Use of Irbesartan to Maintain Sinus Rhythm in Patients With Long-Lasting Persistent Atrial Fibrillation

A Prospective and Randomized Study

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Background—Data from studies of angiotensin-converting enzyme inhibitors provide evidence that the renin-angiotensin-aldosterone system plays a role as a mediator of atrial remodeling in atrial fibrillation. The present study has evaluated the effect of treatment with the angiotensin I type 1 receptor blocker irbesartan on maintaining sinus rhythm after conversion from persistent atrial fibrillation.

Methods and Results—To be included in the present study, patients must have had an episode of persistent atrial fibrillation for >7 days. The patients were then randomized and scheduled for electrical cardioversion. Two groups of patients were compared: Group I was treated with amiodarone, and group II was treated with amiodarone plus irbesartan. The primary end point was the length of time to a first recurrence of atrial fibrillation. From a total of 186 patients assessed in the study, 154 were analyzed with the use of intention-to-treat analysis. Seventy-five patients were randomly allocated to group I and 79 to group II. After 2 months of follow-up in the intention-to-treat analysis, the group treated with irbesartan had fewer patients with recurrent atrial fibrillation (Kaplan-Meier analysis, 84.79% versus 63.16%, P=0.008). The Kaplan-Meier analysis of time to first recurrence during the follow-up period (median time, 254 days [range, 60 to 710]) also showed that patients treated with irbesartan had a greater probability of remaining free of atrial fibrillation (79.52% versus 55.91%, P=0.007).

Conclusions—Patients treated with amiodarone plus irbesartan had a lower rate of recurrence of atrial fibrillation than did patients treated with amiodarone alone. (Circulation. 2002;106:331-336.)

Key Words: angiotensin I receptor blockers (such as irbesartan) after cardioversion of persistent atrial fibrillation.

The development of a therapy directed against remodeling (or the confirmation that some available drugs may prevent this remodeling) could mark an important change in the management of these patients. Recent studies performed on animals have shown the possible role of angiotensin II inhibitors for preventing atrial electrical remodeling. However, there is no controlled data on the value of angiotensin-converting enzyme (ACE) inhibitors or angiotensin I type 1 receptor blockers (such as irbesartan) after cardioversion of persistent atrial fibrillation.

The purpose of the present prospective, randomized trial was to test the hypothesis that the incidence of a recurrence of atrial fibrillation after direct-current cardioversion could be influenced by pretreatment with irbesartan plus amiodarone.

Methods

Patients with persistent atrial fibrillation referred to our Arrhythmia Unit for electrical cardioversion were prospectively included. All were outpatients in stable cardiac condition. The patients had had atrial fibrillation continuously for >7 days. A complete study was performed to detect structural heart disease. The local medical ethics committee approved the study protocol. All patients provided informed written consent before they entered the study (Figure 1).

Inclusion and Exclusion Criteria

Patients had to have an episode of persistent atrial fibrillation lasting >7 days. Electrocardiographic confirmation of persistent atrial fibrillation was required at least 3 times. No patient with paroxysmal and self-terminating atrial fibrillation episodes was included. All...
patients were >18 years of age. Patients were excluded from the study on the basis of the following criteria: a left atrium size >6 cm; myocardial infarction during the previous 6 months; unstable angina; NYHA heart failure class IV; need to continue the use of digitalis; cardiac surgery during the previous 3 months; acute reversible condition; significant thyroid, pulmonary, or hepatic disease and/or contraindications to treatment with amiodarone; significant impairment of renal function; pregnancy or fertile female; QT ≥480 ms in the absence of bundle-branch block; bradycardia <50 bpm while the patient was awake; significant alterations of the atrioventricular conduction; sick sinus syndrome; or any other medical condition that, in the opinion of the investigators, could make the patient inappropriate for the study.

Randomization and Follow-Up
We standardized all the components of the pre- and postcardioversion phase. At the first visit to the arrhythmia unit, the patients were randomized for treatment with amiodarone or amiodarone plus irbesartan. Irbesartan was started soon after randomization. Those randomized for treatment with amiodarone or amiodarone plus irbesartan combination. With an alpha level of 0.05 and a test power of 0.80, the resulting sample size was 49 patients for each treatment group. To observe significant differences at 1 year (assuming 50% and 70% of efficacy, respectively), it was necessary to include 77 patients in each group. A risk of loss of patients to follow-up of 1% to 5% was assumed.

Data are expressed as mean±SD for continuous variables, and frequencies were measured for categorical variables. Baseline characteristics were examined for statistical significance for continuous variables by a Student’s t test or the Mann-Whitney U test. The Fisher’s exact test was used for categorical variables. The end points were analyzed on an intention-to-treat basis. The time to first atrial fibrillation recurrence was analyzed with the Kaplan-Meier method and compared with the log-rank test. Hazard ratio and its confidence intervals were estimated using the Cox regression model. We analyzed the recurrence of atrial fibrillation using Cox proportional hazards regression to control for potentially confounding factors. The factors were selected on the basis of a change in the relative risk ≥20%. A probability value of <0.05 was considered significant. The statistical package used was SPSS 10.0 for Windows.

Results
Baseline Characteristics
From a total of 186 consecutive patients referred to the arrhythmia unit of a university hospital for electrical cardioversion because of persistent atrial fibrillation, 159 were finally randomized to participate in the present study. These patients were referred from the 40 cardiologists in our hospitals, which have a total population of 500,000 inhabitants. Twenty-three patients were excluded from this protocol because they did not meet the inclusion/exclusion criteria. Four patients refused to participate. After randomization, 5 patients were withdrawn from analysis because of the withdrawal of their consent for cardioversion. Finally, 154 patients were analyzed. The baseline demographic and clinical characteristics of each group are shown in Table 1. The median duration of atrial fibrillation before randomization was 6 months (range, 1 to 72), with no differences between the groups. The 2 treatment groups were similar with regard to all pretreatment characteristics (as shown in Table 1), except for the percentage of patients with bundle-branch
block, most of them incomplete (QRS width between 100 and 120 ms).

**Therapy**
Seventy-five patients were allocated for treatment with amiodarone and 79 for treatment with amiodarone plus irbesartan. Table 2 lists the percentages of patients taking several concomitant drugs at baseline. Final blood pressure values were not significantly different in patients treated with irbesartan as opposed to those without (group I: 141 ± 8 mm Hg diastolic; group II: 142 ± 18 mm Hg diastolic; \( P = 0.390 \) and 0.360, respectively).

**Pharmacological Conversion After Randomization**
At the time of the scheduled electrical cardioversion, pharmacological conversion was documented in 62 patients, of whom 29 (38.6%) were in the amiodarone group and 33 (42%) were in the amiodarone plus irbesartan group. These patients recovered sinus rhythm at a mean of 28 ± 6 days after randomization, before electrical cardioversion (Table 3). Patients who did not recover sinus rhythm before cardiover-
had had a significantly longer duration of atrial fibrillation before randomization (median: 10 months versus 5 months, \( P = 0.009 \)).

**Electrical Cardioversion**

Direct-current conversion was performed in 92 patients and was successful in 83 (90.2%). By intention-to-treat analysis, electrical cardioversion was unsuccessful in 6 patients treated with amiodarone, and in 3 patients treated with amiodarone plus irbesartan. Electrical cardioversion was ineffective in 5 patients because of complete shock failure (2 in group I and 3 in group II) and in 4 patients because of immediate recurrence of atrial fibrillation after only a few beats of sinus rhythm (all group I).

Patients in the amiodarone group had a mean body weight of 77±12 kg and a mean height of 163±7 cm, required 1.7±1.5 shocks, and had an electrical threshold for effective cardioversion of 267±79 J. Patients in the amiodarone plus irbesartan group had a similar weight and height (77±14 kg and 164±8.8 cm, \( P = 0.470 \) and 0.350, respectively) but a trend to a lower number of shocks and electrical threshold (1.4±1.6 shocks and 258±77 J), although these variables did not reach statistical significance (\( P = 0.314 \) and 0.280, respectively).

**Recurrence of Atrial Fibrillation**

At the 2-month follow-up visit, 26 patients had a recurrence of atrial fibrillation, with a peak incidence during the first week after electrical cardioversion. By intention-to-treat analysis, at 2 months the recurrence rate was lower in group II (7 patients) than group I (19 patients). Kaplan-Meier analysis demonstrated a 2-month probability of 84.79% for maintaining sinus rhythm in patients who received irbesartan, compared with 63.16% in patients who did not (\( P = 0.008 \)).

Multivariate analysis revealed that the use of the angiotensin II receptor antagonist was the only significant variable related to the maintenance of sinus rhythm after cardioversion. The hazard ratio for a recurrence in patients treated with irbesartan was 0.35, reflecting a 65% reduction in the risk of recurrence of atrial fibrillation (relative risk 0.35; 95% CI 0.12 to 0.46; \( P = 0.018 \)). After the Cox proportional model was used, correcting for those variables that could influence the result (eg, the presence of diabetes, bundle-branch block, or duration of atrial fibrillation), the hazard ratio was 0.19, reflecting an 81% reduction (relative risk 0.19; 95% CI 0.04 to 0.86; \( P = 0.031 \)). When the analysis excluded the patients in whom the electrical cardioversion was ineffective, the probability of remaining in sinus rhythm was still significantly

**TABLE 2. Baseline Concomitant Medication Use at the Time of Cardioversion**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Amiodarone</th>
<th>Amiodarone + Irbesartan</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin, %</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>( \beta )-Blockers, %</td>
<td>7</td>
<td>15</td>
<td>0.086</td>
</tr>
<tr>
<td>Calcium-channel blockers, %</td>
<td>5</td>
<td>9</td>
<td>0.308</td>
</tr>
<tr>
<td>Verapamil or diltiazem</td>
<td>5</td>
<td>9</td>
<td>0.308</td>
</tr>
<tr>
<td>Amlodipine or nifedipine</td>
<td>7</td>
<td>7</td>
<td>0.741</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>5</td>
<td>4</td>
<td>0.656</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors, %</td>
<td>22</td>
<td>16</td>
<td>0.191</td>
</tr>
<tr>
<td>Anticoagulant drugs, %</td>
<td>100</td>
<td>100</td>
<td>1</td>
</tr>
</tbody>
</table>

**TABLE 3. Results: Intention-to-Treat Analysis**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Amiodarone</th>
<th>Amiodarone + Irbesartan</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized, n</td>
<td>75</td>
<td>79</td>
<td>1</td>
</tr>
<tr>
<td>Pharmacological conversion</td>
<td>29</td>
<td>33</td>
<td>0.693</td>
</tr>
<tr>
<td>Successful electrical cardioversion, n</td>
<td>37</td>
<td>41</td>
<td>0.270</td>
</tr>
<tr>
<td>Ineffective electrical cardioversion, n</td>
<td>6</td>
<td>3</td>
<td>0.270</td>
</tr>
<tr>
<td>Complete shock failure</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Immediate recurrence</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Joules, mean±SD</td>
<td>267±79</td>
<td>258±77</td>
<td>0.280</td>
</tr>
<tr>
<td>Number of shocks, n</td>
<td>1.7±1.5</td>
<td>1.4±1.6</td>
<td>0.314</td>
</tr>
<tr>
<td>Sinus rhythm at 2 months, n</td>
<td>42</td>
<td>68</td>
<td>0.008</td>
</tr>
<tr>
<td>Sinus rhythm at the end of follow-up, n</td>
<td>39</td>
<td>66</td>
<td>0.007</td>
</tr>
<tr>
<td>Days to recurrence, median±SD</td>
<td>28±81</td>
<td>29.6±46</td>
<td>0.480</td>
</tr>
<tr>
<td>Systolic blood pressure (end follow-up), mm Hg</td>
<td>141±15</td>
<td>142±18</td>
<td>0.390</td>
</tr>
<tr>
<td>Diastolic blood pressure (end follow-up), mm Hg</td>
<td>82±6</td>
<td>82±8</td>
<td>0.360</td>
</tr>
<tr>
<td>Adverse events at the end of follow-up, n</td>
<td>6</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Deaths at the end of follow-up, n</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
higher among the patients in the amiodarone plus irbesartan group.

At the end of the follow-up (median, 254 days [range, 60 to 710]), a total of 22 patients undergoing treatment with amiodarone had a recurrence of atrial fibrillation, as did 9 patients undergoing treatment with amiodarone plus irbesartan (P = 0.007). Figure 2 shows the probability of remaining in sinus rhythm for both treatment groups at the end of the follow-up (55.91% for group I and 79.52% for group II). The most important factor to predict recurrence was the duration of atrial fibrillation before randomization.

There was a trend for irbesartan plus amiodarone to be superior to amiodarone alone in patients with hypertension (RR 0.49; 95% CI 0.11 to 2.06), structural heart disease (RR 0.37; 95% CI 0.09 to 1.5), or atrial fibrillation of >12 months’ duration (RR 0.20; 95% CI 0.024 to 1.76), although it did not reach statistical significance.

### Adverse Events During Follow-Up in Each Intervention Group

One patient suffered sudden death during the course of the study. He was a 51-year-old male treated with amiodarone plus irbesartan. The patient had no organic heart disease or other risk factors, was in NYHA functional class I, and died 21 days after receiving a successful electrical cardioversion to sinus rhythm. Eleven patients were treated for nonfatal major clinical events: 6 in the group treated with amiodarone and 5 in the group treated with amiodarone plus irbesartan. In total, adverse events requiring the discontinuation of amiodarone occurred in 3 patients in group I and in 2 patients in group II. Suspected pulmonary toxicity occurred in 1 female patient. Two months after starting amiodarone, the patient had persistent cough and progressive dyspnea, and after suggestive chest x-ray, amiodarone was discontinued and the symptoms disappeared. One patient had suspected pulmonary thromboembolism 1 week after the cardioversion. One patient had congestive heart failure and bradycardia, and amiodarone treatment was interrupted (this decision was based on patient preference). Three patients had typical atrial flutter and underwent radiofrequency catheter ablation. Two patients required pacemaker implantation because of sick sinus syn-

### Left Atrial Remodeling and Changes in Persistent Atrial Fibrillation

The term atrial electrophysiological remodeling was first used to describe the changes elicited by long-lasting atrial fibrillation promoting maintenance or recurrences. This may play a role in the transition of paroxysmal to chronic atrial fibrillation and in the loss of efficacy of antiarrhythmic drugs or electrical shock in patients with atrial fibrillation of longer duration. As far as electrophysiology is concerned, 2 mechanisms could be involved: The first is the role of abnormal activity occurring inside the pulmonary veins, and the second is the shortening of the refractory period of atrial muscle. Irbesartan could modify both mechanisms, but neither was assessed by electrophysiological approaches in the present study, and they could be the subject of further investigations. Calcium channel blockade could also be beneficial in acute electrical remodeling, and the use of verapamil with or without other antiarrhythmic drugs before cardioversion has been proposed to reduce the risk of recurrence.

### ACE Inhibitors and Arrhythmias

Pedersen et al investigated the effect of trandolapril on the incidence of atrial fibrillation in patients with reduced left ventricular function. Trandolapril reduced the risk of developing atrial fibrillation by 55%. ACE inhibitors could be effective, on the basis of their favorable effects on cardiovascular fibrosis and apoptosis.

The study performed by Nakashima et al demonstrated for the first time that angiotensin II contributes to atrial electrical remodeling. In their study, the shortening of the atrial refractory period during rapid pacing was prevented by treatment with candesartan or captopril but increased by angiotensin II.

Other recent studies have demonstrated the ability of losartan to regress fibrosis in hypertensives with biopsy-proven myocardial fibrosis, independent of its antihypertensive efficacy, suggesting that blockade of the angiotensin II
type 1 receptor is associated with inhibition of collagen type I synthesis and regression of myocardial fibrosis.19

Possible Mechanisms of Efficacy of Irbesartan in the Present Study
Most of the benefit of irbesartan occurred during the first 2 months after conversion. After that, the 2 curves seem to be parallel. This result is similar to some recent studies and points to the importance of the remodeling just after cardioversion.20 Moreover, after categorizing the failures of electrical cardioversion and recurrences, we demonstrated that irbesartan reduced the immediate recurrence of atrial fibrillation (no patient had recurrence during a time window of 1 hour after cardioversion) and the so-called subacute recurrences during the first weeks.21

Although the lowering of blood pressure could be an important part of the mechanism of benefit, there was no statistically significant difference in the present study in blood pressure between the two groups after the follow-up. Irbesartan could prevent or modify atrial remodeling by means of other mechanisms, including: decreasing atrial stretch, lowering end-diastolic left ventricular pressure and subsequently left atrial pressure, preventing atrial fibrosis, modifying the sympathetic tone, or modulating ion currents or refractoriness.

With regard to the percentage of patients in group II treated with β-blockers and/or calcium blockers with cardiac effects, it is not possible to discount that they may have played a role in the benefit because of the drug-to-drug interactions. However, it should also be noted that a large percentage of patients in group I were treated with ACE inhibitors, which also may have had additional benefits in this group.

Limitations of the Study
We cannot definitely exclude the fact that, between scheduled follow-up visits, some of the patients had asymptomatic recurrences of atrial fibrillation that converted spontaneously. However, patients with paroxysmal and self-terminating atrial fibrillation were not included in the present study. Although the study did not include event recorders, we believe that surveillance for recurrence of atrial fibrillation was sufficient for the purposes of the study, namely the development of recurrent persistent atrial fibrillation. Many hypertensive drugs can stimulate angiotensin secretion. Whereas diuretics invariably cause a rise in plasma renin activity, the β-blockers depress renin activity. However, the percentage of patients using diuretics was low and similar in both groups. Also, some vasodilators, such as hydralazine or prazosin, can stimulate the renin-angiotensin system. However, these drugs were not used in the present study. Although combination therapy was superior to amiodarone alone, monotherapy with irbesartan alone was not tested. The success of irbesartan may differ, depending on the degree of atrial remodeling before cardioversion.

Conclusions
Patients treated with amiodarone and irbesartan had a lower 2-month recurrence rate of atrial fibrillation and a longer time to first arrhythmia recurrence. The additional cost of the treatment with amiodarone plus irbesartan is well balanced with the reduction of arrhythmia recurrence.

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References
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