Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation
The A4 Study

Pierre Jais, MD; Bruno Cauchemez, MD; Laurent Macle, MD; Emile Daoud, MD; Paul Khairy, MD, PhD; Rajesh Subbiah, BSc (Med), MBBS, PhD; Mélèze Hocini, MD; Fabrice Extramiana, MD; Frédéric Sacher, MD; Pierre Bordachar, MD; George Klein, MD; Rukshen Weerasooriya, MBBS; Jacques Clémenty, MD; Michel Haïssaguerre, MD

**Background**—The mainstay of treatment for atrial fibrillation (AF) remains pharmacological; however, catheter ablation has increasingly been used over the last decade. The relative merits of each strategy have not been extensively studied.

**Methods and Results**—We conducted a randomized multicenter comparison of these 2 treatment strategies in patients with paroxysmal AF resistant to at least 1 antiarrhythmic drug. The primary end point was absence of recurrent AF between months 3 and 12, absence of recurrent AF after up to 3 ablation procedures, or changes in antiarrhythmic drugs during the first 3 months. Ablation consisted of pulmonary vein isolation in all cases, whereas additional extrapulmonary vein lesions were at the discretion of the physician. Crossover was permitted at 3 months in case of failure. Echocardiographic data, symptom score, exercise capacity, quality of life, and AF burden were evaluated at 3, 6, and 12 months by the supervising committee. Of 149 eligible patients, 112 (18 women [16%]; age, 51.1±11.1 years) were enrolled and randomized to ablation (n=53) or “new” antiarrhythmic drugs alone or in combination (n=59). Crossover from the antiarrhythmic drugs and ablation groups occurred in 37 (63%) and 5 patients (9%), respectively (P=0.0001). At the 1-year follow-up, 13 of 55 patients (23%) and 46 of 52 patients (89%) had no recurrence of AF in the antiarrhythmic drug and ablation groups, respectively (P<0.0001). Symptom score, exercise capacity, and quality of life were significantly higher in the ablation group.

**Conclusion**—This randomized multicenter study demonstrates the superiority of catheter ablation over antiarrhythmic drugs in patients with AF with regard to maintenance of sinus rhythm and improvement in symptoms, exercise capacity, and quality of life.

**Key Words:** ablation ■ antiarrhythmia agents ■ arrhythmia ■ fibrillation

**The mainstay of treatment for atrial fibrillation (AF) has traditionally been pharmacological, using drugs to control either the rhythm or the rate.** However, nonpharmacological approaches have been effective at restoring sinus rhythm in drug-refractory patients, raising the possibility of using catheter ablation earlier in the management cascade than previously envisaged. Nonrandomized or single-center studies suggesting the superiority of catheter ablation over antiarrhythmic drug (AAD) treatment have been reported. We performed a prospective, randomized controlled trial involving 4 centers, 2 in North America and 2 in Europe, comparing a strategy of additional AADs with catheter ablation for patients with paroxysmal AF who had failed at least 1 AAD.
Patients
Patients >18 years of age who were capable of providing informed consent were included if they had symptomatic, documented paroxysmal AF over a span of ≥6 months with at least 2 episodes during the preceding month. Patients were excluded if they had contraindications to >2 AADs in different classes or to oral anticoagulants, prior AF ablation, an intracardiac thrombus, AF from a potentially reversible cause, pregnancy, or a contraindication to the discontinuation of oral anticoagulation.

Of the 149 patients who were eligible and invited to participate, 112 were enrolled. Twenty-one eligible patients declined, and the referring physician refused participation for the remaining 16 patients. Clinical characteristics of the study population are detailed in Table 1.

Study Design
A 90-day treatment stabilization period after randomization allowed up to 3 ablation procedures and various changes in AADs, individually or in combination. The formal follow-up period started at day 91 and continued to day 365. No blanking period beyond the initial 90 days was used in this study. Recurrent AF lasting ≥3 minutes and occurring after the stabilization period was considered a treatment failure, at which time crossover to the alternative therapy was offered.

Medical Therapy
Once included in the study, patients received “new” AADs (ie, monotherapy or combinations of drugs never administered before enrollment). The following AADs, either alone or in combination, were considered acceptable: amiodarone, quinidine, disopyramide, flecainide, propafenone, cibenzoline, dofetilide, and sotalol. No specific regimen was mandated, although physicians were encouraged to comply with published guidelines for AAD use and dosing.16 When amiodarone was prescribed, a loading dose of 600 mg/d for 21 days followed by 200 mg/d was recommended, with an increase to 300 mg daily if required.17 Sotalol, dofetilide, or amiodarone was recommended in patients with a left ventricular ejection fraction <50%. Alternative drug(s) were introduced in the event of recurrent AF 1 month after the initiation of treatment, with up to 3 attempts at modifying pharmacological therapy during the treatment stabilization period.

Ablation
Therapeutic anticoagulation with warfarin (international normalized ratio maintained between 2 and 3) was required for at least 1 month before and 1 month after each procedure. Transesophageal echocardiography was performed in all patients before an ablation procedure to exclude the presence of left atrial thrombus. After transseptal access to the left atrium, isolation of all 4 pulmonary veins was performed using circumferential applications of radiofrequency energy and verified with a circular mapping catheter (Lasso Catheter, Biosense Webster, Inc, Diamond Bar, Calif). The ablation catheter was either a 3.5- or 5-mm irrigated tip (Thermocool, Biosense Webster; n=95) or a 4-mm nonirrigated tip (n=13). For safety reasons, a power limit of ≤35 W with a tip temperature of ≤50°C

---

Table 1. Baseline Population Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RF (n=53)</th>
<th>AAD (n=59)</th>
<th>Total (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8 (15.1)</td>
<td>10 (16.9)</td>
<td>18 (16.1)</td>
</tr>
<tr>
<td>Male</td>
<td>45 (84.9)</td>
<td>49 (83.1)</td>
<td>94 (83.9)</td>
</tr>
<tr>
<td>Age, mean±S.D, y</td>
<td>49.7±10.7</td>
<td>52.4±11.4</td>
<td>51.1±11.1</td>
</tr>
<tr>
<td>Episodes per month, median (IQR), n</td>
<td>13.5 (4.0–30.0)</td>
<td>12.0 (3.0–30.0)</td>
<td>12.0 (4.0–30.0)</td>
</tr>
<tr>
<td>Duration of episodes, median (IQR), h</td>
<td>4.0 (1.0–12.0)</td>
<td>6.0 (2.0–15.0)</td>
<td>5.5 (1.0–12.0)</td>
</tr>
<tr>
<td>Patients with ≥1 DC shock, n (%)</td>
<td>9 (17.0)</td>
<td>12 (20.3)</td>
<td>21 (18.8)</td>
</tr>
<tr>
<td>Embolic events, n (%)</td>
<td>1 (1.9)</td>
<td>7 (11.9)</td>
<td>8 (7.1)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1 (1.9)</td>
<td>2 (3.4)</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>11 (21.6)</td>
<td>18 (30.5)</td>
<td>29 (26.4)</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>10 (19)</td>
<td>14 (24)</td>
<td>24 (21)</td>
</tr>
<tr>
<td>Ischemic, n (%)</td>
<td>3 (5.7)</td>
<td>6 (10.2)</td>
<td>9 (8.0)</td>
</tr>
<tr>
<td>Valvular, n (%)</td>
<td>4 (7.5)</td>
<td>5 (8.5)</td>
<td>9 (8.0)</td>
</tr>
<tr>
<td>Idiopathic, n (%)</td>
<td>3 (5.8)</td>
<td>1 (1.7)</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Hypertrophic, n (%)</td>
<td>0 (0.0)</td>
<td>2 (3.4)</td>
<td>2 (1.8)</td>
</tr>
</tbody>
</table>

Echocardiographic parameters

<table>
<thead>
<tr>
<th></th>
<th>RF (n=53)</th>
<th>AAD (n=59)</th>
<th>Total (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricle End-diastolic dimension, mm</td>
<td>51.9±4.2</td>
<td>50.5±7.7</td>
<td>51.2±6.2</td>
</tr>
<tr>
<td>End-systolic dimension, mm</td>
<td>33.8±5.1</td>
<td>32.9±4.9</td>
<td>33.4±5.0</td>
</tr>
<tr>
<td>Percentage of shortening</td>
<td>36.3±6.2</td>
<td>35.7±6.5</td>
<td>36.0±6.3</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>63.1±11.0</td>
<td>65.6±7.2</td>
<td>64.3±9.4</td>
</tr>
<tr>
<td>Left atrial dimension Parasternal long axis, mm</td>
<td>39.5±5.6</td>
<td>40.0±5.7</td>
<td>39.8±5.6</td>
</tr>
<tr>
<td>Apical 4 chambers Longitudinal diameter, mm</td>
<td>54.6±8.5</td>
<td>55.8±9.0</td>
<td>55.2±8.7</td>
</tr>
<tr>
<td>Transverse diameter, mm</td>
<td>41.1±5.8</td>
<td>41.3±6.2</td>
<td>41.2±5.9</td>
</tr>
<tr>
<td>Presence of valvular heart disease (grade ≥2), n (%)</td>
<td>2 (3.8)</td>
<td>4 (7.5)</td>
<td>6 (5.7)</td>
</tr>
<tr>
<td>Presence of pericardial effusion, n (%)</td>
<td>1 (1.9)</td>
<td>1 (2.0)</td>
<td>2 (1.9)</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD unless otherwise indicated. RF indicates radiofrequency.
was used according to standard practice. Pulmonary vein angiography was performed after the procedure to assess vein caliber. The use of navigation systems and delivery of additional lesions outside the pulmonary vein regions were left to the discretion of the operator and noted in the report forms. The cavotricuspid isthmus also was ablated with an end point of bidirectional conduction block. When linear lesions were delivered, either at the roof of the left atrium (connecting both superior pulmonary veins) or at the mitral isthmus (mitral annulus to the ostium of the left inferior pulmonary vein), the end point was complete bidirectional conduction block across the line demonstrated by previously defined criteria. After an initial ablation procedure, 2 repeat ablation procedures were permitted during the 90-day treatment stabilization period.

Other Therapeutic Considerations
Continuation of anticoagulation was recommended in both arms of the study but remained at the discretion of the individual treating physician.

Follow-Up and Study Objectives
All patients were systematically followed up for 1 year after the first day of randomization (day 0) in each center, with the following data obtained: 12-lead ECG, Short Form-36 quality-of-life questionnaire, AF symptom frequency and severity checklist, and 24-hour Holter recording at baseline and 3, 6, and 12 months (AF burden was calculated as the median number of minutes in AF over a 24-hour period for each Holter recording); transthoracic echocardiography at baseline, after each ablation procedure, and at day 365; a treadmill exercise test at baseline and day 365; and a monthly clinical questionnaire administered by telephone during the 3-month treatment stabilization period.

Primary End Point
The primary end point of the study was the proportion of patients free of recurrent AF between months 3 and 12. Episodes qualified as AF if they lasted at least 3 minutes and were documented by ECG or reported by the patient as AF, even in the absence of ECG confirmation. Any such episode was considered a treatment failure, with crossover then considered.

Secondary End Points
Secondary end points consisted of time to recurrent AF, complications and adverse effects, change in left heart dimensions and function, quality of life, exercise capacity, AF burden, and efficacy of amiodarone when used for the first time during the study.

Data Management and Statistical Analysis
Data were overseen by an independent monitoring group for data management and statistical analysis. Continuous variables are summarized by mean±SD or median and interquartile range (IQR, 25th and 75th percentiles), depending on the normality of distribution. Categorical variables are represented by frequencies and percentages. Time to AF recurrence after the stabilization period was compared between the ablation and AAD groups by the log-rank test, with median time to recurrence estimated by the Kaplan–Meier product-limit method. The log-rank test and Kaplan–Meier estimates were based on last available records. For continuous clinical parameters without repeated measures, Wilcoxon rank-sum tests or the t test was used to compare differences between treatment groups. For categorical variables such as gender, Fisher exact tests were used. Generalized linear models for repeated measures were created to assess within-subject and treatment effects for quality-of-life metrics and exercise testing. Arrhythmia burden, as quantified by Holter monitoring, was compared by Friedman nonparametric repeated-measures test. Two-sample tests or Fisher exact tests were performed to select candidate variables for multivariate analysis predictive of ablation success. Multivariate stepwise logistic regression was then performed to identify independent predictors by specifying a significance level of 0.10 for entry and 0.15 for exit. All treatment comparisons were performed on an intention-to-treat basis. Two-tailed values of P<0.05 were considered statistically significant. Analyses were performed with SAS software version 9.1 (SAS Institute, Inc. Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All the authors have read and agree to the manuscript as written.
Results

A total of 112 patients, 94 men and 18 women (16%), 51.1±11.1 years of age were enrolled. During the course of the study, 1 patient withdrew consent, and 3 were excluded because of poor compliance with assigned antiarrhythmic therapy. One hundred eight patients completed the study to the end of the 1-year follow-up. Patient demographics are shown in Table 1. Patients had experienced a median of 12 (interquartile range, 4 to 30) episodes of AF per month lasting 5.5 hours (1.0 and 12.0 hours) before randomization and had failed 2 class I or III AADs. At least 1 class I drug had been attempted in 87% of patients, and 75% had recurrent AF despite a class III agent (Table 2).

AF Ablation

Catheter ablation of AF was performed in 53 patients who underwent a mean of 1.8±0.8 procedures (1 to 3; median, 2). Left pulmonary veins were isolated in all patients, whereas the right superior vein was isolated in 98% and the right inferior vein in 94% of patients. In addition, linear lesions were delivered at the cavitricuspid isthmus in 34 patients, roof of the left atrium in 9 patients, and mitral isthmus in 16 patients. Complete block was demonstrated in 97%, 100%, and 89% of these lines, respectively. Foci from nonvenous structures also were targeted in 12 patients and successfully ablated in 11 (92%). The mean procedural duration (including repeat procedures) was 168±62 minutes with a mean fluoroscopy exposure per procedure of 50±24 minutes. Details on repeat procedures are given in Table 3.

Forty-six patients (89%) who underwent ablation remained free of atrial arrhythmias without AADs at 1 year (Figure 1). All patients with recurrent episodes of AF after catheter ablation had electrocardiographically documented arrhythmias. Five patients (9%) crossed over and were treated with AADs.

Antiarrhythmic Drugs

Fifty-nine patients were randomized to AADs; 49 had 88 attempts at pharmacological management with class I drugs alone or in combination, and 45 had 59 attempts involving class III drugs. A total of 147 AADs were used, with a mean of 2.5±1.0 drugs per patient. At least 1 combination of drugs was attempted in all patients, which included amiodarone in 35 patients. Before entering the trial, 19 patients had been treated with amiodarone, all of whom received it as monotherapy.

At 1 year, 13 of 55 patients (23%) remained free of atrial arrhythmias (P<0.0001 versus the ablation group; Figure 1). Recurrent episodes of AF were documented electrocardiographically in all patients in whom treatment failed. Thirty-seven patients (63%; P=0.0001 versus the ablation group) crossed over to ablation at 192±80 days. In the 22 patients without crossover to ablation, amiodarone was used for the first time during the study in 18 and failed in 12 patients (66%).

Predictors of Ablation Outcome

From the univariate analysis, the following were identified as predictors of a successful ablation outcome: shorter duration of AF, higher baseline ejection fraction, and fewer DC shocks. In stepwise multivariate logistic regression analyses, a higher baseline ejection fraction (odds ratio, 1.10; 95% CI, 1.01 to 1.19; P=0.02) was the only independent predictor of lack of recurrent AF after ablation. The baseline left ventricular ejection fraction was 56.2±10.4% in the 13 patients who

| Table 3. Redo Procedures in 23 Patients |
| PV reconnection, n (%) | 13 (58) |
| RS | 13 (58) |
| RI | 6 (26) |
| LS | 6 (26) |
| LI | 2 (9) |
| Gap in previous ablation lines, n (%) | 8 (33) |
| New lesions, n (%) | 10 (42) |
| New non-PV foci | 10 (42) |
| New ablation lines | 4 (16) |

PV indicates pulmonary vein; RS, right superior; RI, right inferior; LS, left superior; and LI, left inferior.
failed catheter ablation compared with 65.3±10.4% in the 40 patients with a successful outcome (P=0.02).

Anticoagulants
At the end of the study, 31 of 52 patients (60%) in the ablation group had discontinued anticoagulation therapy compared with 18 of 53 (34%) in the AAD group (intention-to-treat analysis, P=0.01).

Left Heart Dimension and Function
At 1 year of follow-up, no significant difference was found in left atrial size (38.7±7.0 versus 38.9±6.2 mm; P=0.92), left ventricular end-diastolic dimension (50.0±5.2 versus 51.0±4.5; P=0.35), and left ventricular ejection fraction (65.4±8.9% versus 65.4±5.9%; P=0.99) in patients randomized to catheter ablation versus antiarrhythmic therapy, respectively.

AF Burden
At baseline, the AF burden determined by 24-hour Holter monitoring was similar in both groups (ie, 14.0 minutes [0.0 and 578.0 minutes] versus 14.0 minutes [0.0 and 215.0 minutes] in patients randomized to catheter ablation versus AAD therapy, respectively [P=0.69]). Over the course of follow-up, the AF burden significantly decreased in both groups (P<0.0001). Patients randomized to catheter ablation experienced a greater reduction in AF burden over time (P=0.0001). Compared with baseline, the median withinsubject reduction in AF burden at 365 days was 10.4 minutes (0.0 and 588.0 minutes) in patients randomized to catheter ablation versus 3.2 minutes (0.0 and 154.6 minutes) in patients initially assigned AAD therapy.

Symptoms, Quality of Life, and Exercise Capacity
At baseline, no significant difference was found in Short Form-36 quality-of-life measures between patients randomized to ablation versus AAD therapy. At the 1-year follow-up, the physical and mental component summary scores of the ablation group were significantly higher than those of the AAD group (52.0±7.6 versus 48.9±7.2 and 56.7±7.8 versus 51.9±7.7, respectively; P=0.01). Six of the 8 subscales were significantly higher in the ablation group. The largest magnitude of improvement was observed between baseline and day 91, which was maintained at day 365. As graphically portrayed in Figure 2, the physical component score improved in both groups (within-subject increases of 7.2 and 6.0 from baseline to 365 days in the ablation and AAD groups, respectively; P=0.001), with a significant treatment effect favoring ablation (P=0.015). The mental component score likewise improved in both groups (within-subject increases of 9.7 and 9.1 in the ablation [P<0.0001] and AAD [P=0.0001] groups), with a trend toward greater benefit in the ablation arm (P=0.09). Symptom frequency decreased in both study arms (within-subject changes of 14.0 and 12.2 in the ablation [P<0.0001] and AAD [P=0.002] groups, respectively), with a nonsignificant treatment effect (P=0.10). Both groups of patients experienced a reduction in symptom severity (within-subject changes of 11.5 and 8.8 in the ablation [P<0.0001] and AAD [P<0.0001] treatment arms, respectively), with a significantly greater effect favoring catheter ablation (P=0.001).

At baseline, no differences were found in exercise stress test parameters. As summarized in Table 4, at 1 year of follow-up, maximum workload, total metabolic equivalents achieved, and maximum heart rate increased significantly...
more in patients randomized to catheter ablation compared with AAD therapy.

Complications
A total of 155 ablation procedures were performed. Two episodes of cardiac tamponade requiring pericardiocentesis and 2 groin hematomas were reported, 1 in each group (1 crossover patient), with a favorable outcome in all. A stenosis of the left superior pulmonary vein that required dilatation and stent implantation occurred in 1 crossover patient, with an uneventful course thereafter. One case of hyperthyroidism was observed in the AAD group, as well as 2 deaths that were not deemed related to AADs (acute myeloid leukemia and myocardial infarction).

Discussion
This multicenter, prospective, randomized controlled study demonstrates that catheter ablation of paroxysmal AF is associated with significantly better rhythm control compared with further attempts at AAD therapy in patients who previously failed ≥1 attempts with AADs. In addition, patients randomized to ablation had improved symptoms, quality of life, and exercise capacity.

Although AADs remain the cornerstone of the treatment of AF, catheter ablation is assuming a greater role. This study suggests an earlier role for ablation in patients in whom at least 1 AAD has failed. Only 23% of patients treated with AADs achieved freedom from AF despite the use of a mean of 2.5 class I or III agents. Even when amiodarone was used for the first time during the study, it achieved a success rate of only 34%. This is lower than previously published success rates for AADs and probably reflects multiple factors. Our criteria for freedom from AF were more stringent than those in many studies focused on AADs. Although no consensus exists as to the minimal AF burden of clinical consequence to warrant the designation of “failure,” our intention was to conservatively render criteria for “success” achievable for the first time during the study, lower than reported in the Canadian Trial of Atrial Fibrillation (CTAF) despite the same dosage regimen.

Symptoms are the major motivation for undergoing catheter ablation in patients with paroxysmal AF. Ablation was associated with a significant reduction of symptoms and improved quality of life. The Short Form-36 subscales were superior in the ablation group in 6 of 8 scales. In fact, the quality of life observed at 1 year in the ablation group was comparable to that in prior reports of healthy subjects of a similar age. This improvement is unlikely to be attributable to a placebo effect because it was observed at day 91 and maintained at 1 year.

The improvement observed in exercise capacity at 1 year in the ablation group may be due in part to the reduction in AF burden. Exercise capacity was superior in the ablation group despite a similar proportion of patients in sinus rhythm in both groups (88% and 87%, respectively) at the time of testing. Other mitigating factors may include discontinuation of AADs, as suggested by the higher maximal heart rate achieved in the ablation group. Lack of AADs also may affect the observed improvement in quality of life.

The results of this multicenter trial are consistent with a previous single-center report in which ablation was found to be superior to AADs. The superiority of ablation over mainly class I AADs as “first-line” therapy for AF has also been shown in another single-center report. Amiodarone was used in only 1 of 37 patients in the drug group in the latter study. In comparison, in our study, amiodarone was used with other AADs in 35 of 59 patients randomized to pharmacological therapy.

The role of catheter ablation as first-line therapy for AF remains controversial. Procedural risks of ablation are diminishing but are not insignificant, as detailed in this study and elsewhere. The 2% incidence of tamponade observed in our study is consistent with registry data. Moreover, these patients suffered no long-term sequelae. However, the major benefit of catheter ablation for AF remains symptomatic relief, with few data supporting a reduction in mortality or stroke. Largely for these reasons, current guidelines recommend catheter ablation for AF when AADs have failed or have not been tolerated. Our data would support the earlier use of catheter ablation in patients similar to those enrolled in this study (ie, relatively young and symptomatic), given the demonstrated limitations of AADs and superior outcomes with ablation.

Table 4. Stress Test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline RF (N=53)</th>
<th>Baseline AAD (N=59)</th>
<th>Day 365 RF (N=53)</th>
<th>Day 365 AAD (N=59)</th>
<th>Mean Change per Subject RF (N=53)</th>
<th>Mean Change per Subject AAD (N=59)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate at rest, bpm</td>
<td>81.0±26.4</td>
<td>73.1±21.4</td>
<td>82.0±20.5</td>
<td>74.0±13.9</td>
<td>0.8</td>
<td>−0.5</td>
<td>0.0022</td>
</tr>
<tr>
<td>Heart rate, maximum, bpm</td>
<td>150.2±25.9</td>
<td>140.1±28.3</td>
<td>154.8±18.3</td>
<td>139.2±23.9</td>
<td>4.6</td>
<td>−0.8</td>
<td>0.013</td>
</tr>
<tr>
<td>Exercise duration, min</td>
<td>9.5±4.0</td>
<td>9.1±4.1</td>
<td>12.4±5.3</td>
<td>10.3±4.6</td>
<td>3.1</td>
<td>1.7</td>
<td>0.17</td>
</tr>
<tr>
<td>Maximum workload, W</td>
<td>157.8±56.3</td>
<td>176.1±61.8</td>
<td>187.6±54.4</td>
<td>163.2±49.9</td>
<td>27.7</td>
<td>−1.7</td>
<td>0.021</td>
</tr>
<tr>
<td>METS</td>
<td>8.4±2.6</td>
<td>8.0±2.7</td>
<td>9.5±2.3</td>
<td>8.1±2.6</td>
<td>1.2</td>
<td>0.3</td>
<td>0.0022</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD unless otherwise indicated. RF denotes radiofrequency catheter ablation; METS metabolic equivalents.

*Treatment effect comparing catheter ablation and AAD therapy by means of an intention-to-treat analysis approach.
Study Limitations
This study has a relatively small sample size. However, the superiority of catheter ablation is consistent and of large magnitude, rendering a spurious finding unlikely. In the absence of a sham procedure, a placebo effect should be considered when quality-of-life metrics are interpreted. However, no study thus far has included a sham procedure for ethical reasons. Second, intermittent Holter monitoring would not be expected to be as sensitive as continuous ECG monitoring with an implanted device. However, the relative proportion of patients with exclusively asymptomatic AF is not expected to be systematically different between the 2 groups (ie, non-differential misclassification). Unfortunately, a suitable clinical device for continuous long-term monitoring is currently unavailable. Third, results favoring catheter ablation were obtained with a complex and invasive procedure requiring intensive training and a specialized medical and surgical environment. Repeat ablation procedures were required in a sizeable number of patients, and complications were observed. This finding emphasizes the need for careful patient selection, focusing on those most affected by debilitating symptoms. Finally, the follow-up is relatively short, and the safety of withdrawing anticoagulation in the ablation group, although promising, is not firmly established.

Conclusions
This multicenter randomized trial demonstrates that catheter ablation of AF is superior to AAD therapy in patients with paroxysmal AF who have previously taken and failed AADs. The substantial improvement in quality of life, symptoms, and physical performance in this series of relatively young and healthy patients constitutes an important benefit that may support earlier use of catheter ablation in this context.

Acknowledgments
We are grateful for the significant contributions of Drs Jeremy Ruskin and Albert Waldo, who made up the trial safety committee.

Disclosures
Dr Jaïs reports receiving honoraria from Biosense Webster and St Jude Medical. Dr Macle reports receiving honoraria from Medtronic and St Jude Medical; receiving honoraria from Biosense Webster, Medtronic, and St Jude Medical; and serving on the advisory board for Biosense Webster, Medtronic, and St Jude Medical. Dr Khairy reports receiving research grants from the Canada Research Chair in Electrophysiology and Adult Congenital Heart Disease, the Canadian Institute of Health Research, and Fonds de Recherche en Santé (Quebec) and serving on the speakers’ bureau for St Jude Medical. Dr Hocini reports receiving honoraria from Bard and Biosense Webster. Dr Extramiana reports receiving honoraria from Biosense Webster. Dr Klein reports receiving honoraria from Boston Scientific and St Jude Medical and serving on the board of trustees of CryoCath Technologies and on the advisory board of Medtronic. Dr Weerasooriya reports receiving honoraria from Medtronic and Bard. The other authors report no conflicts.

References

CLINICAL PERSPECTIVE

The mainstay of treatment for atrial fibrillation has historically been pharmacological, using drugs to control either the rhythm or the rate. However, nonpharmacological approaches have been effective at restoring sinus rhythm in drug-refractory patients, raising the possibility of using catheter ablation earlier in the management cascade than previously envisaged. Nonrandomized or single-center studies suggesting the superiority of catheter ablation over antiarrhythmic drug treatment have been reported. We performed a prospective randomized controlled trial involving 112 patients in 4 centers, 2 in North America and 2 in Europe, comparing a strategy of additional antiarrhythmic drugs (59 patients) with catheter ablation (53 patients) for patients with paroxysmal atrial fibrillation who had previously failed at least 1 antiarrhythmic drug. At the 1-year follow-up, 13 of 55 patients (23%) and 46 of 52 patients (89%) had no recurrence of atrial fibrillation in the antiarrhythmic drug and ablation groups, respectively (P<0.0001). Symptom score, exercise capacity, and quality-of-life scores were significantly higher in the ablation group. This multicenter randomized trial demonstrates that catheter ablation of atrial fibrillation is superior to antiarrhythmic drug therapy in patients with paroxysmal atrial fibrillation who have previously taken and failed antiarrhythmic drugs. The substantial improvement in quality of life, symptoms, and physical performance in this series of relatively young and healthy patients constitutes an important benefit that may support earlier use of catheter ablation in this context.
Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation: The A4 Study
Pierre Jaïs, Bruno Cauchemez, Laurent Macle, Emile Daoud, Paul Khairy, Rajesh Subbiah, Mélèze Hocini, Fabrice Extramiana, Fréderic Sacher, Pierre Bordachar, George Klein, Rukshen Weerasooriya, Jacques Clémenty and Michel Haïssaguerre

_Circulation_. 2008;118:2498-2505; originally published online November 24, 2008;
doi: 10.1161/CIRCULATIONAHA.108.772582
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/118/24/2498

An erratum has been published regarding this article. Please see the attached page for:
/content/120/10/e83.full.pdf

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/
In the article, “Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation: The A4 Study,” by Jaïs et al, which appeared in the December 9, 2008, issue of the journal (Circulation. 2008;118:2498–2505), 2 important errors were made.

On page 2500, the words “median” and “minutes” should have been used instead of “mean” and “hours” in the sentence that reads, “(AF burden was calculated as the mean number of hours in AF over a 24-hour period for each Holter recording.)”

On page 2502, under AF Burden, the word “hours” should be replaced throughout by the word “minutes.”

The online version of the article has been corrected. The authors regret these errors.

DOI: 10.1161/CIRCULATIONAHA.109.192636