A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH RECURRENT PERSISTENT ATRIAL FIBRILLATION

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ABSTRACT

Background Maintenance of sinus rhythm is the main therapeutic goal in patients with atrial fibrillation. However, recurrences of atrial fibrillation and side effects of antiarrhythmic drugs offset the benefits of sinus rhythm. We hypothesized that ventricular rate control is not inferior to the maintenance of sinus rhythm for the treatment of atrial fibrillation.

Methods We randomly assigned 522 patients who had persistent atrial fibrillation after a previous electrical cardioversion to receive treatment aimed at rate control or rhythm control. Patients in the rate-control group received oral anticoagulant drugs and rate-slowing medication. Patients in the rhythm-control group underwent serial cardioversions and received antiarrhythmic drugs and oral anticoagulant drugs. The endpoint was a composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, implantation of a pacemaker, and severe adverse effects of drugs.

Results After a mean (±SD) of 2.3±0.6 years, 39 percent of the 266 patients in the rhythm-control group had sinus rhythm, as compared with 10 percent of the 256 patients in the rate-control group. The primary endpoint occurred in 44 patients (17.2 percent) in the rate-control group and in 60 (22.6 percent) in the rhythm-control group. The 90 percent (two-sided) upper boundary of the absolute difference in the primary endpoint was 0.4 percent (the prespecified criterion for noninferiority was 10 percent or less). The distribution of the various components of the primary endpoint was similar in the rate-control and rhythm-control groups.

Conclusions Rate control is not inferior to rhythm control for the prevention of death and morbidity from cardiovascular causes and may be appropriate therapy in patients with a recurrence of persistent atrial fibrillation after electrical cardioversion. (N Engl J Med 2002;347:1834-40.)

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With the rate-control strategy, electrical cardioversion was allowed if ventricular rate-controlling drugs were associated with intolerable symptoms or if there was a recurrence of atrial fibrillation (AF) within six months after the start of this regimen, a loading dose of amiodarone was given (600 mg daily for four weeks), and electrical cardioversion was repeated. If patients had intolerable symptoms due to atrial fibrillation (AF) within six months, electrical cardioversion was repeated and sotalol was replaced by flecainide (200 to 300 mg daily) or propafenone (450 to 900 mg daily). If there was a recurrence within six months of therapy with an antiarrhythmic drug, the regimen was continued. Treatment with amiodarone was started out of the hospital. When these drugs were prescribed, the usual specific restrictions were applied.

From four weeks before until four weeks after electrical cardioversion, all patients received acenocoumarol or fenprocoumon (target international normalized ratio [INR], 2.5 to 3.5). If sinus rhythm was present at one month, the oral anticoagulant could be stopped or changed to aspirin (80 to 100 mg daily). Aspirin was also allowed in patients in the rate-control group who were less than 65 years old if they had atrial fibrillation without underlying cardiac disease. Other patients received oral anticoagulant therapy.10-12

End Points
The primary end point was the composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, the need for implantation of a pacemaker, or severe adverse ef-
fected of antiarrhythmic drugs. We recorded all (component) events that occurred between randomization and July 1, 2001, with a maximum of three years of follow-up. All deaths were considered to be due to cardiovascular causes unless an unequivocal noncardiac cause could be identified.

Heart failure was defined as an episode of left or right ventricular failure necessitating hospitalization. Cerebrovascular events had to be diagnosed by a neurologist, and the cause was determined with the use of computed tomography. Peripheral thromboembolism had to be confirmed by a surgeon. Bleeding was recorded as an end point if the hemoglobin value decreased by more than 2 g per liter, if blood transfusion or hospitalization was necessary, or if the bleeding was fatal. Torsade de pointes, unexpected ventricular tachycardia or fibrillation, 1:1 atrioventricular conduction during atrial flutter, third-degree atrioventricular block, the sick sinus syndrome, digitalis intoxication, and drug-induced heart failure were classified as severe adverse effects of antiarrhythmic drugs. A committee of experts who were unaware of the treatment assignments adjudicated all possible end points.

Statistical Analysis

The primary objective was to show the noninferiority of rate control as compared with rhythm control in terms of the incidence of the primary end point. A two-sided 90 percent confidence interval (which provides the same upper limit as the 95 percent one-sided confidence interval) was calculated for the difference between the incidence of the primary end point in the rate-control group and the incidence in the rhythm-control group. The incidence of the primary end point was calculated for all patients, irrespective of whether they actually received the assigned treatment (on the intention-to-treat principle). Noninferiority was considered to be established if the upper boundary of the confidence interval did not exceed 10 percent. We calculated that with a significance level of 5 percent (one-sided), a power of 80 percent, and an assumed 30 percent decrease in the incidence in the rhythm-control group (as compared with rate control), a total of 522 patients (103 in each group) would be required.

Kaplan–Meier estimates were used to determine the occurrence of the primary end point over time. The components of the primary end point are reported as secondary end points. There were no prespecified subgroup analyses. However, the results of post hoc subgroup analyses are presented for descriptive purposes.

**RESULTS**

**Characteristics of the Patients**

A total of 522 patients were enrolled in the study: 256 in the rate-control group and 266 in the rhythm-control group (Table 1). The characteristics of the patients were typical of a population of patients with persistent atrial fibrillation. Ninety percent of the patients in the rate-control group and 91 percent of those in the rhythm-control group had one or more risk factors for stroke. The proportion of patients with hypertension was higher in the rhythm-control group than in the rate-control group (P=0.007). There were no other significant differences in clinical characteristics between the two groups.

**Treatment**

Patients were followed for a mean (±SD) of 2.3±0.6 years. Figure 1 shows the numbers of patients in the two groups and their treatment at the end of follow-up. In the rhythm-control group, 103 patients (39 percent) had sinus rhythm at the end of the study.
(97 patients) or at the time of withdrawal from the study (6 patients); 116 (44 percent) had atrial fibrillation at the end of the study, and 47 (18 percent) had atrial fibrillation but were scheduled for cardioversion (44 patients) or had atrial fibrillation at the time of withdrawal (3 patients). Patients underwent a median of 2 electrical cardioversions (range, 0 to 7). In the rate-control group, 26 patients (10 percent) had sinus rhythm at the end of the study; half of them had undergone electrical cardioversion because of intolerable symptoms and half had undergone spontaneous conversion.

The mean heart rate in the resting state was significantly lower during rhythm control (73±18 beats per minute) than during rate control (82±16 beats per minute); this difference was related to the presence of sinus rhythm (mean heart rate, 66±14 beats per minute) or atrial fibrillation (mean heart rate, 85±17 beats per minute) rather than to the treatment assignment. The number of patients who received oral anticoagulant therapy during follow-up ranged from 246 (96 percent) to 254 (99 percent) in the rate-control group and from 228 (86 percent) to 263 (99 percent) in the rhythm-control group.

Outcome

The primary end point occurred in 44 of the 256 patients in the rate-control group (17.2 percent) and in 60 of the 266 patients in the rhythm-control group (22.6 percent) (Table 2). The absolute difference of −5.4 percent represents a trend in favor of rate control. The 90 percent confidence interval of −11.0 to 0.4 percent confirmed that rate control met the criterion for noninferiority (absolute difference, 10 percent or less) and approached that for superiority. The noninferiority of rate control as compared with rhythm control was confirmed in an ancillary analysis with statistical adjustment for the unbalanced distribution of patients with hypertension between the two groups; the adjusted absolute difference was −4.2 percent, and the corresponding 90 percent confidence interval was −10.0 to 1.5 percent.

Kaplan–Meier estimates of the first occurrence of the primary end point over time are shown in Figure 2. The hazard ratio for the risk of the primary end point in the rhythm-control group, as compared with the rhythm-control group, was 0.73 (90 percent confidence interval, 0.53 to 1.01; P=0.11). Table 2 shows the incidence of the components of the primary end point. The rate of death from cardiovascular causes was similar in the two groups: 7.0 percent in the rate-control group and 6.8 percent in the rhythm-control group. Thromboembolism (stroke) in six patients in the rhythm-control group and three patients in the rhythm-control group, heart failure in four patients in the rate-control group and one patient in the rhythm-control group, and thromboembolism (stroke) in six patients in the rhythm-control group. Eight patients in each group died suddenly; 2 of the 16 were taking amiodarone, 1 was taking sotalol, and 1 was taking flecainide. At the time of the occurrence of the primary end point, 29 patients (28 percent) had sinus rhythm, and 75 patients (72 percent) had atrial fibrillation.

Thromboembolic complications occurred in 35 patients, all of whom had risk factors for stroke. Thromboembolism was more frequent in the rhythm-control group than in the rate-control group. Six patients, all in the rhythm-control group, had thromboembolic complications after the cessation of oral anticoagulant therapy; five of them had sinus rhythm. Twenty-three patients had thromboembolic complications while re-

<table>
<thead>
<tr>
<th>END POINT</th>
<th>RATE CONTROL (N=256)</th>
<th>RHYTHM CONTROL (N=266)</th>
<th>ABSOLUTE DIFFERENCE (90% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite end point</td>
<td>44 (17.2)</td>
<td>60 (22.6)</td>
<td>−5.4 (−11.0 to 0.4)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>18 (7.0)</td>
<td>18 (6.8)</td>
<td>0.2 (−3.4 to 3.9)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>9 (3.5)</td>
<td>12 (4.5)</td>
<td>−1.0 (−3.8 to 1.8)</td>
</tr>
<tr>
<td>Thromboembolic complications</td>
<td>14 (5.5)</td>
<td>21 (7.9)</td>
<td>−2.4 (−6.0 to 1.2)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>12 (4.7)</td>
<td>9 (3.4)</td>
<td>1.3 (−1.5 to 4.1)</td>
</tr>
<tr>
<td>Severe adverse effects of antiarrhythmic drugs</td>
<td>2 (0.8)</td>
<td>12 (4.5)</td>
<td>−3.7 (−6.0 to −1.4)</td>
</tr>
<tr>
<td>Implantation of a pacemaker</td>
<td>3 (1.2)</td>
<td>8 (3.0)</td>
<td>−1.8 (−3.9 to 0.2)</td>
</tr>
</tbody>
</table>

*Some patients had more than one end point.

†CI denotes confidence interval.
Receiving inadequate anticoagulant therapy (INR, less than 2.0). The majority of patients with thromboembolic events (73 percent) had atrial fibrillation at the time of the event. Twenty of the 21 episodes of bleeding occurred during oral anticoagulant therapy. In 17 patients, bleeding occurred while the INR was greater than 3.

Severe adverse effects of antiarrhythmic drugs occurred mainly in the rhythm-control group: seven patients had the sick sinus syndrome or atrioventricular block; three had torsade de pointes or ventricular fibrillation; one had rapid, hemodynamically significant atrioventricular conduction during flutter; and one had drug-induced heart failure. The four patients who died suddenly while taking antiarrhythmic drugs were not counted separately, since it could not be proved that the death was related to the drug. In the rate-control group, there were only two patients with nonlethal digitalis intoxication. A pacemaker was implanted in three patients in the rate-control group (after atrioventricular-node ablation) and in eight patients in the rhythm-control group (for bradycardia during atrial fibrillation in one, after atrioventricular-node ablation in two, and for the sick sinus syndrome unmasked by cardioversion in five).

Table 3 shows the incidence of the primary end point according to sex and blood-pressure status. Among women and patients with hypertension, the incidence of the primary end point was higher with rhythm control than with rate control.

Post hoc analysis showed that in the rhythm-control group, the incidence of the components of the primary end point did not differ significantly according to whether the patient had sinus rhythm or atrial fibrillation at the end of follow-up. In both the rate-control group and the rhythm-control group, a primary end point occurred in 5 of 18 patients with atrial flutter (27.8 percent).

**DISCUSSION**

Our results show that rate control is an acceptable alternative to rhythm control in patients with recurrent persistent atrial fibrillation. The two strategies were associated with a considerable but similar number of major cardiovascular events. However, events were particularly frequent with rhythm control, especially in patients who had hypertension and in women. These findings substantiate the noninferiority of rate control. Rate control should therefore be considered much earlier in the course of managing recurrent persistent atrial fibrillation than is with current approaches.

Why was rhythm control not associated with fewer cardiovascular events than rate control? At the end of follow-up, only 39 percent of the patients in the rhythm-control group had sinus rhythm, despite a careful treatment protocol. Obviously, safer and more effective methods of maintaining sinus rhythm are needed, and such methods may help reduce morbidity in the future. However, effective preservation of sinus rhythm does not preclude the occurrence of cardiovascular events. We found that among the patients treated with rhythm control, morbidity and mortality were
similar whether sinus rhythm was maintained or atrial fibrillation recurred. This finding suggests that the cardiovascular risk is not reduced with rhythm control even when sinus rhythm is maintained.

Several factors may account for the lack of a reduction in risk with rhythm control. First, although sinus rhythm is believed to prevent tachycardia-induced cardiomyopathy and heart failure, effective rate control may also prevent heart failure, thereby offsetting the relative benefits of rhythm control.15,16 This is demonstrated by our finding that the incidence of heart failure was similar with the two treatments.

Second, although maintaining sinus rhythm is generally believed to reduce the risk of stroke, patients with risk factors may have a stroke after the cessation of anticoagulant therapy, despite the maintenance of sinus rhythm.3,11 Our data strongly support this notion. The study protocol allowed the cessation of anticoagulant therapy after sinus rhythm had been maintained for at least one month. Six thromboembolic events (17.1 percent of the total number) occurred after the cessation of anticoagulant therapy, and in all but one case, the patient was still in sinus rhythm at the time of the event.

Third, rhythm control may reduce the risk of bleeding related to the discontinuation of anticoagulant therapy. In our study, even though anticoagulant therapy could be stopped once long-term sinus rhythm had been achieved, the rate of use of such therapy was similar in the two treatment groups, and consequently, the incidence of bleeding was similar. Our findings also suggest that almost all patients with persistent atrial fibrillation have one or more risk factors for stroke. Therefore, anticoagulant therapy can be stopped only rarely. Consequently, the risk of bleeding will not be reduced by rhythm control.

Fourth, with rhythm control but not rate control, electrical cardioversion, especially in combination with the use of prophylactic drugs, may unmask the sick sinus syndrome or atrioventricular conduction disturbances and lead to the implantation of a pacemaker, as it did in five patients in our rhythm-control group. Likewise, the use of prophylactic antiarrhythmic drugs contributed significantly to the incidence of major cardiac end points in the rhythm-control group but not in the rate-control group.

Thromboembolic events were frequent in our study because of the high prevalence of risk factors for stroke.10,11,14 However, the number of events was surprisingly high, since an effort was made to maintain the INR in the range of 2.5 and 3.5, which is even higher than the currently recommended target range of 2.0 to 3.0.3 Most strokes occurred at an INR below 2.0. Likewise, most bleeding episodes occurred at an INR that exceeded 3.0. These results demonstrate that intermittently inadequate or excessive levels of anticoagulant therapy may be harmful in a substantial number of patients with atrial fibrillation.

There were remarkable differences in the incidence of primary end-point events when the results were analyzed according to blood-pressure status or sex (Table 3). Hypertension and female sex were associated with a higher incidence of an event in the rhythm-control group. These findings suggest that rhythm-control treatment with the use of repeated cardioversion should not be encouraged in patients with hypertension or in women with recurrent persistent atrial fibrillation and that atrial fibrillation can be accepted as the predominant rhythm early in the course of treatment. Since these subgroup analyses were not prespecified, however, the results are useful only for generating hypotheses.

Is there still a place for rhythm control? It should be noted that we included only patients who had a recurrence of atrial fibrillation after at least one previous cardioversion. Therefore, our conclusion that rate control is an acceptable alternative to rhythm control does not necessarily apply to patients seen for the first time with atrial fibrillation. In particular, rhythm control may be indicated in patients with serious symptoms of atrial fibrillation.

**Table 3. Incidence of the Primary End Point According to Sex and Blood-Pressure Status.**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>RATE CONTROL</th>
<th>RHYTHM CONTROL</th>
<th>ABSOLUTE DIFFERENCE (90% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>44/256 (17.2)</td>
<td>60/266 (22.6)</td>
<td>−5.4 (−11.0 to 0.4)</td>
</tr>
<tr>
<td>Men</td>
<td>34/161 (21.1)</td>
<td>29/169 (17.2)</td>
<td>3.9 (−3.2 to 11.1)</td>
</tr>
<tr>
<td>Women</td>
<td>10/95 (10.5)</td>
<td>31/97 (32.0)</td>
<td>−21.5 (−30.8 to −12.1)</td>
</tr>
<tr>
<td>Normotensive patients</td>
<td>25/146 (17.1)</td>
<td>15/120 (12.5)</td>
<td>4.6 (−2.5 to 11.8)</td>
</tr>
<tr>
<td>Hypertensive patients</td>
<td>19/110 (17.3)</td>
<td>45/146 (30.8)</td>
<td>−13.5 (−22.2 to −4.9)</td>
</tr>
</tbody>
</table>

*CI denotes confidence interval.
fibrillation. Rather than rate control, cardioversion in combination with prophylactic drugs is one of the first options in such patients.

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APPENDIX

The following persons participated in the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study (the numbers in parentheses indicate the numbers of patients enrolled): University Hospital, Groningen — H. Crijs, I. Van Gelder, V. Hagensen, T. Kingma (74); St. Antonius Hospital, Nieuwegein — J. Lindemoen, J. Kingma (36); Hospital Midden Twente, Hengelo — S. Saad (34); Rejaunt Hospital, Arnhem — H. Bosker (31); Medisch Spectrum Twente Hospital, Enschede — A. Timmermans (31); Tweedehouw Hospital, Almelo — J. Darmanata, G. Linsen, B. de Rosse (30); Ignatius Hospital, Breda — R. Wielinga (24); Sula Hospital, Zoolle — A. van ‘t Hof, M. Vet (24); Oosterschelde Hospital, Goes — E. Bruyns, A. Liem (22); Free University Medical Center, Amsterdam — M. Miilcokur, O. Kamp (21); Stichting Deventer Hospitals, Deventer — E. Badings, D. Lok (20); Canisius Wilhelmina Hospital, Nijmegen — D. Hertberger (19); St. Lucas Hospital, Winschoten — T. Bouwmeester, A. van der Galien (18); Catharina Hospital, Eindhoven — A. Meyer, F. Bracke (11); Schoper Hospital, Emmen — M. Nagelsmit (11); Onze Lieve Vrouwe Hospital, Amsterdam — T. Slagboom (9); Hospital Hilversum, Hilversum — H. Crijns (10); Antonius Hospital, Sneek — B. Cernobolsky (9); Reiniere de Grenaf Hospital, Delft — D. Roovers, A. Bethagen (8); Ziekenhuis Medisch Centrum, Den Bosch — H. Dohmen (8); Marius Hospital, Groningen — P. Breuls (5); Ikazia Hospital, Rotterdam — J. Kerker (5); Hospital Rijnsburg, Stadskanaal — L. van Vijk (3); St. Elisabeth Hospital, Tilburg — W. Pastoeuning, N. Holberda (3); Albert Schweitzer Hospital, Zwijndrecht — A. Herweijer (3); Deltzussche Hospital, Delfzijl — J. Spanjaard (3); University Hospital, Nijmegen — F. Verheugt (2); Hospital deZonneberg, Dordrecht — A. Hagoort-Kok, E. van den Toren (2); Schauden Hospital, Schiedam — H. Werner, H. Spurrenburg (2); Policy Advisory Board — H. Wellens, K. Lie, N. Van Hemel; End Point Committee — J. Van Der Meer, J. Viersma, M. Van De Linde, A. De Jager; Steering Committee — H. Crijs, I. Van Gelder, H. Bosker, O. Kamp, J. Kingma, J. Tijssen.

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