Results from the Loire-Ardèche-Drôme-Isère-Puy-de-Dôme (LADIP) Trial on Atrial Flutter, a Multicentric Prospective Randomized Study Comparing Amiodarone and Radiofrequency Ablation After the First Episode of Symptomatic Atrial Flutter

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Background—There is no published randomized study comparing amiodarone therapy and radiofrequency catheter ablation (RFA) after only 1 episode of symptomatic atrial flutter (AFL). The aim of the Loire-Ardèche-Drôme-Isère-Puy-de-Dôme (LADIP) Trial of Atrial Flutter was 2-fold: (1) to prospectively compare first-line RFA (group I) versus cardioversion and amiodarone therapy (group II) after only 1 AFL episode; and (2) to determine the impact of both treatments on the long-term risk of subsequent atrial fibrillation (AF).

Methods and Results—From October 2002 to February 2006, 104 patients (aged 78 ± 5 years; 20 women) with AFL were included, with 52 patients in group I and 52 patients in group II. The cumulative risk of AFL or AF was interpreted with the use of Kaplan-Meier curves and compared by the log-rank test. Clinical presentation, echocardiographic data, and follow-up were as follows: age (78.5 ± 5 versus 78 ± 5 years), history of AF (27% versus 21.6%); structural heart disease (58% versus 65%), left ventricular ejection fraction (56 ± 14% versus 54.5 ± 14%), left atrial size (43 ± 7 versus 43 ± 6 mm), mean follow-up (13 ± 6 versus 13 ± 6 months; \(P = \text{NS}\)), recurrence of AFL (3.8% versus 29.5%; \(P < 0.0001\)), and occurrence of significant AF beyond 10 minutes (25% versus 18%; \(P = 0.3\)). Five complications (10%) were noted in group II (sick sinus syndrome in 2, hyperthyroidism in 1, and hypothyroidism in 2) and none in group I (0%) \(P(0.03)\).

Conclusions—RFA should be considered a first-line therapy even after the first episode of symptomatic AFL. There is a better long-term success rate, the same risk of subsequent AF, and fewer secondary effects. (Circulation. 2006;114:1676-1681.)

Key Words: ablation ■ arrhythmia ■ atrial flutter ■ catheter ablation

No data exist assessing medical therapy against radiofrequency catheter ablation (RFA) in patients with only 1 episode of symptomatic atrial flutter (AFL).\(^1\)\(^-\)\(^6\) A randomized prospective study is available comparing antiarrhythmic drugs versus RFA in patients with >2 symptomatic episodes of AFL.\(^7\) That study is weakened by the following: (1) a series not sufficiently powered to provide strong statistical evidence; (2) patient selection based on 2 episodes of symptomatic AFL; (3) the diversity of antiarrhythmic medications tested; and (4) the absence of comparison with amiodarone.\(^7\) All of these limitations must be weighed when treatment options are proposed to patients with a first episode of AFL.\(^2\)\(^8\)\(^-\)\(^11\) Despite the high RFA success rate, the favorable results may be lessened by the presence of atrial fibrillation (AF) in 10% to 50% of patients on...
long-term follow-up. The American College of Cardiology/American Heart Association/European Society of Cardiology guidelines state that a first episode of well-tolerated AFL is classified as an IIA indication with a level of evidence B for RFA treatment. It is a logical extension of the state of the art to establish the value of RFA in AFL versus electric cardioversion followed by amiodarone as an adjunct therapy in a prospective randomized investigation after only 1 episode of symptomatic AFL.

Editorial p 1670
Clinical Perspective p 1681

The Loire-Ardèche-Drôme-Isère-Puy-de-Dôme (LADIP) Trial of Atrial Flutter seeks (1) to prospectively compare safety and efficacy of first-line RFA (group I) versus electric cardioversion and adjunct therapy (group II) for AFL and (2) to establish the long-term risk of subsequent AF in this clinical setting.

Methods

Study Population

The study was approved by the Institutional Research Board of the Saint-Etienne Hospital and by the hospital’s ethics committee in July 2002.

Only patients aged ≥70 years were considered because they represent a higher risk for AF. All patients gave written informed consent. AFL was diagnosed when (1) the surface ECG showed flutter waves that were predominantly negative in leads II, III, and aVF and positive in lead V1, with a regular atrial rate between 240 and 340 bpm; (2) the intracardiac electrogram displayed the following activation sequence: high right atrium then low right atrium, a counterclockwise inferior vena cava–tricuspid isthmus activation sequence followed by left atrial activation established with a electrode; and (3) an isthmus participation in the arrhythmic circuit as demonstrated by entrainment maneuvers (concealed entrainment in the isthmus). All patients had intracardiac recordings to validate the cavotricuspid isthmus circuit, except patients who had a return in sinus rhythm under amiodarone oral treatment. The AFL diagnosis in this subset was based only on the ECG analysis with a typical flutter.

Inclusion Criteria

Eligibility criteria included the following: (1) age ≥70 years; (2) a first documented episode of symptomatic AFL without previous antiarrhythmic treatment; (3) an ECG documenting typical AFL; (4) isthmus participation in the arrhythmic circuit as demonstrated by entrainment maneuvers; and (5) informed patient consent obtained.

Exclusion Criteria

Exclusion criteria were as follows: (1) absence of informed patient consent; (2) amiodarone contraindication; (3) age <70 years; (4) previous antiarrhythmic treatment for AFL; (5) AFL recurrences; (6) inability to catheterize (vena caval clip); (7) poorly tolerated AFL including I/1 AFL; (8) contraindication of antiocoagulation therapy; (9) patients with New York Heart Association class IV heart failure; (10) current or previous treatment with amiodarone; (11) a corrected QT interval of >480 ms or an uncorrected QT interval of >500 ms in the absence of bundle branch block; (12) bradycardia defined as a rate of <50 beats per minute for a period of >1 minute while the patient was awake or second- or third-degree atrioventricular block; and (13) any condition that would make survival for 1 year unlikely.

Over a period of 39 months (October 2002 to February 2006), 104 consecutive patients (aged 78±5 years; 20 women) with AFL were considered eligible, with 52 patients in group I (78±5 years) and 52 patients in group II (78±5 years) (P=0.5).

Baseline Evaluation and Data Collection

Patients were routinely admitted at least 2 days before the inclusion for baseline evaluation. Heart rate and rhythm were monitored during this period by telemetry. Patients were placed on oral or subcutaneous anticoagulants for at least 72 hours before the procedure. In the subset of patients without anticoagulation for at least 3 weeks, transthoracic echocardiography ruled out possible atrial thrombi, and transthoracic echocardiography evaluated cardiac structure and function.

AFL: Radiofrequency Group

Electrophysiological study and catheter ablation were performed by a standard method as described elsewhere. Two ablation catheters could be used for RFA: (1) an 8F quadrupolar deflectable catheter with an 8-mm-tip electrode (Boston EP Technologies, San Jose, Calif) and (2) a irrigated 5-mm-tip thermocouple catheter (Thermocoool F curve, Cordis Biosense Webster, Diamond Bar, Calif) with a temperature-controlled RFA delivery at a power limit of 40 W and a target temperature of 45°C to 50°C applied for 60 seconds at each point. Procedure end point was defined as a complete bidirectional isthmus block according to the combined methods detailed elsewhere.

AFL: Sinus Restoration Group

Persistent AFL was defined as non–self-terminating arrhythmia requiring electric reduction to obtain sinus rhythm. Patients randomly assigned to cardioversion underwent an attempt at electric intracardiac stimulation (overdriving) after right cavotricuspid isthmus AFL validation. If the intracardiac stimulation failed to restore the sinus rhythm, an external or internal cardioversion was applied. A loading dose of 400 mg of amiodarone was given daily for 4 weeks and at least 7 days before sinus rhythm restoration. Amiodarone was lowered to 200 mg daily after this loading period. At least 72 hours before and for 4 weeks after electric cardioversion, patients received acenocoumarol (target international normalized ratio, 2 to 3). If sinus rhythm was present at 1 month, the oral anticoagulant could be changed to aspirin (80 to 300 mg daily) in patients aged <75 years if they had AFL without underlying cardiac disease or stroke risk factors. Other patients received oral anticoagulant therapy.

Follow-Up

Patients were seen in the outpatient department 1, 3, 6, 12, and 18 months after randomization and at the end of the study. At each visit, arrhythmic or cardiovascular events were recorded, and a 12-lead ECG was obtained. Follow-up was continued to document additional end points beyond the initial end point. Cumulative risk of AFL and AF was determined by outpatient follow-up on the basis of recurring symptoms or palpitations and ECG and Holter monitoring. Holter monitoring was performed for 7 days. These analyses were performed by an event recorder, R-Test Evolution (RTE) (Novacor, Rueil Malmaison, France), placed on the patient with 2 electrodes. The RTE event recorder performed a continuous ECG analysis combined with automatic storage of abnormal events detected in a 20-minute solid state memory with autonomy of up to 7 days. In addition, the patient could trigger the Holter manually. The RTE was programmed to recognize 10 types of arrhythmia as events and 1 category of ischemic event. The patients were instructed to report any clinical abnormality that would have occurred during the recording. They were taught to note the description and the true occurrence of any clinical symptom. Supraventricular events (AFL, AF, and atrial tachycardia) were considered symptomatic if there was a temporal correspondence between the symptoms described in the patient logbook and the occurrence of the supraventricular arrhythmia in the recording. All recordings were analyzed by 2 separate observers and a third observer in case of discrepancy.

Statistical Analysis

The baseline characteristics of patients were examined with either the Fisher exact test for categorical variables or a t test. The
Baseline Population Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RFA Group (n=52)</th>
<th>Amiodarone Group (n=51)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>78.5±5</td>
<td>78±5</td>
<td>0.5</td>
</tr>
<tr>
<td>Gender (% women)</td>
<td>11/52 (21%)</td>
<td>9/51 (17.6%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>30/52 (58%)</td>
<td>33/51 (65%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36/52 (69%)</td>
<td>34/51 (67%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10/52 (19%)</td>
<td>11/51 (21.6%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>15/52 (29%)</td>
<td>19/51 (37%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Tobacco</td>
<td>22/52 (42.3%)</td>
<td>25/51 (49%)</td>
<td>0.7</td>
</tr>
<tr>
<td>History of prior AF</td>
<td>14/52 (27%)</td>
<td>11/51 (21.6%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Left atrial systolic diameter, mm</td>
<td>43±7</td>
<td>43±6</td>
<td>0.7</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>56±14</td>
<td>54±14</td>
<td>0.5</td>
</tr>
<tr>
<td>Systolic pulmonary pressure, mm Hg</td>
<td>35±12</td>
<td>34±12</td>
<td>0.7</td>
</tr>
<tr>
<td>Long-term follow-up agent Aspirin</td>
<td>25/52 (48%)</td>
<td>14/51 (27.5%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Oral anticoagulant agent</td>
<td>27/52 (52%)</td>
<td>37/51 (72.5%)</td>
<td></td>
</tr>
</tbody>
</table>

differences among groups were analyzed by ANOVA. Summary values are reported as mean±SD. All reported levels of significance are 2-sided. A probability value of $P<0.05$ was accepted as statistically significant. The primary end point was time to recurrence of AFL confirmed by ECG. The secondary end point was time to first occurrence of AF confirmed by ECG. Only episodes lasting $>10$ minutes were considered clinically significant. Episodes lasting 1 minute to 10 minutes were quantified. The primary analysis was an intention-to-treat comparison of the time to AFL recurrence. For all time-to-event analyses, rates were estimated by the Kaplan-Meier method and were compared by the log-rank test. Patient data were censored at the time of last contact, withdrawal from the study, or time of death. Symptomatic and asymptomatic episodes of AF were recorded. A data and safety monitoring board reviewed the study results. It was estimated that the enrollment of 88 patients with symptomatic AFL would be necessary to detect a reduction of 60% in flutter recurrence, with 80% power, in the RFA group at 1 year with a 2-sided $\alpha$ level of 0.05 and a 5% loss to follow-up in this elderly population.

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

Results

Study Population

Patient characteristics are summarized in the Table. Sixty-four patients (61.5%) had structural heart disease. Structural heart disease included 24 cases of ischemic cardiomyopathy (prior bypass surgery in 6), 15 of dilated cardiomyopathy, 7 of hypertrophic cardiomyopathy, 4 of right ventricular dysfunction due to pulmonary hypertension, and 14 of valvular heart diseases: mitral regurgitation in 10 patients, moderate aortic stenosis in 2 patients, and aortic prosthesis in 2 cases. Before inclusion, 25 patients had a history of AF (24%). At randomization, all patients were in AFL and were symptomatic. Symptoms were as follows: heart failure in 56 patients, angina pectoris in 10, both in 5, palpitations in 18, dyspnea in 12, presyncope in 2, and stroke in 1. All patients had a confirmed AFL in group I, and 51 of 52 had a confirmed AFL in group II (98%). This last group II patient was diagnosed with a left reentrant atrial tachycardia, and the patient was excluded from the study.

Procedures

RFA Results

Bidirectional block was obtained in 100% of patients (52 of 52) with a mean RF application time of 12.8±13 minutes and mean fluoroscopic time of 12±13 minutes. There were no procedure-related complications.

Conversion to Sinus Rhythm

Flutter conversion to sinus rhythm was obtained in all patients (51 of 51): 12 at the initiation of amiodarone oral treatment, 17 by intracardiac atrial overdriving pacing, 10 by internal direct cardioversion, and 12 by external direct cardioversion.

Follow-Up

After a mean follow-up of 13±6 months, AFL recurred in 2 of 52 patients (3.8%) in group I and in 15 of 51 patients (29.5%) of group II ($P<0.0001$) (Figure 1). In group I, 1 patient required a second, successful ablation, and the other asymptomatic patient refused the additional procedure. All patients with a recurrence in group II were successfully treated by RFA. The occurrence of significant symptomatic or asymptomatic AF beyond 10 minutes did not differ between group I (25%) and group II (18%) ($P=0.3$) (Figure 2). The occurrence of significant symptomatic AF was 8% in group I and 8% in group II at 1 year. At the end of the study, 3 patients were in chronic AF (2 in group I versus 1 in group II; $P=NS$), and 3 patients were in AFL rhythm (1 in group I versus 2 in group II; $P=NS$). Sinus rhythm was documented in the rest of the population. When all AF episodes were taken into account, including those asymptomatic <10 minutes and documented by the RTE, the 2 groups did not differ significantly, with 29% of patients in group I and 20% episodes in group II ($P=0.4$). The mean duration of recordings (hours) with the RTE was 140±60, 150±40, 160±35, 140±45, and 150±50 at 1, 3, 6, 12, 18 months, respectively. Because of the occurrence of AF, 4 patients of group I were treated with amiodarone and 2 patients with flecainide. One patient with ischemic cardiomyopathy in the RFA group needed an amiodarone treatment for ventricular tachycardia.
The only significant predictor of AF identified after the first episode of AFL was a previous episode of AF ($P=0.0034$).

**Major Clinical Events**

During the course of the study, 11% (n = 6) assigned to group I died compared with 16% (n = 8) assigned to group II ($P=0.7$). The cause of death was noncardiovascular in 8 patients (4 in each group: 3 died of cancer, 2 of acute infectious respiratory disease, 1 of multisisceral failure, 1 of digestive occlusion, and 1 of septic shock). Death was due to a vascular cause in 2 patients assigned to RFA: refractory heart failure in 1 and sudden death in 1 patient with severe ischemic myocardial dysrythmia (left ventricular ejection fraction = 20%) 9 months after the ablation. In the amiodarone group, cause of death was known in 2 patients, with massive pulmonary embolism in 1 patient and during coronary artery bypass graft surgery in the other. In 2 elderly patients of group II, the cause of death was unknown. Five major clinical events occurred in group II: hypothyroidism in 2, hyperthyroidism in 1, and symptomatic sick sinus syndrome in 2. In these 5 patients, amiodarone was discontinued. No related procedural complication occurred in group I ($P=0.03$).

**Discussion**

**Major Findings**

This randomized study showed that (1) RFA of AFL yields results that are superior to conversion to sinus rhythm plus amiodarone treatment after the first episode of symptomatic AFL with a lower risk of secondary effects, and (2) the risk of a subsequent AF episode ($\geq 10$ minutes) after RFA of AFL is equivalent to that in the amiodarone treatment group after a first episode of AFL.

**AFL Treatments**

The results of this prospective study, the largest to date in this clinical setting, show that RFA is more effective than amiodarone in preventing the recurrence of AFL after a first symptomatic episode. The difference in efficacy is striking; the percentage of recurrence of flutter in the amiodarone group agrees with the results obtained with this drug in patients with AF ($\approx 30\%$), whereas the number of recurrences in the RFA group is the same as that reported after cavitricuspid isthmus bidirectional block validation ($< 5\%$). The percentage of recurrence of AFL after a first episode is not well known because of the lack of evaluation of medical therapy versus placebo in a large AFL population. Crijns et al reported that the percentages of patients in sinus rhythm after a single cardioversion, without prophylactic antiarrhythmic drugs, were 53%, 47%, and 42% after 0.5, 1, and 5 years, respectively, in a population of 50 consecutive patients. The number of recurrences under amiodarone in our study (29.5%) confirmed the notion that AFL recurrence is not as high as expected after a first episode. Recently, Elesber et al reported their experience of atrial arrhythmia relapse after cardioversion of new-onset versus recurrent AFL. At 1 year of follow-up, 63% of the patients in the new-onset AFL group maintained normal sinus rhythm despite the lower use of antiarrhythmic medication. By contrast, Natale et al reported 93% of AFL recurrence under antiarrhythmic therapy after sinus rhythm restoration, but patients were included after a second episode of AFL. Our findings indicate that RFA warrants consideration as first-line therapy after a first symptomatic episode of AFL. Moreover, RFA was well tolerated without serious adverse events despite the older age of our population (78 years). By contrast, we observed 10% of side effects with amiodarone at 12 months. When the superiority of RFA in term of AFL recurrence is disregarded, the theoretical advantage of amiodarone in terms of noninvasive versus invasive treatment is lessened by the risk of significantly more long-term secondary effects.

**Impact of RFA and Amiodarone on Occurrence of AF After a First AFL Episode**

Even though AFL RFA terminates the arrhythmia and prevents its recurrence, its influence on the progression of the atrial disease is unknown after a first AFL episode. As a result, the occurrence of AF because of a common substrate is frequent on long-term follow-up after RFA. The percentage of symptomatic significant AF episodes seems to be lower after a first or a pure AFL episode, at close to 10%, but was likely underestimated in several published studies because of the asymptomatic and paroxysmal forms. The rate of symptomatic significant AF is close to 10% at 1 year, and the rate of overall symptomatic or asymptomatic significant AF episodes is close to 25% in our study. These results are in agreement with those reported by Elesber et al after cardioversion of a first pure AFL episode: 11% of symptomatic AF occurred at 1 year in 78 patients. Despite the absence of knowledge concerning the impact of RFA on atrial remodeling after AFL ablation, our study demonstrates that the occurrence of symptomatic or asymptomatic significant episodes of AF ($\geq 10$ minutes) between patients assigned to RFA or amiodarone did not differ significantly. This finding is of clinical value for considering RFA as first-choice treatment after an episode of AFL. Despite its high efficacy compared with the other antiarrhythmic drugs, amiodarone did not reduce the risk of subsequent AF in patients with AFL, supporting the notion that 20% to 27% of our patients had had a previous episode of AF. Moreover, maintenance of long-term follow-up sinus rhythm is demonstrated to be of
clinical value because of the correlation with a lower mortality compared with patients with AFL and/or AF relapses.

Implications of the Study
This study is the first to demonstrate the superiority of RFA compared with amiodarone for preventing AFL recurrence after a first episode of symptomatic AFL. As expected, the risk of AF is not lower in either group (Figure 2). Despite a trend toward a higher rate of AF in the subset of patients with a history of AF treated with RFA, the curves are similar in patients with lone AFL (Figure 3). The strategy of RFA first-line therapy should be recommended in light of our results, especially when the AFL is isolated without a previous documented AF episode.

Limitations
Only patients older than 70 years were included, and therefore the mean age of the study population was high (78 years). Therefore, the results of our study cannot be transferred per se to other (and younger) patient populations. This age inclusion criterion was chosen because we considered that patients aged ≥70 years represented a high-risk AF population,14 and we wanted to test the impact of RFA on the risk of subsequent AF.

Determining the economic impact of catheter ablation on total healthcare costs would have been of clinical value, but our study was not designed to evaluate this, and further studies are needed to clarify this point.

Finally, it can be argued that oral amiodarone treatment might not be efficacious in the first days, and we cannot exclude the fact that the long-term efficacy of ablation and amiodarone could have been similar if intravenous amiodarone was used. However, only 2 patients had a recurrence during the first week (day 5 in the first patient and day 7 in the second), and the statistical significance between the 2 groups was unchanged whether or not those 2 patients were included in the analysis.

Conclusions
RFA should be considered as first-choice therapy even after the first episode of symptomatic AFL. RFA is associated with fewer secondary effects and offers a higher long-term success rate than the more conventional amiodarone treatment.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

Medical therapy for the common type of atrial flutter often fails to adequately control the arrhythmia and can be associated with bradyarrhythmias and other troublesome side effects, particularly in the elderly. Catheter ablation can be effective but is generally considered only after drug therapy has failed, and some patients go on to develop atrial fibrillation despite successful ablation of flutter. Moreover, medical therapy has not previously been compared with catheter ablation after a first episode of symptomatic atrial flutter, although the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines provide a IIa indication, level of evidence B, in these patients. We compared catheter ablation with electric cardioversion followed by long-term amiodarone therapy in a prospective randomized study in elderly patients. Compared with medical therapy with amiodarone, catheter ablation was followed by fewer recurrences of atrial flutter, a similar risk of subsequent atrial fibrillation, and fewer antiarrhythmic drug side effects. These findings support the use of catheter ablation as a first-line therapy, even after the first episode of symptomatic atrial flutter, in elderly patients.

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