Comparison of Antiarrhythmic Drug Therapy and Radiofrequency Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation: A Randomized Controlled Trial

David J. Wilber, MD
Carlo Pappone, MD, PhD
Petr Neuzil, MD
Angelo De Paola, MD
Frank Marchlinski, MD
Andrea Natale, MD
Laurent Macle, MD
Emile G. Daoud, MD
Hugh Calkins, MD
Burr Hall, MD
Giuseppe Augello, MD
Matthew R. Reynolds, MD, MSc
Chandan Vinekar, MS
Christine Y. Liu, MPH
Scott M. Berry, PhD
Donald A. Berry, PhD
for the ThermoCool AF Trial Investigators

Atrial fibrillation (AF) represents an important public health problem. Patients with AF have an increased long-term risk of stroke, heart failure, and all-cause mortality. Furthermore, patients with AF have a considerably impaired quality of life (QOL) that is independent of the severity of the disease. Restoration and maintenance of normal sinus rhythm following treatment directly correlates with improved QOL in these patients.

Although antiarrhythmic drugs are generally used as first-line therapy to treat patients with AF, effectiveness remains inconsistent. The likelihood of AF recurrence within 6 to 12 months approaches 50% with most drugs. Antiarrhythmic drugs are also associated with cumulative adverse effects over time. Catheter ablation has accordingly become an alternative therapy for AF. Several recent studies have investigated this treatment.
compared antiarrhythmic drug therapy (ADT) with catheter ablation. These investigations were characterized by small study populations, variable entry criteria and definitions of success, and were conducted in a single or limited number of centers.

This prospective, multicenter, randomized study was designed to compare catheter ablation with ADT in patients with symptomatic AF who had not improved with at least 1 drug. Our primary goal was to evaluate freedom from symptomatic AF recurrence following treatment. Total atrial arrhythmia recurrence during follow-up was also evaluated.

**METHODS**

The study protocol was approved by the institutional review board or ethics committee at each of the 19 centers (15 in the United States, 2 in Europe, and 1 each in Canada and Latin America). All patients enrolled in the study provided written informed consent.

**Study Population**

At each center, potential study candidates with the diagnosis of AF were identified from outpatient and inpatient discharge logs of the respective institutions or by physician or self-referrals in response to institutional review board–approved study announcements. Enrollment required at least 3 symptomatic AF episodes (≥1 episode verified by electrocardiogram) within the 6 months before randomization, and not responding to at least 1 antiarrhythmic drug (class I, class III, or atrioventricular nodal blocker).

Exclusion criteria included patients with AF of more than 30 days duration, aged younger than 18 years, an ejection fraction of less than 40%, previous ablation for AF, documented left atrial thrombus, amiodarone therapy in the previous 6 months, New York Heart Association class III (marked limitation in activity due to symptoms) or IV (severe limitations), myocardial infarction within the previous 2 months, coronary artery bypass graft procedure in the previous 6 months, thromboembolic event in the previous 12 months, severe pulmonary disease, a prior valvular cardiac surgical procedure, presence of an implanted cardioverter-defibrillator, contraindication to antiarrhythmic or anticoagulation medications, life expectancy of less than 12 months, and left atrial size of at least 50 mm in the parasternal long axis view.

**Study Design**

Patients were randomly assigned 2:1 to ablation or a previously unused antiarrhythmic drug (classes I or III). Upon enrollment, participants were assigned a sequential identification number at each site and a corresponding sealed envelope was opened. Randomization sequences were generated by the sponsor statistician by using SAS version 8.2 (SAS Institute Inc, Cary, North Carolina) and stratified by site with treatment block size of 11 (7 to catheter ablation and 4 to ADT).

**Protocol**

After randomization, patients in the catheter ablation group were observed in the clinic at 1, 3, 6, 9, and 12 months, and patients in the ADT group were observed at 5 to 10 days, 11 to 21 days, and 3, 6, and 9 months. Patients were followed up for comparable 9-month effectiveness evaluation period after a 3-month blanking (healing and stabilization) period for those randomized to ablation (days 91-361) and, after a 14-day dose-titration period, for those randomized to the ADT group. Electrocardiograms were obtained at all follow-up visits.

Transtelephonic monitoring (MicroER; LifeWatch Inc, Rosemont, Illinois) was performed during the 9-month period for patients in both groups. Patients were required to transmit all symptomatic cardiac episodes. They were also required to provide additional scheduled transmissions irrespective of symptoms: weekly for the first 8 weeks, then monthly until the final visit. Holter monitoring (DigiTrak Plus; Philips Medical Systems, Andover, Massachusetts) was conducted at the baseline and final visit for all patients. For patients undergoing ablation, a computed tomography (CT) scan or magnetic resonance imaging (MRI) scan was required within 30 days before the procedure and at 3 months and 12 months after the procedure. Pulmonary vein (PV) stenosis identified by CT or MRI scan was defined as at least 70% reduction of the PV diameter compared with the baseline scan. Independent core laboratories were used to process and analyze transtelephonic, Holter monitors, and CT or MRI scan results. An independent data and safety monitoring committee reviewed and adjudicated causality of all adverse events.

**ADT Group**

Patients randomized to the ADT group received a not previously administered, Food and Drug Administration–approved medication for treating AF (dofetilide, flecainide, propafenone, sotalol, or quinidine). The choice of drug was at the discretion of the investigator. Dosages were based on recommendations from the American College of Cardiology/American Heart Association/European Society of Cardiology 2001 Practice Guidelines for Management of Patients With Atrial Fibrillation. The drug and dosage at the end of the titration period were then maintained throughout the study. Amiodarone was not allowed per study protocol. Patients in the ADT group were allowed to crossover and undergo an ablation procedure after 90 days of therapy if the treatment failed.

**Catheter Ablation Group**

In all patients, PV isolation with confirmation of entrance block was required. The ablation catheter (Navistar ThermoCool Irrigated Tip Catheter; Biosense Webster, Diamond Bar, California) was introduced under fluoroscopic guidance, and the Carto Navigation System (Biosense Webster) was used to map and document the placement of radiofrequency lesions. The PVs were isolated by circumferential lesions. Additional ablation was allowed at investigator discretion.
cretion and included left atrial linear lesions, ablation at sites with electrogram fractionation, and cavotricuspid isthmus ablation. Infusion of isoproterenol (≤20 μg/min) was recommended postablation to confirm that all AF foci had been eliminated or isolated. After the initial procedure, patients in the catheter ablation group were allowed up to 2 repeat ablation procedures within 80 days. At the discretion of the investigator, a previously ineffective drug could be continued during the effectiveness evaluation period. Following ablation, anticoagulation with warfarin was required for the initial 3 months. Subsequent use of anticoagulation during the effectiveness evaluation period followed current guidelines.1

**Primary End Point**

The primary end point was freedom from protocol-defined treatment failure, which included documented symptomatic paroxysmal AF during the effectiveness evaluation period. Patients in the ablation group with repeat ablation after day 80 after the initial ablation, absence of entrance block confirmed in all PVs at the end of the ablation procedure, or changes in specified drug regimen postblanking (including class I/III drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and atrioventricular nodal blocker) were also considered treatment failures, even if they remained free from symptomatic paroxysmal AF. In the ADT group, an adverse event requiring discontinuation of the assigned drug was also considered a treatment failure.

**Safety Outcomes**

Major treatment-related adverse events were defined as those that occurred within 30 days of the ablation procedure or within 30 days following initiation of drug therapy. Prespecified major adverse events included death, myocardial infarction, PV stenosis, diaphragmatic paralysis, atrio-esophageal fistula, transient ischemic attack, thromboembolic events, pericarditis, cardiac tamponade, pericardial effusion, pneumothorax, vascular access complications, pulmonary edema, or congestive heart failure, heart block, life-threatening ventricular arrhythmias, and intolerance to assigned antiarrhythmic drug requiring discontinuation.

**Additional Comparisons**

Additional comparisons included freedom from symptomatic atrial arrhythmia (AF, atrial tachycardia, atrial flutter), freedom from any atrial arrhythmia (symptomatic or asymptomatic), and QOL outcomes. Instruments used to evaluate QOL included the 36-item Short-Form Health Survey (SF-36), Version 2.17 and the AF Symptom Frequency and Severity Checklist.18

**Statistical Methods**

The statistical design was prospective and Bayesian. The protocol-defined primary statistical analysis of the primary end points was Bayesian.19,22 Study success required a probability of superiority of catheter ablation over ADT in the primary end point at the final analysis of at least 98% to control the type I error rate at no more than 2.5%, which was verified by simulations. Maximal sample size was 230 patients with preplanned interim analyses to occur after accruing 150, 175, and 200 patients. If at any interim Bayesian analysis the predictive probability of eventual study success (≥98% probability of superiority when all patients have full follow-up) based on the currently accrued patients (including longitudinal modeling of those patients with <9 months of follow-up) was at least 99%, accrual would stop with study success declared. If the predictive probability of eventual study success was less than 99% but at least 90% at the 150 patient analysis, or 80% at the 175 and 200 patient analyses, accrual would end, but patient follow-up would continue until such time that study success could be declared. If the predictive probabilities of study success for the current sample size and also for the maximum sample size (230 patients) were less than 1% for the 150, 175, or 200 patient analyses, the trial would stop for futility.

The conclusion of the primary statistical analysis was Bayesian predictive and posterior probabilities at the interim analysis at the time the trial was stopped. The probability of superiority based on the study results updated with full follow-up through the 9-month effectiveness period for all patients was also assessed. This calculation was based on intention-to-treat using multiple imputations for the patients who dropped out; this latter analysis was specified in the protocol for patients who did not have 9 months of follow-up. We used 3 parameter piecewise exponential models, with breaks at 2 weeks and 2 months, for imputation within each treatment group. The posterior distributions of the 3 parameters included all available information from patients within the respective treatment group. Patients with missing data were included in the final analysis of 9–month success using Bayesian multiple imputations from the 3 parameter exponential models.

For the updated results, we present the more conventional frequentist measures of P values and confidence intervals (CIs). These are provided without adjustments for interim analyses and so are “nominal” in the sense that they assume that the final sample size was fixed in advance. Continuous variables were expressed as mean (95% CI) and were compared using t tests or Wilcoxon rank sum test as appropriate. Categorical variables were compared with Fisher exact tests.

Additional analyses include Kaplan-Meier representations for time-to-event data. Univariable and multivariable Cox regression analyses were conducted to identify and account for factors predictive of time to failure: age, sex, structural heart disease, diabetes, hypertension, number of symptomatic AF episodes, duration of AF history, prior failure of class II or IV drug only, left atrial dimension, and study center. Factors with P≤.05 were included in the final multivariable model. All tests of signifi-
cance were 2-sided, with P<.05 considered statistically significant.

In the Kaplan-Meier and Cox regression results presented, 8 patients who did not receive assigned treatment were excluded. The remaining patients were censored at the end of the 9-month evaluation period or last known follow-up, whichever occurred first. Analyses were also run in which the 8 randomized but untreated patients were handled in a “worst case” scenario. Specifically, nontreated test patients were assumed to have an event (failure) on day 1, and nontreated control patients were assumed to not have an event (success) through day 270. The Kaplan-Meier and Cox regression results did not appreciably change and conclusions did not change from those generated when the 8 patients were excluded.

The Bayesian analysis was conducted by using Fortran 90 (Intel Fortran 11.0 compiler). The code was written and verified by Berry Consultants and went through the review process by the Center for Devices and Radiological Health division of the Food and Drug Administra-tion. The frequentist analyses were conducted by using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS
Patient Characteristics
Between October 25, 2004, and October 11, 2007, 167 patients were enrolled in the study, with the last follow-up performed on January 19, 2009. Sixty-one and 106 patients were randomized to ADT and catheter ablation groups, respectively. Five patients from the ADT group and 3 patients from the catheter ablation group did not complete the assigned treatment (Figure 1). Overall, the mean age was 55.7 (95% CI, 54.1-57.4) years and 33.5% of the patients were women. Patients had a history of symptomatic AF for 5.7 (95% CI, 4.8-6.6) years and had discontinued an average of 1.3 (95% CI, 1.1-1.4) antiarrhythmic drugs before enrollment. The 2 groups were well matched with respect to baseline characteristics (Table 1). The median (interquartile range) for follow-up times in the catheter ablation and ADT groups were 12.5 (11.9-13.1) months and 14.3 (9.4-15.5) months, respectively.

Interim Analysis and Bayesian Probabilities
The first preplanned interim analysis was conducted after accruing 150 patients. The trial was stopped (although follow-up was continued) when this analysis showed the predictive probability of success to be 99.9%. This was more than the protocol-specified boundary of 99% and enabled an immediate claim of study success (ie, superiority of catheter ablation over ADT). Based on the updated study results of 167 patients (including multiple imputation for the 8 patients who did not receive assigned treatment), the probability of superiority was 99.9%.

Initial Treatment
Most patients in the ADT group were assigned to either flecainide (20/56 [36%]) or propafenone (23/56 [41%]). Sotalol and dofetilide were assigned to 11 and 2 patients, respectively. For the catheter ablation group, confirmation of entrance block following PV isolation was achieved in all patients. The mean procedure time was 208 (95% CI, 191.2-224.8) minutes and the mean fluoroscopy time was 48.6 (95% CI, 40.5-56.7) minutes. Of the 103 patients undergoing catheter ablation procedures, linear ablation of the cavitricuspid isthmus was performed in 37 patients (35.9%). At least 1 left atrial linear lesion (including mitral isthmus and roof lines) was performed in 23 patients (22.3%). The superior vena cava was targeted in 17 patients (16.5%) and other left or right atrial foci were targeted in 17 patients (16.5%). A repeat ablation procedure was performed in 13 patients (12.6%) within 80 days of the initial catheter ablation procedure.

Effectiveness Outcome Analyses
Kaplan-Meier curves for the effectiveness outcomes are shown in Figure 2. At the end of the 9-month effectiveness evaluation period, 66% of patients in the catheter ablation group remained free from protocol-defined treatment failure vs 16% of patients.
treated with ADT (hazard ratio [HR], 0.30; 95% CI, 0.19-0.47; P < .001). Similarly, 70% of patients treated by catheter ablation remained free of symptomatic recurrent atrial arrhythmia vs 19% of patients treated with ADT (HR, 0.24; 95% CI, 0.15-0.39; P < .001). In addition, 63% of patients treated by catheter ablation were free of any recurrent atrial arrhythmia vs 17% of patients treated with ADT (HR, 0.29; 95% CI, 0.18-0.45; P < .001).

In multivariable Cox regression modeling, the only statistically significant factor in predicting failure was treatment group, with HRs as indicated above.

In the catheter ablation group, only 5 of 67 patients classified as protocol-defined successes were taking previously ineffective class I or III antiarrhythmic drugs during the last 6 months of the effectiveness evaluation period. In the ADT group, of the 47 patients that had protocol-defined treatment failures, 36 subsequently underwent catheter ablation. For these 36 patients, the mean time to undergo ablation was 3.9 (95% CI, 3.1-4.6) months from the onset of the effectiveness evaluation period.

**Major Adverse Events**

Thirty-day major treatment-related adverse events occurred in 5 patients (1 pericardial effusion, 1 pulmonary vascular event, 2 episodes of symptomatic hypotension requiring treatment). One patient died in the catheter ablation group, from sepsis related to pacemaker insertion, 1 month after the procedure. No deaths occurred in the ADT group.

**Table 1. Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Catheter Ablation</th>
<th>Antiarrhythmic Drug Therapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>55.5 (53.7-57.3)</td>
<td>56.1 (52.9-59.4)</td>
<td>.72</td>
</tr>
<tr>
<td>Sex, male</td>
<td>73 (68.9)</td>
<td>38 (62)</td>
<td>.40</td>
</tr>
<tr>
<td>Patient history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF duration, median [IQR], y</td>
<td>5.4 (4.3-6.5)</td>
<td>6.2 (4.6-7.9)</td>
<td>.43</td>
</tr>
<tr>
<td>Hypertension</td>
<td>51 (48.6)</td>
<td>30 (50)</td>
<td>.87</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 (9.5)</td>
<td>7 (12)</td>
<td>.79</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>10 (9.5)</td>
<td>9 (15)</td>
<td>.32</td>
</tr>
<tr>
<td>Cerebrovascular accident/TIA</td>
<td>2 (1.9)</td>
<td>3 (5)</td>
<td>.35</td>
</tr>
<tr>
<td>Prior thromboembolic events</td>
<td>2 (1.9)</td>
<td>2 (3)</td>
<td>.62</td>
</tr>
</tbody>
</table>

NYHA class

<table>
<thead>
<tr>
<th>Class</th>
<th>Catheter Ablation</th>
<th>Antiarrhythmic Drug Therapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>81 (87)</td>
<td>50 (88)</td>
<td>.99</td>
</tr>
<tr>
<td>II</td>
<td>12 (13)</td>
<td>8 (14)</td>
<td></td>
</tr>
</tbody>
</table>

LVEF, mean (SD), %

<table>
<thead>
<tr>
<th></th>
<th>Catheter Ablation</th>
<th>Antiarrhythmic Drug Therapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>62.3 (60.4-64.3)</td>
<td>62.7 (60.7-64.7)</td>
<td>.79</td>
</tr>
</tbody>
</table>

Left atrial dimension, mean (SD), mm

<table>
<thead>
<tr>
<th></th>
<th>Catheter Ablation</th>
<th>Antiarrhythmic Drug Therapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>40.5 (38.9-41.1)</td>
<td>40.5 (39.0-41.9)</td>
<td>.62</td>
</tr>
</tbody>
</table>

**Prior antiarrhythmic drug failures**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Catheter Ablation</th>
<th>Antiarrhythmic Drug Therapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotalol</td>
<td>36 (34.3)</td>
<td>22 (37)</td>
<td>.87</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>3 (2.9)</td>
<td>1 (2)</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Propafenone</td>
<td>53 (50.5)</td>
<td>30 (50)</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>33 (31.4)</td>
<td>13 (22)</td>
<td>.21</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>7 (6.7)</td>
<td>6 (10)</td>
<td>.55</td>
</tr>
</tbody>
</table>

**Failed antiarrhythmic drug class**

<table>
<thead>
<tr>
<th>Class</th>
<th>Catheter Ablation</th>
<th>Antiarrhythmic Drug Therapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/II only</td>
<td>20 (18.9)</td>
<td>7 (11)</td>
<td>.28</td>
</tr>
</tbody>
</table>

**Baseline QOL scores, mean (95% CI)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Catheter Ablation</th>
<th>Antiarrhythmic Drug Therapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental Component Summary</td>
<td>44.5 (42.2-46.7)</td>
<td>44.0 (40.7-47.3)</td>
<td>.79</td>
</tr>
<tr>
<td>Physical Component Summary</td>
<td>46.1 (44.4-47.8)</td>
<td>47.6 (45.3-50.0)</td>
<td>.29</td>
</tr>
</tbody>
</table>

**Symptom Frequency Score**

<table>
<thead>
<tr>
<th>Score</th>
<th>Catheter Ablation</th>
<th>Antiarrhythmic Drug Therapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Severity Score</td>
<td>20.7 (18.9-22.6)</td>
<td>18.6 (16.2-21.1)</td>
<td>.18</td>
</tr>
</tbody>
</table>

**Abbreviations:** AF, atrial fibrillation; CI, confidence interval; LVEF, left ventricle ejection fraction; IQR, interquartile range; NYHA, New York Heart Association; QOL, quality of life; TIA, transient ischemic attack.

Data are presented as No. (%) unless otherwise specified. NYHA heart failure class I and II indicate no symptoms and no limitation in ordinary physical activity and mild symptoms and slight limitation during ordinary activity, respectively. For continuous outcomes, comparison by t test. For categorical outcomes, comparison by Fisher exact test.

©2010 American Medical Association. All rights reserved. (Reprinted) JAMA, January 27, 2010—Vol 303, No. 4 337

---

**Figure 2. Kaplan-Meier Curves of Time to Protocol-Defined Treatment Failure, Recurrence of Symptomatic Atrial Arrhythmia, and Recurrence of Any Atrial Arrhythmia by Treatment Group**
edema, 1 pneumonia, 1 vascular complication, and 1 heart failure) in the catheter ablation group (5/103 [4.9%]) and 5 patients (2 with life-threatening arrhythmias and 3 with disabling drug intolerance requiring discontinuation) in the ADT group (5/57 [8.8%]). One patient in the catheter ablation group who had undergone PV isolation alone died 284 days after the procedure due to acute myocardial infarction deemed unrelated to the procedure.

Quality of Life
Baseline QOL measures were similar between treatment groups (Table 1). After the initial 3 months of the effectiveness evaluation period, mean SF-36 physical and SF-36 mental summary scores were significantly higher compared with those scores in patients treated with ADT, in whom scores changed minimally (Table 2). Patients in the catheter ablation group also reported significantly lower (better) mean symptom frequency and severity scores at 3 months. In the catheter ablation group, the improvement in SF-36 scores and decrease in symptom frequency and severity persisted without significant change at the 6- and 9-month QOL assessments. In the ADT group, crossover to ablation after 3 months resulted in progressively fewer patients still receiving drug therapy, precluding meaningful statistical comparisons.

COMMENT
Our multicenter, prospective, randomized study demonstrates that in patients with frequent symptomatic paroxysmal AF unresponsive to initial drug therapy (including ≥1 type 1 or III antiarrhythmic drug in 84% of patients), radiofrequency catheter ablation resulted in significantly better outcomes vs continued attempts at rhythm control with alternative drug therapy. These outcomes included a substantial reduction in the risk of recurrent atrial arrhythmias and clinically meaningful improvement in symptoms and QOL.

These data strongly support the use of catheter ablation in patients with paroxysmal AF who do not respond to initial ADT. In patients with paroxysmal or short-duration persistent AF who have had limited prior drug exposure, 20% to 40% of patients treated with class I drugs or sotalol and 60% to 70% of patients treated with amiodarone have no recurrence of AF at 1 year.9-11 However, failure of prior ADT (due to either recurrence or intolerance) has previously been shown to predict failure of subsequent attempts at pharmacologic rhythm control, irrespective of the specific antiarrhythmic drug.22 This latter observation is consistent with the results of our study and previously reported randomized trials that required at least 1 prior drug failure for study entry.14,15 In these trials, treatment with alternative “new” antiarrhythmic drugs, including amiodarone, resulted in prevention of AF recurrence in only 9% to 23% of patients at 1 year. These data confirm that the efficacy of drug therapy for rhythm control may be considerably lower following previously failed drug trials compared with outcomes in patients not previously exposed to antiarrhythmic drugs.

In this study, both scheduled and symptom-driven transtelephonic monitoring and electrocardiogram recording were used to identify recurrences during follow-up. Ablation was associated with elimination of symptomatic atrial arrhythmia in 70% of patients, and elimination of any atrial arrhythmia irrespective of symptoms in 63% of patients at 1 year. The latter end point has been recommended by the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society Consensus Document for standardized reporting of clinical trial outcomes.12 In prior randomized trials of catheter ablation vs ADT for paroxysmal AF, 1 year freedom from recurrent AF was reported in 56% to 89% of patients treated by catheter ablation.14,15 This range of outcomes may reflect differences in patient selection, intensity of rhythm monitoring and auditing during follow-up, end points, and procedural technique. The results of this study predominantly reflect outcome after a single procedure (mean, 1.1 procedures per patient), similar to some,14,15 but not all,16 previous trials.

In patients with paroxysmal AF, elimination or amelioration of symptoms is a major driving force for therapy. A single self-limited recurrence of atrial arrhythmia following therapy may be an overly stringent criterion for failure. Assessment of total AF burden throughout follow-up by extended monitoring, while potentially the optimal end point, is technically impractical, costly, and poorly tolerated by most patients.23 In our study, catheter ablation therapy was associated with an early and sustained reduction in symptom frequency and severity, and a parallel early and sustained improvement in QOL scores. In contrast, these indices demonstrated little change over time in patients treated with ADT. The superiority of catheter ablation in this regard may be multiplier advantage.

Table 2. Quality of Life Assessment With Change From Baseline to 3 Months

<table>
<thead>
<tr>
<th>Scale</th>
<th>Catheter Ablation</th>
<th>Antiarrhythmic Drug Therapy</th>
<th>Mean Difference Between Groups (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 mental</td>
<td>90</td>
<td>8.5 (5.9 to 11.1)</td>
<td>39</td>
<td>1.6 (−1.1 to 4.3)</td>
</tr>
<tr>
<td>SF-36 physical</td>
<td>90</td>
<td>6.9 (5.2 to 8.6)</td>
<td>39</td>
<td>0.4 (−1.7 to 2.6)</td>
</tr>
<tr>
<td>Symptom frequency</td>
<td>82</td>
<td>−11.1 (−12.9 to −9.3)</td>
<td>29</td>
<td>0.7 (−2.4 to 3.9)</td>
</tr>
<tr>
<td>Symptom severity</td>
<td>65</td>
<td>−9.4 (−10.9 to −7.9)</td>
<td>23</td>
<td>0.0 (−3.3 to 3.4)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; SF-36, 36-item Short-Form Health Survey.
tificial, reflecting both the absence of adverse drug effects as well as improved rhythm control.

Catheter ablation was associated with a favorable safety profile in this study. Major adverse events have been reported in up to 6% of patients undergoing AF ablation, including thromboembolic events, atrioesophageal fistula, cardiac perforation, phrenic nerve palsy, and death. None of these more serious complications occurred in our study. Although use of open irrigated catheters has been reported to reduce the risk of thrombus formation at the electrode-tissue interface, it is unclear whether this factor alone was responsible for the absence of thromboembolic events in this study. Major adverse events or drug intolerance requiring early withdrawal of the assigned drug occurred in approximately 10% of study patients, which is comparable with other studies. Our study has several limitations. Although the trial encompassed a broad and diverse range of ablation practices, participating investigators had considerable experience in AF ablation. Outcomes at less experienced centers or with other ablation technologies or catheters may differ. A variety of additional ablation techniques were added to the PV isolation procedure. The impact of these techniques on outcome could not be determined based on study design. The effectiveness of ablation may decrease with longer follow-up, however, it is likely that similar decreases in efficacy, as well as an increase in toxicity, may occur with ADT over time. Our study did not address the long-term effect of either therapy on mortality, stroke risk, heart failure, or progression of paroxysmal AF to more persistent or permanent forms. A potential benefit for ablation with respect to these end points has been suggested in previous retrospective uncontrolled studies, but will be more definitively examined by upcoming large-scale clinical trials, such as Catheter Ablation vs Antiarrrhythmic Drug Therapy for Atrial Fibrillation (CABANA NCT00911508). In addition, study patients were relatively young with a lower incidence of cardiovascular comorbidity compared with the general population of patients with paroxysmal AF. Patients with significant left ventricular dysfunction, more persistent forms of AF, and advanced degrees of heart failure were excluded. The results of our study cannot be extrapolated to these latter populations.

Our multicenter randomized trial demonstrates the superiority of catheter ablation over ADT in the treatment of patients with paroxysmal AF who did not respond to 1 or more drugs. Catheter ablation provided significantly better rhythm control and improved QOL with a favorable safety profile. These findings argue for early use of catheter ablation therapy in patients with paroxysmal AF unresponsive to initial attempts with pharmacologic control.

Author Affiliations: Cardiovascular Institute, Department of Medicine, Loyola University Medical Center, Maywood, Illinois (Dr Wilber); Department of Medicine, Hospital San Raffaele, Milan, Italy (DrS Pappone and Augello); Department of Medicine, Na Homolce Hospital, Prague, Czech Republic (DrS Neuzil and Reddy); Department of Medicine, Hospital Sao Paulo/UNIFESP, Sao Paulo, Brazil (Dr De Paola); Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia (Dr Marchlinski); Department of Medicine, Cleveland Clinic Foundation, Cleveland, Ohio (Dr Natale); Department of Medicine, Montreal Heart Institute, Montreal, Quebec, Canada (Dr Macle); Department of Medicine, Ohio State University, Columbus (Dr Daoud); Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland (Dr Calkins); Department of Medicine, University of Rochester Medical Center, Rochester, New York (Dr Hall); Harvard Clinical Research Institute, Boston, Massachusetts (Dr Reynolds); Biosense Webster, Diamond Bar, California (Mr Vinekar and Ms Liu); Berry Consultants, College Station, Texas (Dr S. Berry); and University of Texas M.D. Anderson Cancer Center, Houston (Dr D. Berry).

Author Contributions: Dr Wilber 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. Study concept and design: Wilber, Pappone, Natale, Calkins, Vinekar, Liu, S. Berry, D. Berry. Acquisition of data: Wilber, Pappone, Neuzil, De Paola, Marchlinski, Macle, Daoud, Hall, Reddy, Augello, Reynolds. Analysis and interpretation of data: Wilber, Pappone, Marchlinski, Calkins, Augello, Reynolds, Vinekar, Liu, S. Berry, D. Berry. Drafting of the manuscript: Wilber, Natale, Hall, Vinekar, Liu.

Critical revision of the manuscript for intellectual content: Wilber, Pappone, Neuzil, De Paola, Marchlinski, Natale, Macle, Daoud, Calkins, Reddy, Augello, Reynolds, Liu, S. Berry, D. Berry. Statistical analysis: Marchlinski, Calkins, Reynolds, Liu, S. Berry, D. Berry. Administrative, technical, or material support: Wilber, Pappone, Neuzil, Marchlinski, Reddy, Augello, Vinekar. Study supervision: Wilber, Pappone, Marchlinski, Natale, Daoud. Financial Disclosures: Dr Wilber reported receiving grants from Biosense Webster, Boston Scientific, Medtronic, and St Jude Medical; consulting fees from Biosense Webster, Medtronic, and Sanofi-Aventis; honoraria from Biosense Webster, Boston Scientific, Medtronic, and St Jude Medical; and royalties from Blackfriars/Futura. Dr Pappone reported receiving grants and consulting fees from St Jude Medical and Johnson & Johnson, and honoraria from Biosense Webster. Dr Neuzil reported receiving grants from Biosense Webster, Cardiofocus, Cryocath Technologies, Hansen Medical, NIH BARI 2D, and St Jude Medical; consulting fees from Stereotaxis; and honorarium from Biosense Webster. Dr De Paola reported receiving a grant from Bristol-Myers Squibb. Dr Marchlinski reported receiving grants and honoraria from Biosense Webster, Boston Scientific, and St Jude Medical; consulting fees from Biosense Webster, Boston Scientific, GE Healthcare, Medtronic, and St Jude Medical; and speakers’ bureau fees from Biosense Webster. Dr Natale reported receiving grants from Biosense Webster and St Jude Medical, and speakers’ bureau fees from Biosense Webster, Boston Scientific, Medtronic, and St Jude Medical. Dr Macle reported consulting fees from Stereotaxis and honorarium from Biosense Webster. Dr Daoud reported receiving consulting fees from BARD and Biosense Webster, and honorarium from Biosense Webster. Dr Calkins reported receiving consulting fees from Ablation Frontiers, Attricure, BARD, Biosense Webster, Boston Scientific, CryoCor, CyberHeart, Medtronic, ProRhythm, Sanofi-Aventis, and TASER International; a grant; and honorarium from Biosense Webster; speakers’ bureau fees from Attricure, BARD, Biosense Webster, Boston Scientific, Medtronic, and Reliant; and fellowship fees from BARD, Boston Scientific, and Medtronic; Dr Hall reported consulting fees from Biosense Webster. Dr Reddy reported receiving grants from Attech, Boston Scientific, Biosense Webster, Cardiofocus, CryoCath Technologies, and Biosense Hansen Medical; J Medical; and honoraria from Boston Scientific, Biosense Webster, Medtronic, and St Jude Medical. Dr Augello reported receiving honoraria from BARD, Biosense Webster, and St Jude Medical. Dr Reynolds reported receiving consulting fees from Biosense Webster, Cardiome Pharma Corp, and Sanofi-Aventis. Mr Vinekar and Ms Liu are employees of Biosense Webster. Drs S. Berry and D. Berry reported receiving consulting fees from Biosense Webster, Veri- dex LLC, Boston Scientific, Endologics, R.R. Bard, W.L. Gore, Medtronic, Bristol-Myers Squibb, Pfizer, and Teva Pharmaceuticals.

Funding/Support: This study was funded by Biosense Webster, who provided the catheters used.

Role of the Sponsor: The sponsor designed the study protocol, in collaboration with the US Food and Drug Administration (FDA) and participating investigators. The study was intended to support market approval of the NavStar ThermoCool RF ablation catheter, which was manufactured by the sponsor. The sponsor had the overall responsibility for the conduct of the study, including assurance that the study met the regulatory requirements of the FDA. The sponsor’s general duties consisted of submitting the Investigational Device Exemption application to the FDA, obtaining FDA and institutional review board approvals before shipping the devices, approval of the investigators, ensuring proper clinical site monitoring, and ensuring patient informed consent was obtained. The sponsor was responsible for providing quality data that satisfied federal regulations and informing proper authorities of serious unanticipated adverse events and deviations from the protocol, and for training all participating investigators on the study device and protocol and monitoring the study for data integrity throughout the duration of the investigation. In addition, the sponsor was responsible for data collection and basic data analysis. The sponsor participated in additional data analy-
ANTIARRHYTHMIC DRUG THERAPY AND RADIOFREQUENCY CATHETER ABLATION

s, data interpretation, and the drafting of the manuscript in conjunction with the principal and other investigators, as well as the decision to submit the manuscript for publication.

Independent Statistical Analysis: All efficacy and primary safety results and conclusions presented in this manuscript have been confirmed by an independent statistical review and analysis performed by Joe Massaro, PhD (Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts) and Senior Biostatistical Consultant, Harvard Clinical Research Institute (HCRI), Boston, Massachusetts). Dr Massaro was provided the raw SAS data sets, analysis SAS data sets, the study protocol containing a statistician’s manual, a blank copy of the case report forms, and the original version of the manuscript by the authors/sponsor of the trial. Overall, Dr Massaro was in agreement with the statistical methods, findings, and conclusions presented in the final manuscript. Based on Dr Massaro’s analysis, the final manuscript also includes Bertrand L. Ramon, Maria C. Pajar, Helen C. Cropley, John Mays, David Lin, Andrea Russo, Gerilyn Schott, Ralph Verdin, Erica Zado; Cleveland Clinic Foundation, Cleveland, Ohio, for chairing the Clinical Events Committee; and Byron Allen, MD (Department of Cardiology, University of California, Irvine), for adjudicating all electrocardiographic data from the TTM transmitters. Dr Allen was compensated for his efforts by Biosense Webster. We also express our appreciation to the following affiliates from Biosense Webster, who were compensated for their efforts, in the design and execution of this study: Marciya Yaros, PhD, Brenda Aker, Robert Stagg, PhD, Kendra Lan Franco, Don Nguyen, Cheyi Lin, MS, and Brian Ramos, MS.

REFERENCES


