Radiofrequency Catheter Ablation and Antiarrhythmic Drug Therapy
A Prospective, Randomized, 4-Year Follow-Up Trial: The APAF Study

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Background—Information on comparative outcome between radiofrequency catheter ablation (RFA) and antiarrhythmic drugs (AADs) >1 year after randomization is important for clinical decision-making.

Methods and Results—A total of 198 patients (age, 56±10 years) with paroxysmal atrial fibrillation were randomly assigned to RFA (99 patients) or to AADs (99 patients). We evaluated efficacy of RFA or AADs in a comparable 48-month follow-up period according to intention-to-treat analysis. Cardiac rhythm was assessed with daily transtelephonic transmissions. Quality of life was also analyzed. At 4 years, among the 99 patients first assigned to RFA, the procedure was repeated because of recurrent atrial fibrillation/atrial tachycardia in 27 patients (27.3%). Among the 99 patients randomly assigned to AADs, 87 (87.9%) crossed over to undergo RFA and 4 years after random assignment only 12 (12.1%) were in sinus rhythm with AAD alone without ablation. Despite the high level of crossovers, at 4 years the intention-to-treat analysis showed that 72.7% of patients in the ablation arm and 56.5% of those initially randomly assigned to AADs were free of recurrent atrial fibrillation/atrial tachycardia (P=0.017). During the follow-up, 19.2% of AAD patients progressed to persistent atrial fibrillation before switching to RFA. RFA significantly improved quality of life (P<0.001), whereas before crossing over to RFA, patients receiving AADs showed poorer quality of life. Except for new left atrial tachycardia, there were no serious complications caused by RFA.

Conclusions—With follow-up extended to 4 years after randomly assigned, ablation remains superior to antiarrhythmic drug in these patients with paroxysmal atrial fibrillation.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00340314.

Key Words: atrial fibrillation • catheter ablation • antiarrhythmic drugs • quality of life

Atrial fibrillation (AF) represents an important public health problem with increased long-term risks and complications that impair quality of life (QoL). Many patients with symptomatic paroxysmal AF are treated either with chronic antiarrhythmic drug (AAD) therapy or with radiofrequency catheter ablation (RFA). RFA as class I with level of evidence A is now recommended for patients with symptomatic paroxysmal AF and normal or mildly dilated left atrium (LA) and normal or mildly reduced left ventricular ejection fraction (LVEF), but long-term data on outcomes to substantiate such recommendation are very limited. Paroxysmal AF naturally progresses toward persistent AF at an estimated rate of 15–30% over a 1- to 3-year period, but the role of RFA or chronic AADs in affecting such progression and associated complications is still unknown. Recent long-term observational studies have reported that pulmonary vein (PV) isolation, as performed many years ago between 2001 and 2003, with repeat interventions as necessary, is associated with an acceptable long-term relief from symptomatic recurrences up to 5 years after RFA. It is reasonable, however, that a more appropriate patient selection as well as modifications in ablation technologies and procedure strategies over time could further improve the long-term outcome of RFA, potentially limiting the number of repeat procedures. Although studies of RFA for treatment of AF report higher efficacy rates than do studies of AAD therapy and a lower rate of complications, 2 systematic literature reviews and meta-analyses of these studies concluded that the relative safety and efficacy of these 2 therapeutic approaches in the long-term is still limited to short follow-up data. Currently, available evidence by randomized studies supports the 1-year superiority of RFA over conventional AADs to prevent...
recurrent AF, which is a rather short follow-up period considering the nature of the disease, its progression, and associated complications. This study represents the extension phase of a previously reported randomized study among selected patients with paroxysmal AF that assessed the comparative effectiveness of RFA and AADs at 1 year, but now reports data on outcomes at 4 years of follow-up.

Methods

The APAF study was a 4-year, randomized trial comparing RFA (99 patients) and oral AADs therapy (ie, monotherapy or combinations of 3 drugs (flecainide, sotalol, and amiodarone) never administered before enrollment, 99 patients). Oral flecainide was given at an initial dosage of 100 mg every 12 hours, sotalol at an initial dose of 80 mg every 8 hours, and amiodarone at an initial loading of 600 mg/d for the first week, 400 mg/d for the next week, after which a daily maintenance dose of 200 mg a day was given. The maximum tolerable dosage (300 mg/d for flecainide, 320 mg/d for sotalol) was based on the clinical response and/or the occurrence of side effects. Doses were reduced if intolerable adverse reactions occurred, and treatment was stopped if they persisted. The protocols for AADs dose escalation or combinations have been reported previously in detail, and the 1-year results were published in 2006. The first patient was enrolled in January 2005 and the last one on May 11, 2005. Inclusion criteria were age >18 or <70 years, AF history >6 months, and AF burden >2 episodes per month in the last 6 months as assessed by daily transtelephonic monitoring. Persistent AF, LA diameter >65 mm, LVEF <35%, heart failure symptoms, and New York Heart Association functional class II were considered as exclusion criteria. Residents outside of Italy were also excluded. The patient characteristics and catheter ablation procedure have been reported previously in detail. Briefly, using 3D-electroanatomic mapping systems, left- and right-sided PVs were isolated by creating large circumferential lesions up to 2 cm from the PV ostia, excluding 20–30% of the left atrium. To prevent postablation LA tachycardias, an ablation line was applied to the mitral isthmus (between the mitral annulus and left inferior PV) and between contralateral superior veins. The end point was PV isolation by voltage abatement around and within ablated areas. The completeness of the lines was assessed with voltage and activation maps within the circles. Cavotricuspid isthmus block to prevent isthmus-dependent atrial flutter was also performed. If AF did not terminate during RFA, transdiaphragmatic cardioversion was performed at the end of the procedure. After RFA, patients were admitted to an inpatient telemetry bed for 24 hours. Heparin was administered intravenously for 24 hours. Heparin was started 3 hours after the sheath removal at 1000 U/h without a bolus. Low-molecular-weight heparin, 0.5 mg/kg SQ bid, was administered for 4 days after the discharge. Warfarin was started immediately after the procedure. All patients were maintained on the assigned antiarrhythmic agent for 6 weeks after the ablation procedure, and recurrences within this period were not considered as a failure (blanking period). If there was a recurrence of AF beyond the first 6 weeks after the ablation or there was left or right atrial tachycardia, then a redo procedure was performed if the patient wished to proceed. Among the redo ablation, the same catheters and ablation strategy to eliminate conduction gaps as in the initial procedure were used. In patients who progressed to persistent AF in addition to ablation of standard targets, RFA was extended to the entire LA posterior wall down to the coronary sinus and within coronary sinus. Any recurrence after the index procedure of an incessant atrial tachycardia (AT) was mapped and ablated using conventional 3D electroanatomic mapping systems. As in patients first assigned to RFA, in crossover patients who were first assigned to AAD therapy, a same blanking period was considered after ablation and any AF/AT recurrence during this period was ignored. The institutional review board approved the 4-year follow-up study protocol, and written informed consent was obtained for this long-term follow-up study. The study design and flow are presented in Figure 1.

Data Collection and Follow-Up

An independent safety committee monitored the study. Intensive follow-up visits for the initial phase of the trial were scheduled 3, 6, and 12 months after random assignment. After the initial year of close follow-up, patients were followed for 3 years quarterly and whenever they felt the need to seek medical attention. At each visit, 12-lead ECG, 48-hour Holter monitoring, and transthoracic echocardiography were scheduled. Patients were provided with TT 12-lead ECG (Life Watch, Buffalo Grove, IL). After the first year, patients were asked to record their rhythm twice a week and whenever they had symptoms suggestive of AF. All 1-minute rhythm tracings were interpreted in a blinded fashion by 2 physicians who did not otherwise participate in the study. An arrhythmia had to last more than 30 seconds to be classified as AF or AT. QoL was measured by using the Medical Outcomes Study 36-item short-form health survey (SF-36) attached to the case record form to assess the impact of each treatment on the QoL. Patients answered SF-36 at baseline and at 4 years after random assignment or just before crossover. Anticoagulation was stopped in patients with CHADS2 score 0. In patients with no recurrence for more than 6 months without any episode of symptomatic or asymptomatic AF and CHADS2 score = 1, warfarin
was replaced by aspirin at 6 months after ablation. In the case of failure of the first assigned drug at the maximum tolerable dosage, the choice of a second AAD regimen was left to the primary physician, to be chosen from the other 2 antiarrhythmic agents in different classes or a combination of 2 of the 3 agents used in this study; the minimum period after which the second AADs trial was considered unsuccessful was set at 30 days. Crossover from AAD therapy to RFA was permitted only after intolerance, serious side effects, or failure of AADs in different classes and/or combination or after sustained recurrences (>12 hours).

End Points
The primary end point of the study was freedom from AF and AT, irrespective of crossover 4 years after random assignment in an intention-to-treat basis. Repeated ablation procedures with or without AADs were considered as failure. Complications, adverse effects, arrhythmia progression, and changes in QoL were also evaluated.

Definitions
Paroxysmal AF was defined as recurrent AF that was self-terminating with episode durations of <7 days. Persistent AF was defined as AF that was not self-terminating with episode durations of >7 days. Subclinical thyrotoxicosis was defined as suppressed thyroid-stimulating hormone levels (below lower reference value) without elevated levels of free thyroxine (FT4) and/or triiodothyronine (PT3), and newly manifesting while the patient was taking amiodarone.

Statistical Methods
For the randomized cohort, we determined that a sample size of a minimum of 85 patients was required in each group at a power of 90% to reach a 2-tailed α of 0.05. Considering the possibility of dropouts, we planned to increase the number of patients by 15% for each. For the new follow-up study, we did not increase the sample size of the initial cohort because we hypothesized that recurrences would be greater during a much longer follow-up, particularly in the AADs arm. Follow-up data were analyzed using the intention-to-treat method, and all times are from enrollment. Continuous data are expressed as mean and standard deviation and compared by the independent-samples t test and paired-samples t test. Categorical variables were analyzed by Pearson χ² test or Fisher exact test. Observed event-free survival curves for both groups, presented as Kaplan-Meier plots, were compared among them by 2-sample log-rank test. All tests of significance were 2-sided. A probability value less than 0.05 indicated statistical significance. The PASW (Predictive Analytics Software) Statistics for Windows (Release 18.0.0, July 30, 2009; SPSS Inc, Chicago, IL) was used for statistical analysis.

Results
The mean age of enrolled patients was 55±10 years for RFA patients and 57±10 years for AADs patients.⁸ Although many patients had a history of hypertension, few had significant structural heart disease. Only a minority of patients had diabetes mellitus, coronary artery disease, or valvular heart disease.⁸

Follow-Up and Long-Term Outcome
All patients were followed for 3 years at each of the prespecified time points and 95% for 4 years. The completeness of follow-up was 99.6% for RFA group and 99.5% for AADs group. A total of 935±102 TT strips of 1-minute duration per patient was analyzed. Four years after random assignment, 12-lead ECG strips were performed twice weekly in 69% of patients, whereas in 45% of those who became asymptomatic, 12-lead ECG strips were performed just once a week in the last 2 years. The mean clinic visits per patient over the 4-year period were 3.3±0.7. Recurrences in the majority of AAD patients were highly symptomatic and were characterized by prolonged (>12 hours) and frequent episodes of paroxysmal AF, and no patient had recurrences lasting <1 hour. In the AAD group, AADs, alone or in combination, were frequently discontinued because of lack of efficacy or less frequently because of adverse reactions. Episodes of AF recurrence were silent in 2 patients assigned to RFA and in 33 patients assigned to AAD therapy. Throughout the 4-year follow-up period, new-onset heart failure, hypertension, newly diagnosed or worsening coronary artery disease did not develop in any patient. Two patients with hypertension (50- and 54-year-old men) after random assignment developed newly diagnosed type 2 diabetes mellitus with poor glycemic control.

Primary End Point
According to the intention-to-treat analysis, 72 of 99 patients (72.7%) in the group that underwent RFA after a single procedure and 56 of 99 patients (56.5%) in the AAD group (44 after crossover to a single RFA procedure off AADs and 12 after AADs alone) reached the primary end point (P=0.017). However, excluding crossovers in the group randomly assigned to AADs, only 12 of 99 (12.1%) patients of the AAD group (Figure 2; P<0.001 by log-rank test) were AF/AT-free at the end of the study, as documented by daily TT and Holter monitoring. After redo procedures in 27 patients in the RFA arm (median 2 procedures per patient), freedom from AT/AF at 4 years was 90.9% (Figure 1).

Crossover to RFA
In the AADs group, 87 patients (87.9%) with recurrent paroxysmal AF (68 patients) or persistent AF (19 patients) crossed over to undergo RFA. The mean time to crossover was 10.1±7.2 months (min-max, 4–31), with a steeper rate of crossover early in follow-up, which then exhibited a stable pattern throughout the remainder of follow-up (Figure 3). The characteristics of crossover patients are shown in Table 1. After crossover, sinus rhythm was maintained in 62 of these 87 patients (71.3%) at 48 months of follow-up (44 patients after RFA off drugs and 18 after RFA and previously ineffective AADs). At the end of the study, only 12 of the 99 patients in the AADs group who did not cross over were free of recurrent AF (12.1%, P<0.001 for the comparison with the group that underwent catheter ablation). Overall, recurrent AF/AT was still present in 19 patients (19.2%) in the group initially randomly assigned to AADs (Figure 1). The reasons for crossover were symptomatic and sustained episodes of arrhythmia recurrences frequently caused by AADs failure, which required several hospitalizations. Of note, 5 patients who had amiodarone-induced subclinical thyrotoxicosis continued to have recurrent episodes of AF after crossover to ablation, but, in all cases, recurrences were associated with abnormally low thyroid-stimulating hormone levels and normal FT3 and FT4 values up to 4 months despite amiodarone withdrawal.

LA Tachycardia
During a median follow-up of 18.5 months (6–26) among a total of 186 patients who underwent RFA, new left AT developed in 9 patients who also had AF recurrence (3 patients after crossover
and repeat RFA). AT was incessant in 7 of them, requiring activation mapping with conventional 3D mapping system and ablation, which was successfully performed with a stable sinus rhythm up to the end of follow-up. A centrifugal activation pattern was found in 3 patients, suggesting a focal AT, whereas a macroreentrant AT was documented in 3 other patients with residual gaps along multiple LA sites in 1 patient. Two patients, a 55-year-old man, first assigned to RFA, and a 62-year-old man, first assigned to AADs, had rare and brief (shorter than 1 minute) episodes of self-terminating AT that were successfully treated by AADs.

**AF Progression**

Among AADs patients, 19 patients (mean age, 63.6±9.2 years, 12 males) progressed to persistent AF before crossover and repeat RFA. Progression was silent in 8 patients, whereas in the remaining 11 patients the arrhythmia exhibited a mixed pattern (both symptomatic and asymptomatic). There were single or multiple comorbidities including diabetes mellitus (4 patients), arterial hypertension (16 patients), valvular heart disease (1 patient), and coronary artery disease (1 patient). Among RFA patients, persistent AF developed just in a 59-year-old man with previous myocardial infarction, hypertension, diabetes mellitus, and LA enlargement (59 mm), which at the time of progression further increased to 65 mm. Patients with progression compared with those who did not progress had comparable baseline LA dimensions (41±4.7 versus 39±6.2; \( P=0.144 \)) that became larger at the time of progression (44.6±5.5 versus 39.6±6.12; \( P<0.001 \)).

### Complications and Other Events

In the group that underwent RFA including redo procedures after the index ablation or crossover, there were no serious complications except atrial tachycardias. Three femoral hematomas, 1 transient transient ischemic attack shortly after the procedure, and 1 pericardial effusion not requiring pericardectomy developed in patients who underwent RFA, all of which were treated conventionally with no long-term sequelae. No procedure-related late complications were observed.

In the group assigned to AADs, 68 patients discontinued taking AADs because of lack of efficacy or adverse events. Many patients (11 patients) had sexual dysfunction on sotalol and marked QRS duration increase (median, 40 ms; 10 patients) on flecainide at a dose of 200 mg/d. Lack of efficacy of chronic amiodarone therapy required multiple hospitalizations for electric cardioversion and frequent recurrences of AF at rapid ventricular rates. Amiodarone-induced adverse events at a median dose of 400 mg/d in the absence of concomitant AADs were transient and included symptomatic bradyarrhythmias not requiring medical intervention (15 patients), subclinical thyrotoxicosis (19 patients), hepatitis (1 patient), or visual or dermatologic events (2 patients). Amiodarone-induced thyroid dysfunction was difficult to manage long-term in 7 patients reverting after 55 days (35–78).

Among patients who progressed to persistent AF and before crossover, there were no serious adverse events at a median dose of 400 mg/d in the absence of concomitant AADs were transient and included symptomatic bradyarrhythmias not requiring medical intervention (15 patients), subclinical thyrotoxicosis (19 patients), hepatitis (1 patient), or visual or dermatologic events (2 patients). Amiodarone-induced thyroid dysfunction was difficult to manage long-term in 7 patients reverting after 55 days (35–78). Among patients who progressed to persistent AF and before crossover, there were no serious adverse events at a median dose of 400 mg/d in the absence of concomitant AADs were transient and included symptomatic bradyarrhythmias not requiring medical intervention (15 patients), subclinical thyrotoxicosis (19 patients), hepatitis (1 patient), or visual or dermatologic events (2 patients). Amiodarone-induced thyroid dysfunction was difficult to manage long-term in 7 patients reverting after 55 days (35–78).

### Table 1. Baseline Characteristics of Crossover Patients

<table>
<thead>
<tr>
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<th>Noncrossovers (n = 12)</th>
<th>Crossovers (n = 87)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>7 (58.3)</td>
<td>57 (65.5)</td>
<td>0.749</td>
</tr>
<tr>
<td>Age, y</td>
<td>59.7±10.3</td>
<td>56.6±10.3</td>
<td>0.315</td>
</tr>
<tr>
<td>AF duration, y</td>
<td>5 (3–6.75)</td>
<td>4 (2–7)</td>
<td>0.584</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>33 (32.25–33)</td>
<td>39 (35–42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>62.5 (60–65)</td>
<td>60 (55–65)</td>
<td>0.289</td>
</tr>
<tr>
<td>Episode/month</td>
<td>3 (3–3)</td>
<td>3 (3–8.5)</td>
<td>0.141</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; LA, left atrium; and LVEF, left ventricular ejection fraction.

Figure 2. Freedom from atrial fibrillation/atrial tachycardia (AF/AT) recurrence in both groups 4 years after random assignment, according to a single radiofrequency catheter ablation (RFA) procedure off drugs or to antiarrhythmic drugs (AADs) alone.

Figure 3. Cumulative probability of crossover to catheter ablation among patients assigned to antiarrhythmic drugs.
cations. At the end of the study, no further thromboembolic events occurred in either group.

Hospital Admissions
Among patients assigned to RFA, there were 61 hospital admissions for cardiovascular causes, including repeated procedures. Among the AADs group, there were 325 cardiovascular-event-related hospital admissions including hospitalizations for crossovers to RFA.

QoL Changes From Baseline to the End of the Study
None of the baseline SF-36 scores significantly differed between the randomized groups. For all scores, statistically significant increases were observed in each group at the end of the study (Table 2). However, within-group comparisons by the intention-to-treat analysis were not statistically different for all comparisons (Table 2). During follow-up, however, before switching to ablation, 3 of 8 SF-36 subscale scores were significantly lower in crossovers than among AAD patients who did not cross over, as were the Physical Component Summary and Mental Component Summary scores, which were well below population norms (Table 3).

Discussion
The principal finding of this study was that 4 years after random assignment in a select AF patient population with no or minimal structural heart disease, the intention-to-treat analysis showed a significant treatment effect favoring RFA in terms of arrhythmia recurrence. At the end of the study, excluding crossovers, only 12% of patients initially randomly assigned to the AAD arm were free of AF/AT recurrences as detected with TT daily rhythm monitoring. The strategy of chronic conventional AAD therapy at standard dosages and switching to RFA only if the patient did not have a response was less effective as the strategy of performing RFA initially.

Comparison With Previous Studies
Most studies on RFA among patients with paroxysmal AF have limited follow-up to 1 year or less, with few outcome data beyond 3 years. A short-term superiority of RFA over AAD therapy (1 year) has been reported in prior randomized studies,8–15 but longer-term data on outcomes are clinically important particularly if one considers that RFA is offered to relatively young highly symptomatic patients with a poor baseline QOL.

Table 2. Comparison of Quality-of-Life Scores Between and Within Groups by Intention-to-Treat Analysis Among Patients Randomly Assigned to RFA or AADs

<table>
<thead>
<tr>
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<th>RFA (n = 99)</th>
<th>AADs (n = 99)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>4-Year Follow-Up</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>69±18</td>
<td>85±12</td>
</tr>
<tr>
<td>Role physical</td>
<td>63±19</td>
<td>82±14</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>68±19</td>
<td>80±17</td>
</tr>
<tr>
<td>General health</td>
<td>65±17</td>
<td>79±15</td>
</tr>
<tr>
<td>Vitality</td>
<td>56±22</td>
<td>71±23</td>
</tr>
<tr>
<td>Social functioning</td>
<td>68±22</td>
<td>87±14</td>
</tr>
<tr>
<td>Role emotional</td>
<td>70±24</td>
<td>86±18</td>
</tr>
<tr>
<td>Mental health</td>
<td>66±21</td>
<td>81±17</td>
</tr>
<tr>
<td>PCS</td>
<td>44.4±9</td>
<td>52.3±9</td>
</tr>
<tr>
<td>MCS</td>
<td>43.7±11</td>
<td>52.9±9</td>
</tr>
</tbody>
</table>

RFA indicates radiofrequency ablation; AAD, antiarrhythmic drug; PCS, Physical Component Summary; and MCS, mental component summary.

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) is a self-administered, 36-item questionnaire that assesses the concepts of physical functioning, role limitations due to physical problems, social function, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health perceptions. The physical and mental component summaries (PCS and MCS, respectively) are normalized to an overall population mean±SD of 50±10. Scores range from 0–100, with higher scores indicating better health status.

Table 3. Comparison of Quality-of-Life Scores at Baseline and Before Crossover Among Patients Randomly Assigned to AAD Therapy

<table>
<thead>
<tr>
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<th>AADs (n = 87)</th>
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<tr>
<td></td>
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<tr>
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</tr>
<tr>
<td>PCS</td>
<td>45.3±9</td>
</tr>
<tr>
<td>MCS</td>
<td>43.2±11</td>
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</tbody>
</table>

AAD indicates antiarrhythmic drug; PCS, physical component summary; and MCS, Mental Component Summary.

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) is a self-administered, 36-item questionnaire that assesses the concepts of physical functioning, role limitations due to physical problems, social function, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health perceptions. The physical and mental component summaries (PCS and MCS, respectively) are normalized to an overall population mean±SD of 50±10. Scores range from 0–100, with higher scores indicating better health status.
as it was in our study. The number of patients enrolled in the present study is larger than other randomized studies, and the 4-year follow-up is the longest follow-up to date. The results demonstrated that in a selected patient population with no or minimal structural heart disease, RFA is more effective that AADs up to 4 years in many patients (70%) with repeat interventions in about one-third of patients. By contrast, conventional AAD therapy in the majority of patients was ineffective requiring crossover to RFA for frequent arrhythmia recurrence, associated complications, and arrhythmia progression. However, despite the large number of crossovers to RFA, at the end of the study the intention-to-treat analysis showed that RFA was still superior to AADs. The results of the present randomized study suggest that RFA strategy with repeat interventions (about 30%), as necessary, rather than chronic AADs, may provide long-term benefits, confirming recent observational studies.5,6,16,17 Our experience also suggests that in patients with paroxysmal AF and minimal structural heart diseases, PV isolation by larger encircling of the ipsilateral veins, as now performed in almost all electrophysiology laboratories, may further improve the long-term outcome up to 4 years of follow-up, as hypothesized by prior studies.5 We also observed a low incidence of progression to persistent AF after RFA, which confirms the results of prior observational studies at 5 years of follow-up.5,6 In our study, AF progression was higher in the AAD group than in the RFA group, and this was probably due to prevention of electric or structural atrial remodeling after RFA. Indeed, patients with progression despite similar baseline LA dimensions showed larger LA at the time of progression as compared with those who did not progress, suggesting the crucial role of atrial remodeling. These findings taken together suggest that an early use of RFA may be of benefit to avoid or limit arrhythmia recurrence and/or progression.18,19

Quality of Life
Observational series have shown significant improvements in QoL after RFA in the short-term follow-up (≤1 year), but establishing that QoL benefit lasts beyond 1 year may justify a broader use of RFA in symptomatic patients with AF.20–23 In the present study, 4 years after random assignment, patients initially randomly assigned to RFA had a significant long-term improvement of QoL scores. By contrast, within the first years after random assignment, almost all patients initially randomly assigned to AADs (about 90%) and before crossing to RFA showed a poorer QoL, which, at the end of the study and after crossover to RFA in an intention-to-treat analysis, showed no difference between the 2 groups, suggesting that switch to RFA was of benefit in patients initially randomly assigned to AADs.

Complications
Beyond periprocedural complications, no new sequelae of RFA other than LA tachycardia were attributable to the ablative procedure. During the 4-year follow-up, a transient ischemic attack lasting a few seconds occurred shortly after the procedure in 1 patient randomly assigned to RFA, but thromboembolic events did not occur in either group in the long-term, and this may be explained by the fact that most patients did not have coexisting comorbidities. By contrast, many patients on long-term AAD therapy developed numer-ous and severe adverse reactions confirming prior drug trials.9–15 Of note, a high incidence of subclinical thyrotoxicosis and symptomatic bradyarrhythmia was observed during long-term amiodarone therapy at a dose of 400 mg/d.

Clinical Implications
The results of this study suggest that in selected young patients with paroxysmal AF with no or minimal structural heart disease, the use of RFA to perform PV isolation with larger encircling of PVs as first-line therapy instead of chronic conventional AADs may be an effective and safe treatment option available to maintain a stable sinus rhythm long-term in many patients.

Study Limitations
Catheter ablation has been performed in a selected group of patients with AF and at a single highly experienced center, and the results may not apply to all patient populations with AF or to other less experienced centers. Indeed, our patient population consisted predominantly of younger, healthier, nonobese patients with small atria and no or minimal structural heart disease. The substantial number of crossovers could underestimate the true progression rate from paroxysmal to persistent AF among patients on long-term AAD therapy. We cannot exclude that continuous (implantable devices) or longer-term monitors such as repeat 7-day Holter could have resulted in higher rate of recurrence or earlier detection of recurrences.

Conclusions
With follow-up extended to 4 years after random assignment, ablation remains superior to antiarrhythmic drug in these patients with paroxysmal AF. Catheter ablation may be considered as first-line strategy in a selected patient population with AF, necessitating long-term sinus rhythm maintenance.

Acknowledgments
We thank the staff of the Arrhythmology Department for the continued support and assistance throughout the 4-year follow-up study. In addition, we are extremely grateful to patients and families who took part in this long-term study for their patience, understanding, and adherence to the scheduled follow-up visits and study design.

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Disclosures
Dr Pappone has advisory board appointments at Johnson & Johnson, St Jude Medical, Medtronic Inc, Boston Scientific Co, and Biotronik SE.

References
Long-term follow-up data for radiofrequency catheter ablation (RFA) of atrial fibrillation (AF) are limited. The present study presents the long-term follow-up of the APAF study. A total of 198 patients with paroxysmal AF were randomly assigned to RFA (99 patients) or antiarrhythmic drugs (AADs) (99 patients). By 4 years, the RFA procedure was repeated because of recurrent arrhythmias in 27.3% of patients, whereas only 12.1% of the AAD group remained in sinus rhythm without ablation. During the follow-up, 87.9% of patients initially randomly assigned to AADs crossed over to RFA because of AAD failure or side effects, and 19 of them had progressed to persistent AF before switching to RFA. In an intention-to-treat analysis, 72.7% of patients in the RFA group and 56.5% in the AAD group were free of recurrent AF/atrial tachycardia ($P=0.017$). RFA significantly improved quality of life ($P<0.001$), whereas AADs patients showed poorer quality of life before crossing over to RFA. Except for new left atrial tachycardias, there were no serious complications caused by RFA. Thus, our data support the superiority of RFA to AAD therapy during longer-term follow-up in this selected patient population with paroxysmal AF.
Radiofrequency Catheter Ablation and Antiarrhythmic Drug Therapy: A Prospective, Randomized, 4-Year Follow-Up Trial: The APAF Study

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