

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 end point 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 (\pm 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 end point 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 end point was 0.4 percent (the prespecified criterion for noninferiority was 10 percent or less). The distribution of the various components of the primary end point 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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ATRIAL fibrillation is not a benign condition.^{1,2} For many clinicians, maintenance of sinus rhythm is the main therapeutic goal. In patients with persistent atrial fibrillation, repeated electrical cardioversion and prophylactic antiarrhythmic drugs are used to maintain sinus rhythm.³ However, frequent recurrences of atrial fibrillation and adverse effects of drugs decrease the potential benefits of electrical cardioversion.⁴⁻⁶ Also, the beneficial effects of rhythm control may be nullified by life-threatening cardiovascular events. Such events may be related not to the rhythm but, rather, to underlying cardiovascular abnormalities.⁴ Since the rhythm is not the main determinant of the prognosis, it is questionable whether rhythm control is better than ventricular rate control.^{7,8} We performed a randomized, prospective study to compare the long-term effects of rate control with those of rhythm control, using electrical cardioversion for persistent atrial fibrillation. Our hypothesis was that rate control is not inferior to rhythm control for the treatment of persistent atrial fibrillation.

METHODS

Study Design

Thirty-one centers in the Netherlands participated in the study. The institutional review boards at each participating hospital approved the study protocol, and all patients gave written informed consent. The study was conducted from June 1, 1998, until July 1, 2001. The follow-up period was at least two years. The study design is shown in Figure 1.

Only patients with recurrent persistent atrial fibrillation or flutter, in whom oral anticoagulation was not contraindicated, were included. Persistent atrial fibrillation and flutter were defined as non-self-terminating arrhythmia requiring electrical cardioversion to obtain sinus rhythm.^{3,9} Atrial flutter was defined as a supraventricular tachycardia with a regular atrial rhythm between 240 and 430 beats per minute. Patients were excluded if arrhythmia had lasted longer than one year. In addition to the usual exclusion criteria for studies of

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*The participants in the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group are listed in the Appendix.

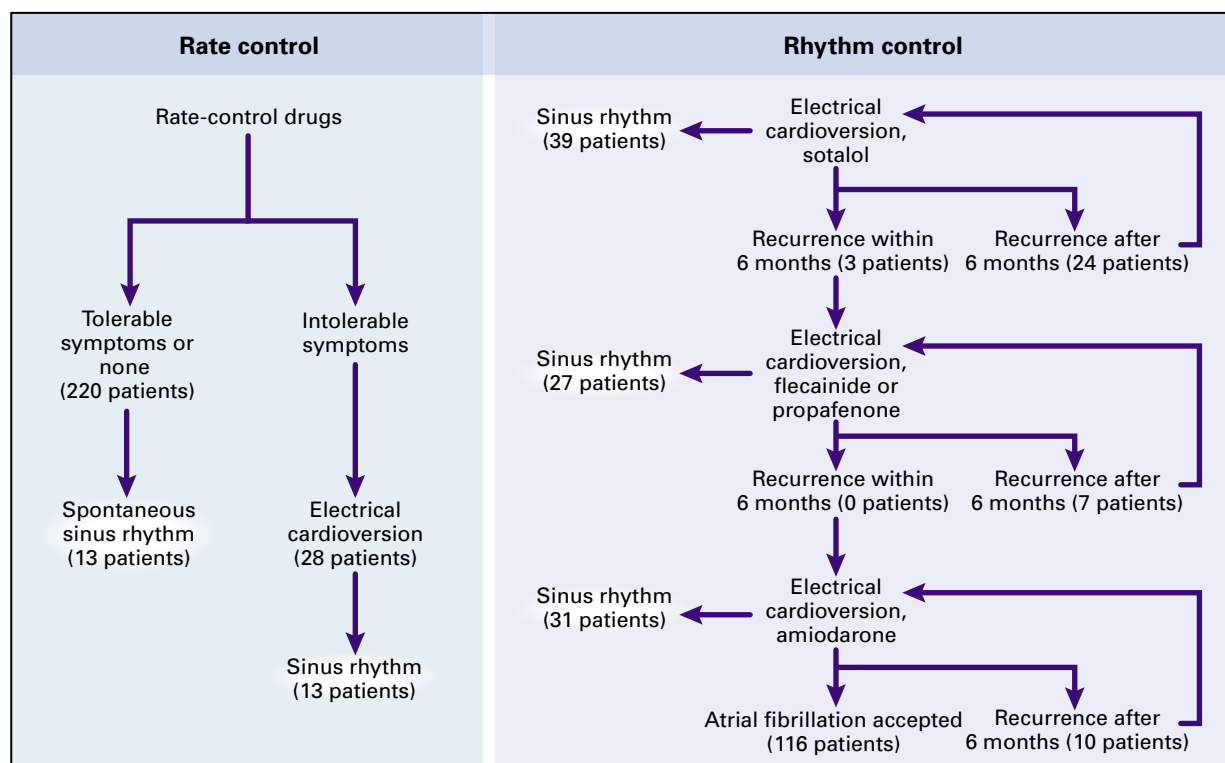


Figure 1. Study Design.

With the rate-control strategy, electrical cardioversion was allowed if ventricular rate-controlling drugs were associated with intolerable symptoms. The numbers in parentheses indicate the numbers of patients at the end of follow-up. Eight patients in the rate-control group and nine in the rhythm-control group withdrew from the study early. In the rhythm-control group, a total of 44 patients had atrial fibrillation at the end of follow-up, including 3 with a recurrence within six months. These patients were scheduled for a new cardioversion. Atrial fibrillation was accepted if there was no response to the last cardioversion or if there was a recurrence within six months.

electrical cardioversion, we also excluded patients with New York Heart Association class IV heart failure, current or previous treatment with amiodarone, or a pacemaker. Patients were required to have undergone one electrical cardioversion during the previous two years, with a maximum of two.

Patients were seen in the outpatient department 1, 3, 6, 12, and 24 months after randomization and at the end of the study. At each visit, any cardiovascular events were recorded, and a 12-lead electrocardiogram was obtained. All events had to be reported on a special form. After documentation of one (nonfatal) end point, follow-up was continued to document additional end points.

Rate control was achieved with the administration of digitalis, a nondihydropyridine calcium-channel blocker, and a beta-blocker, alone or in combination. The target was a resting heart rate of less than 100 beats per minute (monitored with a 12-lead resting electrocardiogram). If patients had intolerable symptoms due to atrial fibrillation, unacceptable adverse effects of the atrioventricular-node-blocking drugs, or progressive left ventricular dysfunction despite treatment (i.e., tachycardia-induced cardiomyopathy), cardioversion or atrioventricular-node ablation and implantation of a pacemaker were performed.

Patients randomly assigned to the rhythm-control group underwent electrical cardioversion without previous treatment with antiarrhythmic drugs. Thereafter, patients received sotalol (160 to 320 mg daily, depending on body weight and renal function). If there

was a recurrence 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 after the start of this regimen, a loading dose of amiodarone was given (600 mg daily for four weeks), and electrical cardioversion was repeated. The dose of amiodarone was then lowered to 200 mg daily. In the case of a recurrence after six months of therapy with an antiarrhythmic drug, the regimen was continued. The administration of sotalol, flecainide, and propafenone was initiated in the hospital with telemetric monitoring. 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. All 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-

fects 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 incidence of the primary end point, 260 patients per 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 pre-specified 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.^{4,13} 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.^{10,11,14} 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 (\pm 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

TABLE 1. CHARACTERISTICS OF THE PATIENTS ACCORDING TO THE ASSIGNED TREATMENT.*

CHARACTERISTIC	RATE CONTROL (N=256)	RHYTHM CONTROL (N=266)
Age — yr	68 \pm 9	68 \pm 8
Male sex — no. (% of patients)	161 (63)	170 (64)
Atrial fibrillation — % of patients	93	93
Atrial flutter — % of patients	7	7
Duration of atrial fibrillation — days		
Median	337	309
Range	14–4820	10–14,399
Duration of current episode of atrial fibrillation — days		
Median	32	34
Range	1–399	1–395
Coronary artery disease — % of patients	29	26
Old myocardial infarction — % of patients	16	14
Valve disease — % of patients	18	16
Mitral	13	10
Aortic	5	5
Aortic and mitral	0	1
Cardiomyopathy — % of patients	11	7
Dilated	7	3
Hypertrophic	2	2
Other	2	2
History of hypertension — % of patients	43	55
History of chronic obstructive lung disease — % of patients	23	17
History of diabetes mellitus — % of patients	12	9
No heart disease — % of patients	21	21
History of heart failure — % of patients	51	49
History of cerebrovascular accident — % of patients	16	12
NYHA class — % of patients†		
I	49	51
II	48	46
III	3	3
Treatment — % of patients		
Digitalis alone	32	38
Beta-blocker alone	26	33
Verapamil or diltiazem alone	16	11
Digitalis and beta-blocker	15	10
Digitalis and calcium antagonist	4	5
Beta-blocker and calcium antagonist	6	2
Digitalis, beta-blocker, and calcium antagonist	1	1
Angiotensin-converting-enzyme inhibitor	26	32
Heart rate		
Mean — beats/min	91 \pm 21	90 \pm 20
>100 beats/min — % of patients	25	22
Blood pressure — mm Hg		
Systolic	142 \pm 21	145 \pm 22
Diastolic	85 \pm 11	86 \pm 11
Echocardiographic findings — mm		
Size of left atrium, long axis	45 \pm 7	45 \pm 7
Left ventricular end-diastolic diameter	53 \pm 7	52 \pm 7
Left ventricular end-systolic diameter	37 \pm 8	37 \pm 8
Septal thickness	10.1 \pm 2	10.5 \pm 3
Posterior-wall thickness	9.4 \pm 2	9.7 \pm 2
Fractional shortening — %	30 \pm 10	30 \pm 10

*Plus-minus values are means \pm SD.

†NYHA denotes New York Heart Association.

(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 rate-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. The causes of death were cerebral or retroperitoneal bleeding in six patients in the rate-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.

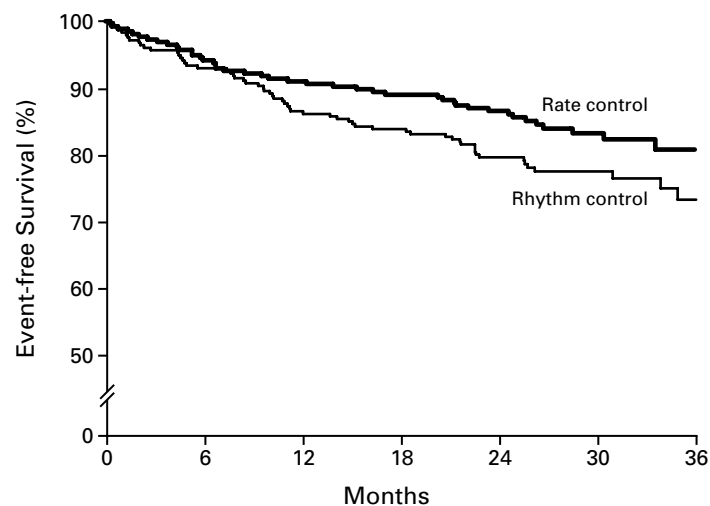
Thromboembolic complications occurred in 35 patients, all of whom had risk factors for stroke. Thromboembolism was more frequent in the rhythm-control group than in the rate-control group. Six patients, all in the rhythm-control group, had thromboembolic complications after the cessation of oral anticoagulant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

TABLE 2. INCIDENCE OF THE PRIMARY END POINT AND ITS COMPONENTS ACCORDING TO THE TREATMENT GROUP.*

END POINT	RATE CONTROL (N=256)	RHYTHM CONTROL (N=266)	ABSOLUTE DIFFERENCE (90% CI)†
	no. (%)		
Composite end point	44 (17.2)	60 (22.6)	-5.4 (-11.0 to 0.4)
Death from cardiovascular causes	18 (7.0)	18 (6.8)	0.2 (-3.4 to 3.9)
Heart failure	9 (3.5)	12 (4.5)	-1.0 (-3.8 to 1.8)
Thromboembolic complications	14 (5.5)	21 (7.9)	-2.4 (-6.0 to 1.2)
Bleeding	12 (4.7)	9 (3.4)	1.3 (-1.5 to 4.1)
Severe adverse effects of antiarrhythmic drugs	2 (0.8)	12 (4.5)	-3.7 (-6.0 to -1.4)
Implantation of a pacemaker	3 (1.2)	8 (3.0)	-1.8 (-3.9 to 0.2)

*Some patients had more than one end point.

†CI denotes confidence interval.



NO. AT RISK		0	6	12	18	24	30	36
Rate control		256	239	232	222	212	99	25
Rhythm control		266	243	224	218	207	85	24

Figure 2. Kaplan–Meier Curves for Event-free Survival in the Rate-Control and Rhythm-Control Groups.

ceiving 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 it 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

TABLE 3. INCIDENCE OF THE PRIMARY END POINT ACCORDING TO SEX AND BLOOD-PRESSURE STATUS.

GROUP	RATE CONTROL	RHYTHM CONTROL	ABSOLUTE DIFFERENCE (90% CI)*
	no./total no. (%)		
All patients	44/256 (17.2)	60/266 (22.6)	-5.4 (-11.0 to 0.4)
Men	34/161 (21.1)	29/169 (17.2)	3.9 (-3.2 to 11.1)
Women	10/95 (10.5)	31/97 (32.0)	-21.5 (-30.8 to -12.1)
Normotensive patients	25/146 (17.1)	15/120 (12.5)	4.6 (-2.5 to 11.8)
Hypertensive patients	19/110 (17.3)	45/146 (30.8)	-13.5 (-22.2 to -4.9)

*CI denotes confidence interval.

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.^{3,17} 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 disturb-

ances 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. 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. Crijns, I. Van Gelder, V. Hagens, T. Kingma (74); *St. Antonius Hospital, Nieuwegein* — J. Lindeboom, J. Kingma (36); *Hospital Midden-Twente, Hengelo* — S. Said (34); *Rijnstate Hospital, Arnhem* — H. Bosker (31); *Medisch Spectrum Twente Hospital, Enschede* — A. Timmermans (31); *Twenteborg Hospital, Almelo* — J. Darmanata, G. Linssen, B. de Rode (30); *Ignatius Hospital, Breda* — R. Wielinga (24); *Isala Hospital, Zwolle* — A. van 't Hof, M. Vet (24); *Oosterschelde Hospital, Goes* — E. Bruyns, A. Liem (22); *Free University Medical Center, Amsterdam* — M. Mihciokur, O. Kamp (21); *Stichting Deventer Hospitals, Deventer* — E. Badings, D. Lok (20); *Canisius Wilhelmina Hospital, Nijmegen* — D. Hertzberger (19); *St. Lucas Hospital, Winschoten* — T. Bouwmeester, A. van der Galiën (18); *Catharina Hospital, Eindhoven* — A. Meyer, F. Bracke (11); *Scheper Hospital, Emmen* — M. Nagelsmit (11); *Onze Lieve Vrouwe Hospital, Amsterdam* — T. Slagboom (9); *Hospital Hilversum, Hilversum* — K. Liem (9); *Antonius Hospital, Sneek* — B. Cernohorsky (9); *Reinier de Graaf Hospital, Delft* — D. Rehorst, A. Withagen (8); *Bosch Medicentrum Hospital, Den Bosch* — H. Dohmen (8); *Martini Hospital, Groningen* — P. Bernink, M. Niemeijer, J. Posma (8); *Hospital de Tjongerschans, Heerenveen* — S. Oei, J. van Os, G. Jochemsen (8); *Hospital Medisch Centrum, Leeuwarden* — R. Breedveld, W. Schenkel, C. de Vries (8); *University Hospital, Maastricht* — C. Kirchhof (8); *Haven Hospital, Rotterdam* — C. Leenders (7); *de Honte Hospital, Terneuzen* — R. Ciampriotti, R. Taverne, G. Paulussen (6); *Albert Schweitzer Hospital, Dordrecht* — P. Breuls (5); *Ikazia Hospital, Rotterdam* — J. Kerker (5); *Hospital Refaja, Stadskanaal* — L. Van Wijk (3); *St. Elisabeth Hospital, Tilburg* — W. Pasteuning, N. Holwerda (3); *Albert Schweitzer Hospital, Zwijndrecht* — A. Herweijer (3); *Delfzicht Hospital, Delfzijl* — J. Spanjaard (3); *University Hospital, Nijmegen* — F. Verheugt (2); *Hospital de Sionsberg, Dokkum* — A. Hagoort-Kok, E. van den Toren (2); *Schieland Hospital, Schiedam* — H. Werner, H. Spierenburg (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. Crijns, I. Van Gelder, H. Bosker, O. Kamp, J. Kingma, J. Tijssen.

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