Radiofrequency Ablation vs Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation (RAAFT-2)  
A Randomized Trial

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**IMPORTANCE**  Atrial fibrillation (AF) is the most common rhythm disorder seen in clinical practice. Antiarrhythmic drugs are effective for reduction of recurrence in patients with symptomatic paroxysmal AF. Radiofrequency ablation is an accepted therapy in patients for whom antiarrhythmic drugs have failed; however, its role as a first-line therapy needs further investigation.

**OBJECTIVE**  To compare radiofrequency ablation with antiarrhythmic drugs (standard therapy) in treating patients with paroxysmal AF as a first-line therapy.

**DESIGN, SETTING, AND PATIENTS**  A randomized clinical trial involving 127 treatment-naive patients with paroxysmal AF were randomized at 16 centers in Europe and North America to receive either antiarrhythmic therapy or ablation. The first patient was enrolled July 27, 2006; the last patient, January 29, 2010. The last follow-up was February 16, 2012.

**INTERVENTIONS**  Sixty-one patients in the antiarrhythmic drug group and 66 in the radiofrequency ablation group were followed up for 24 months.

**MAIN OUTCOMES AND MEASURES**  The time to the first documented atrial tachyarrhythmia of more than 30 seconds (symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia), detected by either scheduled or unscheduled electrocardiogram, Holter, transtelephonic monitor, or rhythm strip, was the primary outcome. Secondary outcomes included symptomatic recurrences of atrial tachyarrhythmias and quality of life measures assessed by the EQ-5D tool.

**RESULTS**  Forty-four patients (72.1%) in the antiarrhythmic group and in 36 patients (54.5%) in the ablation group experienced the primary efficacy outcome (hazard ratio [HR], 0.56 [95% CI, 0.35-0.90]; P = .02). For the secondary outcomes, 59% in the drug group and 47% in the ablation group experienced the first recurrence of symptomatic AF, atrial flutter, atrial tachycardia (HR, 0.56 [95% CI, 0.33-0.95]; P = .03). No deaths or strokes were reported in either group; 4 cases of cardiac tamponade were reported in the ablation group. In the standard treatment group, 26 patients (43%) underwent ablation after 1 year. Quality of life was moderately impaired at baseline in both groups and improved at the 1 year follow-up. However, improvement was not significantly different among groups.

**CONCLUSIONS AND RELEVANCE**  Among patients with paroxysmal AF without previous antiarrhythmic drug treatment, radiofrequency ablation compared with antiarrhythmic drugs resulted in a lower rate of recurrent atrial tachyarrhythmias at 2 years. However, recurrence was frequent in both groups.

**TRIAL REGISTRATION**  clinicaltrials.gov Identifier: NCT00392054

Atrial fibrillation (AF) affects approximately 5 million people worldwide and is associated with an increased risk of stroke. The primary treatment of patients with paroxysmal AF is the relief of symptoms measured by reducing the frequency and recurrence of episodes. Atrial fibrillation considerably impairs quality of life, independently of the severity of the disease. Maintenance of sinus rhythm is usually the goal for patients with paroxysmal AF because it reportedly improves quality of life.

Antiarrhythmic drugs are recommended by practice guidelines as a first-line therapy in patients with symptomatic paroxysmal AF. However, efficacy varies among different agents. Multiple studies and meta-analyses suggest that preventing recurrence of AF at 6 to 12 months is only 46% effective, with a significant proportion of patients discontinuing therapy due to adverse events.

Radiofrequency catheter ablation for the treatment of AF is currently recommended by guidelines as a second-line therapy in patients with paroxysmal and persistent AF after treatment with at least 1 antiarrhythmic drug has failed and, under special circumstances, can be offered as first-line therapy. Small nonrandomized and randomized trials and meta-analyses comparing antiarrhythmic drugs with ablation in patients for whom at least 1 antiarrhythmic drug has failed have reported an approximate 60% efficacy with a single ablation procedure significantly delaying first-time recurrence of AF without using antiarrhythmic drugs. A pilot randomized trial comparing antiarrhythmic drugs with catheter ablation as a first-line therapy in patients with paroxysmal AF reported that catheter ablation was associated with a lower rate of AF recurrence than were antiarrhythmic drugs, supporting the indication of offering catheter ablation as first-line therapy. However, a recent randomized trial did not demonstrate its superiority as a first-line therapy in patients with a high burden of paroxysmal AF, in which the primary end points were the cumulative and per visit burden of AF. The purpose of the second Radiofrequency Ablation vs Antiarrhythmic Drugs for Atrial Fibrillation Treatment (RAAFT-2) Study was to determine whether ablation is superior to antiarrhythmic drugs as a first-line therapy in patients with paroxysmal AF who had not been exposed to antiarrhythmic treatment. The primary outcome was time to first recurrence of any atrial tachyarrhythmia lasting more than 30 seconds that was detected by either a 12-lead electrocardiogram (ECG), Holter, transtelephonic monitor, or rhythm strip.

Methods

Study Design

The RAAFT-2 study was a randomized multicenter trial sponsored and coordinated by the Population Health Research Institute at McMaster University. The trial was designed by the co-principal investigators (C.A.M, A.N.) and the steering committee. The study protocol was approved by the institutional review board or ethics committee of each recruiting center (8 in Canada, 3 in Germany, 2 in the Czech Republic, 2 in the United States, and 1 in Italy). Adverse events were reported annually to the ethics committee. All patients enrolled provided written informed consent.

Study Population

Eligible patients had a history of paroxysmal AF. Patients were enrolled if they were older than 18 and no older than 75 years; were symptomatic with recurrent paroxysmal AF lasting more than 30 seconds (≤4 episodes within the prior 6 months); experienced at least 1 episode that was documented by surface ECG, 6 months before randomization; and had no previous antiarrhythmic drug treatment. Patients were excluded if they had documented left ventricular ejection fraction of less than 40%; had left atrial diameter larger than 5.5 cm; had moderate to severe left ventricular hypertrophy (wall thickness >1.5 cm), valvular disease, coronary artery disease, or postcardiac surgery within 6 months; had undergone a left heart ablation procedure, either by surgery or by radiofrequency catheter ablation for AF; or had a complete contraindication for the use of heparin, warfarin, or both (eAppendix 1 in the Supplement).

Patients were randomly assigned 1:1 to either treatment. The randomization schedule was computer generated and stratified by site with variable block size. After randomization, patients entered a 90-day blanking period in which antiarrhythmic drugs were titrated or ablation was performed (mean time to ablation procedure, 39 days; interquartile range, [IQR], 29-47 days). The primary outcome events were recorded and included after the 90-day blanking period. All patients were followed up at 1, 3, 6, 12, and 24 months after randomization. Each patient received a transtelephonic monitor system and were instructed how to use it after the 90-day blanking period (PER900, Braemar Inc). Patients were required to record and transmit every time they experienced symptomatic episodes of possible AF. Throughout the follow-up period, patients were also instructed to transmit biweekly recordings on a Friday, regardless of whether they had experienced symptoms. Transtelephonic monitor adherence was defined as receiving at least 75% of all scheduled recordings during follow-up. All recordings were analyzed at a core laboratory and blindly reviewed by experienced electrophysiologists.

Before undergoing ablation and 3 months after the procedure, patients underwent computed tomographic or magnetic resonance imaging scans. Pulmonary vein stenosis was defined as a reduction in pulmonary vein diameter of at least 70% compared with the baseline measure.

Antiarrhythmic Drug Group

Patients randomized to the antiarrhythmic drug group were administered medications approved for treatment of AF by the regulatory bodies of each participating country. The selection of antiarrhythmic drugs was left to the discretion of the investigator, and dosages were based on guidelines (eAppendix 2 in the Supplement). Drug dosages titrated during the 90-day blanking period were maintained throughout the study. Patients in the antiarrhythmic drug group were allowed to crossover and to undergo ablation after 90 days if treatment had failed, which was defined as drug discontinuation due to intolerance, adverse events, or inefficacy (ie, recurrence of documented AF or any atrial tachyarrhythmias lasting >30 seconds).
Radiofrequency Catheter Ablation

All patients received oral anticoagulation targeting an international normalized ratio of 2.0 or higher for at least 3 weeks or received low-molecular-weight heparin for at least 1 week before ablation and transesophageal echocardiogram was performed prior to the procedure. Patients randomized to ablation underwent circumferential isolation of the pulmonary veins with confirmation of entrance block to each vein. Selection of ablation catheter, power and irrigation settings, and use of navigation systems were left to the discretion of the investigator. Additional ablation lesions including linear lesions in the left atrium, targeting of fractionated electrogram regions, ganglionic plexi, superior vena cava isolation, and cavotricuspid isthmus ablation were also allowed at investigator discretion.

Antiarrhythmic drugs and electrical cardioversion were allowed during the 90-day blanking period but were discontinued at the end of the blanking period. A second catheter ablation was allowed if AF recurred after the 90-day blanking period but was not included in the primary outcome analysis. Following catheter ablation, anticoagulation with warfarin was maintained for at least 3 months after ablation, targeting an international normalized ratio between 2 and 3. Continuation of anticoagulation was determined by current recommendations.6-9

Primary Efficacy Outcome

Time to first recurrence of symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia lasting more than 30 seconds documented by ECG or transtelephonic monitor was the primary efficacy outcome. Secondary outcomes included first documented recurrence of AF, atrial flutter, and atrial tachycardia episodes; repeated episodes of symptomatic or asymptomatic AF, atrial flutter, and atrial tachycardia episodes; and quality of life at the 1-year follow-up. Quality of life was measured by the EQ-5D, a generic health-related tool in which mobility, self-care, usual activities, pain or discomfort, and anxiety or depression are self-reported. A score of 0 or less is the worst score, and a score of 1 indicates excellent health.10,20 Additionally, the EQ-5D tool includes a visual analog scale by which patients mark their health state on a thermometer calibrated from 0 (worst imaginable) to 100 (best imaginable; eAppendix 3 in the Supplement). Serious predefined adverse events were recorded and reported for both groups (eAppendix 4 in the Supplement).

Statistical Analysis

The primary objective of the trial was to demonstrate the superiority of radiofrequency ablation over antiarrhythmic drug therapy. Cox regression analysis, stratified by clinical site, was performed and presented as hazard ratios (HRs) with 95% confidence intervals and a 2-sided P value ≤ .05 for the Wald test. Event rates were plotted over time using Kaplan-Meier method. Only events occurring after the 90-day treatment period were included in the final analysis. Patients who dropped out of the study or died due to a cardiac event within the 90-day blanking period were recorded as having had the primary event at the beginning of the follow-up period. Treatment groups were analyzed on an intention-to-treat basis.

All transtelephonic monitor recordings were centrally adjudicated as were clinical events. Only adjudicated events were included in the final analysis.

Secondary analyses, rates of AF, atrial flutter, and atrial tachycardia (episodes per month) were compared using a linear regression mixed model, with clinical site as a random effect. An Andersen-Gill Cox multiplicative hazards model for analyzing multiple occurrences as a counting process was used.21 All analyses were conducted using SAS version 9.2 for Unix (SAS Institute Inc).

Sample Size

Based on the pilot RAAF1 and on data available at the time of study design, the initial sample size calculation estimated that 400 patients, approximately 50% in the antiarrhythmic drug group and 27% in the ablation group would experience recurrent symptomatic AF. For an 80% power to reject the null hypothesis, 200 patients in each group were required for a 2-sided type I error rate of 0.017 after adjustment for planned interim analyses. During the conduct of the trial, several metanalyses indicated a potentially greater treatment-size effect of ablation so the sample size was recalculated to reflect the current treatment-size effect.10,15 The observed treatment effect of ablation compared with antiarrhythmic drugs had an odds ratio (OR) of 0.33 (95% CI, 0.21-0.51). Similarly, the Heart Rhythm Society consensus statement recommended including any atrial tachycardia recurrence (symptomatic or asymptomatic) as a primary outcome in clinical trials assessing the efficacy of ablation to treat AF.7 Given these data, a conservative estimate of the HR between the 2 groups was assumed to remain constant at 0.53. Based on an anticipated overall event rate within the trial of 65%, 80 primary outcome events were needed to achieve a 90% power to detect a 37% relative risk reduction in events in the ablation group and 80% power to detect a 33% reduction with a sample of 125 patients. This sample calculation estimated a more conservative treatment effect of ablation based on the more intense ECG or transtelephonic monitoring required in the RAAF1 trial and the inclusion of both symptomatic and asymptomatic recurrences as part of the primary outcome.22

Results

Study Population

From July 2006 to January 2010, 127 patients were enrolled at 16 centers with the last follow-up being February 2012. Sixty-six patients were randomized to undergo ablation and 61 to receive an antiarrhythmic drug. No significant differences among groups were noted in baseline characteristics (Table 1). Only 1 patient in each group did not receive the treatment assigned at the time of randomization (Figure 1).

Initial Treatment

Sixty-nine percent of the patients in the antiarrhythmic drug group received flecainide at a mean (SD) dose of 175.8 (50.9)
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Catheter Ablation, No. (%) (n = 66)</th>
<th>Antiarrhythmic Drug, No. (%) (n = 61)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>56.3 (9.3)</td>
<td>54.3 (11.7)</td>
<td>.30b</td>
</tr>
<tr>
<td>Men</td>
<td>51 (77.3)</td>
<td>45 (73.8)</td>
<td>.65</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>65 (98.5)</td>
<td>59 (96.7)</td>
<td>.61c</td>
</tr>
<tr>
<td>No. of AF episodes past 6 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>47.4 (97.9)</td>
<td>33 (48.7)</td>
<td>.79d</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>10.0 (5.0-40.0)</td>
<td>10.0 (4.0-40.0)</td>
<td></td>
</tr>
<tr>
<td>Episodes in the past 6 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-11</td>
<td>28 (42.4)</td>
<td>27 (44.3)</td>
<td>.83</td>
</tr>
<tr>
<td>12 to 89</td>
<td>20 (30.3)</td>
<td>19 (31.1)</td>
<td>.92</td>
</tr>
<tr>
<td>Previous electrical cardioversion</td>
<td>22 (33.3)</td>
<td>32 (52.5)</td>
<td>.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (42.4)</td>
<td>25 (41.0)</td>
<td>.87</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (1.5)</td>
<td>4 (6.6)</td>
<td>.14</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>3 (4.6)</td>
<td>4 (6.6)</td>
<td>.71c</td>
</tr>
<tr>
<td>MI/CAD</td>
<td>6 (9.1)</td>
<td>2 (3.3)</td>
<td>.28c</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>2 (3.0)</td>
<td>1 (1.6)</td>
<td>&gt;.99e</td>
</tr>
<tr>
<td>CHADS2,a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.5 (0.7)</td>
<td>0.7 (0.8)</td>
<td>.48d</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.0 (0.0-1.0)</td>
<td>0.0 (0.0-1.0)</td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction, mean (SD), %</td>
<td>61.4 (4.6)</td>
<td>60.8 (7.0)</td>
<td>.65b</td>
</tr>
<tr>
<td>LA size, mean (SD), cm</td>
<td>4.0 (0.5)</td>
<td>4.3 (0.5)</td>
<td>.09c</td>
</tr>
<tr>
<td>Oral anticoagulation</td>
<td>35 (53.0)</td>
<td>19 (31.1)</td>
<td>.01</td>
</tr>
<tr>
<td>Aspirin</td>
<td>38 (57.6)</td>
<td>29 (47.5)</td>
<td>.26</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>40 (60.6)</td>
<td>36 (59)</td>
<td>.86</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>14 (21.2)</td>
<td>13 (21.3)</td>
<td>.99</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; CHADS2, congestive heart failure, hypertension, age greater than 75, diabetes, and history of stroke; IQR, interquartile range; LA, left atrium; LV, left ventricle; MI, myocardial infarction; TIA, transient ischemic attack.

a All P values are derived from the χ² test unless otherwise specified.
b P values calculated from using analysis of variance.
c P values calculated from the Fisher exact test.
d P values calculated from using Wilcoxon2-sample test.
e The CHADS2 score is a measure of the risk of stroke in patients with atrial fibrillation, with scores ranging from 0 to 6 and higher scores indicating a greater risk. Congestive heart failure, hypertension, an age of 75 y or older, and diabetes mellitus are each assigned 1 point, and previous stroke or TIA is assigned 2 points; the score is calculated by summing all the points for a given patient.

Radiofrequency Ablation Group

Of the 66 patients in the ablation group, only 1 did not undergo the procedure. Complete pulmonary vein isolation was confirmed by entrance block in 87% of the patients. The mean (SD) procedure time was 3.5 (1.2) hours with a fluoroscopy time of 70 (60) minutes. Nonfluoroscopic mapping systems were used in 86% of patients. Additional radiofrequency lesions in-

mg/d; 25%, propafenone, at a dose of 487.7 (122.4) mg/d; and 16.4% tried more than 1 type of drug during the 90-day blanking period (eTable 1 in the Supplement). Three patients (4.9%) in the antiarrhythmic drug group underwent ablation during the blanking period. Another 26 patients (42%) who had AF breakthroughs underwent ablation after a mean (SD) of 362 (199) days (Figure 1).
included complex atrial electrograms in 17%; roof line in 21.3%, and a cavotricuspid isthmus line in 18.7% of patients. Only 1 patient underwent a second ablation during the blanking period. Nine patients (13.6%) underwent repeat ablation during follow-up. The mean (SD) time to the second ablation was 345 (211) days. Only 6 patients (9.09%) received antiarrhythmic drug treatment during the follow-up.

### Transtelephonic Monitor Adherence

Overall, 6632 transtelephonic monitor recordings were received with only 9% deemed uninterpretable. Overall, 83% of the patients had monitored transmissions of the symptomatic and biweekly recordings during the follow-up period: 79% in the drug group vs 86% in the ablation group (χ², P = .25).

### Primary Efficacy Outcome

Recurrence of any atrial tachyarrhythmia lasting longer than 30 seconds occurred in 44 patients (72.1%) in the antiarrhythmic drug group compared with 36 patients (54.5%) in the ablation group (HR, 0.56; 95% CI, 0.35-0.90; P = .02; Figure 2A).

Asymptomatic AF was observed in 11 patients (18%) in the antiarrhythmic drug group compared with 6 patients (9%) in the ablation group.

### Secondary Efficacy Outcomes

A secondary outcome of only symptomatic recurrence of AF, atrial flutter, and atrial tachycardia occurred in 36 patients (59%) in the antiarrhythmic drug group compared with 31 patients (47%) in the ablation group (HR, 0.56; 95% CI, 0.33-0.95; P = .03; Table 2). Recurrence of symptomatic AF (excluding atrial flutter and other atrial tachyarrhythmias) occurred in 35 patients (57.4%) in the antiarrhythmic drug group compared with 27 patients (40.9%) in the ablation group (HR, 0.52; 95% CI, 0.30-0.89; P = .02; eFigure 1 in the Supplement).

In an analysis that included multiple recurrences of symptomatic or asymptomatic atrial tachyarrhythmia lasting longer than 30 seconds using a recurrence-event model showed an advantage to ablation (HR, 0.33; 95% CI, 0.28-0.40; P < .001; Table 2; eFigure 1 in the Supplement).

The frequency of asymptomatic and symptomatic AF, atrial flutter, and atrial tachycardia documented by transtelephonic monitor, 12-lead ECG, Holter, or rhythm strips was analyzed using a linear-mixed model. Overall, this outcome was reached in 70.5% patients in the antiarrhythmic drug group compared with 53% patients in the ablation group (P = .03; fixed-effect estimate, −5.09; P = .003).

### Table 2. Secondary Outcomes

<table>
<thead>
<tr>
<th>No. (%) of Patients</th>
<th>Radiofrequency Ablation</th>
<th>Antiarrhythmic Drugs</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First recurrence of symptomatic AF, atrial flutter, and atrial tachycardia</td>
<td>31 (47)</td>
<td>36 (59)</td>
<td>0.56 (0.33-0.95)</td>
<td>.03</td>
</tr>
<tr>
<td>First recurrence of symptomatic AF</td>
<td>27 (41)</td>
<td>35 (57)</td>
<td>0.52 (0.3-0.89)</td>
<td>.02</td>
</tr>
<tr>
<td>First recurrence of symptomatic AF, atrial flutter, and atrial tachycardia excluding transtelephonic monitor*</td>
<td>16 (24)</td>
<td>19 (31)</td>
<td>0.86 (0.42-1.72)</td>
<td>.66</td>
</tr>
<tr>
<td>Total No. of AF, atrial flutter, or atrial tachycardia (recurrent episodes model; count &gt; = 1)</td>
<td>213 (6.6)</td>
<td>502 (14.7)</td>
<td>0.33 (0.28-0.4)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; HR, hazard ratio.

* eFigure 2 in the Supplement.
Radiofrequency Ablation vs Antiarrhythmic Drugs

Original Investigation Research

approximately 60%.10-15 These randomized trials have been favor of catheter ablation with an overall relative reduction of drug treatment had failed show a marked treatment effect in involving patients with AF for whom at least 1 antiarrhythmic

duration of repeated episodes, potentially having an effect on AF progression.

Table 3. Quality of Life

<table>
<thead>
<tr>
<th></th>
<th>Radiofrequency Ablation (n=66)</th>
<th>Antiarrhythmic Drugs (n=61)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ5D Tariff score*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>Median (IQR)</td>
<td>0.86 (0.82-1)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>Median (IQR)</td>
<td>1 (0.84-1)</td>
<td>.25</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Anxiety depression, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>31.8b</td>
<td>26.2</td>
<td>.70</td>
</tr>
<tr>
<td>12 mo</td>
<td>13.6</td>
<td>23</td>
<td>.25</td>
</tr>
<tr>
<td>Visual analog score, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>75 (70-83)</td>
<td>80 (70-85)</td>
<td>.53*</td>
</tr>
<tr>
<td>12 mo</td>
<td>85 (85-90)</td>
<td>80 (75-90)</td>
<td>.26*</td>
</tr>
</tbody>
</table>

* When comparing the change in the EQSD Tariff score from baseline to 12 months in the ablation group, P = .03 and in the antiarrhythmic drug group P = .22 (1 is the highest possible and 0 is the worst possible quality-of-life score). When comparing the change in the EQSD visual analog score from baseline to 12 months in the ablation group, P = .002 and in the antiarrhythmic drug group P = .02 (0 is the worst imaginable and 100 is the best imaginable health state for the visual analog score).

bSigned rank test.

Quality of Life at 1-Year Follow-up
Quality of life assessed by an EQSD score was moderately decreased compared with age-matched patients without AF at baseline in both groups (Table 3). The median EQ-5D Tariff score at baseline was 0.86 (IQR, 0.82-1) in the ablation group compared with 0.84 (IQR, 0.83-1) in the antiarrhythmic drug group (P > .99). The EQ-5D Tariff score at 12 months increased to the range of normal in the ablation group (median, 1; IQR, 0.84-1) and in the antiarrhythmic drug group (median, 1; IQR, 0.83-1; P = .25). However, the EQ-5D Tariff score change from baseline to 12 months significantly improved in the ablation group (P = .03) compared with the antiarrhythmic drug group (P = .22). The visual analog scale change from baseline to 12 months was significantly improved in both groups: P = .002 for the ablation group and P = .02 for the antiarrhythmic drug group (Table 3).

Adverse Events
There were no deaths or strokes in either group. Overall, the ablation group had a 9% rate of serious adverse events, the most frequent of which was pericardial effusion with tamponade experienced by 4 patients (6.0%). Serious adverse events are summarized in Table 2 (eTable 2 in the Supplement).

Discussion
Our multicenter, randomized clinical trial demonstrated that among patients with paroxysmal AF without previous antiarrhythmic drug treatment, radiofrequency ablation resulted in a significantly lower rate of recurrent atrial tachyarrhythmias at 2 years. Ablation also significantly reduced the frequency of repeated episodes of AF. However, recurrence of AF was documented in almost half of the patients after 2 years. Quality of life was improved in both groups.

Several recent randomized trials and meta-analyses involving patients with AF for whom at least 1 antiarrhythmic drug treatment had failed show a marked treatment effect in favor of catheter ablation with an overall relative reduction of approximately 60%.10-15 These randomized trials have been primarily single-center studies with only 12 months of follow-up. Furthermore, detection of AF during follow-up ranged widely with some studies solely relying on Holter monitor or 12-lead ECG recordings obtained during scheduled follow-up visits. The recently published Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) trial17 randomized 294 patients to either catheter ablation or antiarrhythmic drugs as first-line therapy. This trial did not demonstrate any significant difference in the primary study outcome that was the burden of AF defined as the percentage of time in AF on each Holter recording and the cumulative burden of AF (percentage of time in AF on all Holter recordings obtained during follow-up). However, the secondary outcomes that included freedom from any AF were significantly reduced in the ablation group. This finding is in keeping with our results of a significant but modest reduction in time to first recurrence of AF in patients who have not been previously exposed to antiarrhythmic drugs.

The RAAFT-2 trial required biweekly scheduled transtelephonic monitor recordings and symptomatic recordings throughout the 24-month follow-up period. Interestingly, when transtelephonic monitor recordings were excluded and only 12-lead ECG, Holter, or rhythm strip recordings were analyzed, no significant difference between the 2 treatment strategies were found (Table 2). This finding highlights the importance of strict documentation of both symptomatic and asymptomatic AF recurrences with rigorous monitoring in the context of clinical trials evaluating therapeutic strategies in AF and supports the Heart Rhythm Society consensus recommendations.7

In the current study, freedom from symptomatic AF was 68% at the 2-year follow-up with 14% requiring a second procedure. These findings highlight the fact that although ablation is effective, there are still approximately 50% of patients who have AF recurrences 24 months after undergoing a single procedure. Ablation extends the time free of both symptomatic and asymptomatic AF and significantly reduced the recurrence of repeated episodes, potentially having an effect on AF progression.
Quality of life has been reported in some clinical trials comparing antiarrhythmic drugs to ablation with overall improvement in both strategies with greater improvement from baseline to 12 and 24 months in patients undergoing ablation.13-23 The EQ-5D score was moderately impaired at baseline and similarly improved at 12 months in both groups. The improvement from baseline to 1 year was significantly better in the ablation group; however, there was no significant difference among treatment groups. Our inability to demonstrate a difference in quality of life may be related to several factors, including the overall modest baseline impairment in quality of life, the inclusion of patients who were antiarrhythmic drug naive, and the poor specificity of the tools used to assess quality of life in this context.24 Safety of radiofrequency catheter ablation has been extensively reported by single-center observational studies, small-randomized clinical trials, and international surveys,25,26 with major adverse events including death reported in 6% of patients. All centers participating in the RAAFT-2 trial were highly experienced (>200 AF ablation procedures per year). No deaths or strokes were reported in the current study and the most frequent complication in the ablation group was cardiac tamponade (6.0%). This finding is higher than previously reported and highlights the fact that ablation carries considerable risks that need to be discussed with the patient when offering it as a therapeutic alternative to patients who have not yet taken antiarrhythmic drugs.

This study has several limitations. The findings are limited to younger patients with paroxysmal AF with little or no evidence of structural heart disease in addition to their not having taken antiarrhythmic drugs. The study sample was small and the treatment effect, although significant, may be clinically modest, and the risks of ablation were not negligible. Despite a strict transtelephonic ablation vs antiarrhythmic drugs treatment strategy individually recommended.

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Author Contributions: Dr Morillo had full access to all of the data and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Morillo, Verma, Connolly, Kuck, Nair, Champagne, Sterns, Natale. Acquisition of data: Morillo, Verma, Kuck, Nair, Champagne, Sterns, Natale. Analysis and Interpretation of Data: Morillo, Connolly, Healey, Beresh, Natale. Drafting of the manuscript: Morillo, Verma, Connolly, Healey, Natale. Critical revision of the manuscript for important intellectual content: Morillo, Verma, Connolly, Kuck, Nair, Champagne, Sterns, Beresh, Healey. Statistical Analysis: Morillo, Verma, Connolly, Natale. Administrative, technical, or material support: Morillo, Connolly, Beresh. Study Supervision: Morillo, Connolly, Beresh, Natale.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Morillo reported receiving grants from Biosense Webster, Boston Scientific, Medtronic, St Jude Medical and consulting fees from Biosense Webster, Boston Scientific, Biotronik, Boehringer Ingelheim, Merck. Dr Verma reported receiving grants and consulting fees from St Jude Medical, Medtronic, and Boehringer Ingelheim. Dr Kuck reported receiving grants and consulting fees from Biosense Webster and St Jude Medical. Dr Healey reported receiving grants and consulting fees from St Jude Medical and Boston Scientific and consulting fees from St Jude Medical, Medtronic, and Boehringer Ingelheim. Dr Natale reported receiving grants and consulting fees from Biosense Webster and St Jude Medical. Drs Connolly, Nair, Champagne, and Sterns reported no disclosures.

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Role of the Sponsors: The study was designed by the sponsor (PHRI) and coprincipal investigators (Drs Morillo and Natale) in addition with the steering committee (Drs Verma, Connolly, Kuck, Nair, Sterns, Healey, Wilber, MD, Cardiovascular Institute, Department of Medicine, Loyola University Medical Center, and Callans, MD, Hospital of the University of Pennsylvania, Philadelphia). Biosense Webster had no role in the design or analysis of the data. The PHRI under the leadership of the principal investigator Dr Morillo had the overall responsibility for the conduct of the study, including assurance that the study met the regulatory requirements of the US Food and Drug Administration (FDA) and EUDRA-CT. The sponsor’s general duties consisted of submitting the Investigational Device Exemption application to the FDA, obtaining FDA and institutional review board approvals, approvals of the investigators, ensuring proper clinical site monitoring and ensuring patient informed consent was obtained. The Population Health Research Institute was responsible for providing quality data that satisfied federal and national regulations and informing proper authorities of serious unanticipated adverse events and deviations from the protocol and for monitoring all participating investigators on the data protocol and monitoring the study for data integrity throughout the duration of the investigation. In addition, the PHRI was responsible for data collection and all data analysis, interpretation and drafting of the manuscript in conjunction with the principal investigators and steering committee members, as well as the decision to submit the manuscript for publication.

Conclusions
Among patients with paroxysmal AF without previous antiarrhythmic drug treatment, ablation compared with antiarrhythmic drugs resulted in a lower rate of recurrent atrial tachyarrhythmias at 2 years. However, recurrence was documented in approximately 50% of patients. Quality of life was improved overall by both treatments but not significantly different between groups. When offering ablation as a therapeutic option to patients with paroxysmal AF naive to antiarrhythmic drugs, the risks and benefits need to be discussed and treatment strategy individually recommended.
Radiofrequency Ablation vs Antiarrhythmic Drugs

Statistical Analysis: All efficacy and primary safety results and conclusions presented in this manuscript were independently reviewed by the PHRI Senior Biostatistician and Director of the Biostatistics Division, Janice Pogue, PhD. All analyses were conducted by Purnima RaoMelacini, Biostatistician at PHRI. All analyses were reviewed and interpreted in conjunction by Drs Morillo, Connolly, Natale, and Pogue.

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REFERENCES


