results in the rate-control vs rhythm-control trials might be explained by the fact that the benefits of antiarrhythmic drugs in restoring sinus rhythm were negated by offsetting detrimental effects of antiarrhythmic drug therapy. In theory, a therapy that restores and maintains sinus rhythm while avoiding the deleterious effects of antiarrhythmic drugs would improve survival. Pulmonary vein isolation may be such a therapy. In a recent observational study involving a relatively large number of patients, Pappone et al reported that AF ablation was associated with significantly lower mortality and adverse events compared with drug therapy.

In current clinical practice, ablation therapy for AF is reserved for patients with symptoms who have failed multiple antiarrhythmic drug regimens. The primary concern in offering an ablation procedure to treat AF as first-line therapy is that complications from the procedure can occur. A recent worldwide survey of more than 8000 AF ablation procedures reported an overall major complication rate of 6%. However, it should be noted that many of the complications, although serious, typically result in only acute and not long-term morbidity. These complications include femoral pseudoaneurysm, arteriovenous fistula, pneumothorax, hemorrhage, transient ischemic attack, and cardiac tamponade. The most serious complications resulting in permanent disability were uncommon (death in 0.05% and stroke in 0.28%). Significant pulmonary vein stenosis was reported in 1.3%, but this can be treated with percutaneous interventional procedures. A recently recognized complication of catheter-based AF ablation is left atrial-esophageal fistula, which could lead to death.

Contrasting the risks of PVI are the risks associated with antiarrhythmic drug therapy, which may not be trivial. In 1 trial, antiarrhythmic drugs were associated with a 49% increased risk of death after taking into account the presence of sinus rhythm. In addition, because antiarrhythmic drugs are frequently ineffective in maintaining sinus rhythm, patients taking antiarrhythmic drugs may remain at risk for long-term complications of AF, such as stroke. The balance between the acute risks of PVI vs the long-term risks of AF is unclear.

Our study had several limitations, which included a pilot study with a small number of relatively young patients and the ablation procedures performed at highly specialized centers. The sample size and 1-year follow-up period were not large enough to assess the effects of therapy on important but infrequent outcomes, such as stroke. The long-term cure rate for the PVI procedure is unknown. Quality of life was only assessed at baseline and 6-month follow-up. Although many patients were receiving atioventricular nodal blocking agents, there was no rate-control group. Because of the potential for end-organ toxicity, the use of amiodarone was discouraged and used infrequently. However, amiodarone may be slightly more effective at maintaining sinus rhythm than other antiarrhythmic drugs. The technique used for performing PVI is similar but not identical to other catheter-based techniques for performing AF ablation. Which ablation technique is best is controversial. Also, techniques for performing AF ablation continue to change as knowledge, experience, and technology advance. Additionally, cost-effectiveness was not addressed in our study. In future studies, the initial 2-month follow-up period would most likely be taken into account when studying cost-effectiveness.

Based on the results of our study, we conclude that PVI is a feasible first-line approach for the treatment of selected patients with symptomatic AF. To further assess whether the benefits of AF ablation outweigh the inherent risks of an invasive procedure requires a multicenter randomized trial with a larger number of centers and patients, and longer follow-up. Until such a study is performed, PVI should not be considered standard of care as first-line therapy for AF. Nevertheless, the results of our study suggest that ablation to cure AF may become the treatment of first choice in appropriately selected patients with AF.

Author Contributions: Dr Natale had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Marrouche, Bharagara, Natalie.

Drafting of the manuscript: Wazni, Martin, Natalie.

Critical revision of the manuscript for important intellectual content: Marrouche, Verma, Bharagara, Saliba, Bash, Schweikert, Brachmann, Gunther, Gutleben, Pisano, Potenza, Fanelli, Raviele, Themistoclakis, Rossillo, Bonso, Natalie.

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Study supervision: Marrouche, Martin, Bharagara, Saliba, Schweikert, Brachmann, Gunther, Gutleben, Potenza, Fanelli, Raviele, Themistoclakis, Rossillo, Bonso, Natalie.

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REFERENCES