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

THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) INVESTIGATORS*

ABSTRACT

Background There are two approaches to the treatment of atrial fibrillation: one is cardioversion and treatment with antiarrhythmic drugs to maintain sinus rhythm, and the other is the use of rate-controlling drugs, allowing atrial fibrillation to persist. In both approaches, the use of anticoagulant drugs is recommended.

Methods We conducted a randomized, multicenter comparison of these two treatment strategies in patients with atrial fibrillation and a high risk of stroke or death. The primary end point was overall mortality.

Results A total of 4060 patients (mean [±SD] age, 69.7±9.0 years) were enrolled in the study; 70.8 percent had a history of hypertension, and 38.2 percent had coronary artery disease. Of the 3311 patients with echocardiograms, the left atrium was enlarged in 64.7 percent and left ventricular function was depressed in 26.0 percent. There were 356 deaths among the patients assigned to rhythm-control therapy and 310 deaths among those assigned to rate-control therapy (mortality at five years, 23.8 percent and 21.3 percent, respectively; hazard ratio, 1.15 [95 percent confidence interval, 0.99 to 1.34]; P=0.08). More patients in the rhythm-control group than in the rate-control group were hospitalized, and there were more adverse drug effects in the rhythm-control group as well. In both groups, the majority of strokes occurred after warfarin had been stopped or when the international normalized ratio was subtherapeutic.

Conclusions Management of atrial fibrillation with the rhythm-control strategy offers no survival advantage over the rate-control strategy, and there are potential advantages, such as a lower risk of adverse drug effects, with the rate-control strategy. Anticoagulation should be continued in this group of high-risk patients. (N Engl J Med 2002;347:1825-33.)

ATRIAL fibrillation is the most common sustained cardiac arrhythmia, yet the optimal strategy for its management remains uncertain.[1-4] During atrial fibrillation, most symptoms (but perhaps not all) are caused by a poorly controlled or irregular ventricular rate, and the associated risk of death is doubled in patients who have a history of atrial fibrillation.[5-10] Although adequate anticoagulation with warfarin substantially lowers the risk of stroke,[11-13] this drug is frequently not administered.[14]

Initial therapy for atrial fibrillation is often directed toward the maintenance of sinus rhythm by means of cardioversion and the use of antiarrhythmic drugs.[15] The rationale for this "rhythm-control" approach includes the possibility of fewer symptoms, better exercise tolerance, a lower risk of stroke, eventual discontinuation of long-term anticoagulant therapy, better quality of life, and better survival, if sinus rhythm can be maintained.[3] However, atrial fibrillation is often poorly responsive to antiarrhythmic drugs, which may also have serious adverse effects.[16-19]

An accepted, though often secondary, alternative to antiarrhythmic-drug therapy is a strategy simply to control the ventricular response rate of atrial fibrillation with the use of atrioventricular nodal blocking agents or ablation of the atrioventricular junction and pacemaker implantation,[3,4,20,21] in conjunction with continuing anticoagulation.[5-7] This "rate-control" approach may simplify therapy and permit the use of drugs that are less toxic than antiarrhythmic drugs,

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although anticoagulation is thought to be more important with this strategy.

In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, we compared the effects of long-term treatment with these two strategies.[3,22,23]

METHODS

Patients

Patients who were at least 65 years of age or who had other risk factors for stroke or death could be enrolled in this study. The overriding criteria for enrollment were that (in the clinical judgment of the investigators) atrial fibrillation was likely to be recurrent; atrial fibrillation was likely to cause illness or death; long-term treatment for atrial fibrillation was warranted; anticoagulant therapy was not contraindicated; the patient was eligible to undergo trials of at least two drugs in both treatment strategies; and treatment with either strategy could be initiated immediately after randomization.[22,23]

The institutional review boards of the University of Washington and each of the 213 individual clinical sites and their satellite sites approved of the protocol. Every patient gave written informed consent for the study.

Rhythm-Control Strategy

In the rhythm-control group, the antiarrhythmic drug used was chosen by the treating physician.[24,25] Attempts to maintain sinus rhythm could include cardioversion as necessary. The following drugs were acceptable for use, according to the protocol: amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, and combinations of these drugs. When dofetilide became available, it also could be used. Specific guidelines for the use of antiarrhythmic drugs were imposed.[22,26]

Rate-Control Strategy

The therapeutic target in this group was heart-rate control. Drugs that were acceptable in the protocol for this purpose were beta-blockers, calcium-channel blockers (verapamil and diltiazem), digoxin, and combinations of these drugs. Heart-rate control during atrial fibrillation was assessed both at rest and during activity, which usually consisted of a six-minute walk.[22,27] The goal was a heart rate not higher than 80 beats per minute at rest and not higher than 110 beats per minute during the six-minute walk test.

Other Therapeutic Considerations

After standard approaches to treatment were exhausted, but not before the failure of at least two trials of either a rhythm-control drug or a rate-control drug, patients could be considered for nonpharmacologic therapy, such as radio-frequency ablation, a maze procedure, and pacing techniques, as appropriate to their randomized strategy.[22] The goal for anticoagulation with warfarin was an international normalized ratio (INR) of 2.0 to 3.0. In the rhythm-control group, continuous anticoagulation was encouraged but could be stopped at the physician's discretion if sinus rhythm had apparently been maintained for at least 4, and preferably 12, consecutive weeks with antiarrhythmic-drug therapy. In the rate-control group, continuous anticoagulation was mandated by the protocol.[5-7]

Statistical Analysis

The primary end point was overall mortality. A composite secondary end point comprised death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest.

Randomization was stratified only according to clinical site. The base-line characteristics of patients were compared with chi-square tests and t-tests. The primary analysis was an intention-to-treat comparison of the time to death from any cause, adjusted for 10 interim analyses. For all time-to-event analyses, rates were estimated by the method of Kaplan and Meier[28] and were compared by the log-rank test. Patients' data were censored at the time of last contact or withdrawal from the study or at the time of death, if the analysis was for an end point other than death.

Secondary analyses were conducted to evaluate results within prespecified subgroups and to adjust the primary end point for base-line characteristics. The prespecified covariates were age (as a continuous variable), sex, rhythm at randomization (sinus rhythm vs. atrial fibrillation), a first episode of atrial fibrillation (vs. a recurrent episode), the presence or absence of coronary artery disease, the presence or absence of hypertension, the presence or absence of congestive heart failure, the left ventricular ejection fraction ($\geq$50, 40 to 49, 30 to 39, or $<$30 percent), and the duration of atrial fibrillation. Unadjusted hazard ratios for death from any cause with the rhythm-control strategy as compared with the rate-control strategy were estimated in each subgroup. In addition, these covariates were used to construct a multivariate Cox proportional-hazards survival model with a stepwise procedure. Covariates that were significantly associated with mortality were then used to adjust the primary treatment comparison. All P values were two-tailed.

A data and safety monitoring board reviewed the study twice yearly. A group sequential monitoring technique, with a Lan–DeMets boundary and an O'Brien–Fleming–type alpha spending function, was used.[22,29-31]

RESULTS

Characteristics of the Patients

Of the 7401 patients who were eligible and offered enrollment, 4060 were enrolled. During the course of the study, 71 patients withdrew their consent for participation, and survival at the end of follow-up was ultimately unknown in 26 patients. The mean follow-up time was 3.5 years, with a maximum of 6 years. Base-line clinical data for the 4060 enrolled patients are summarized in Table 1 and elsewhere.[23] The mean ($\pm$SD) age was 69.7$\pm$9.0 years; 39.3 percent were women and 11.4 percent members of an ethnic minority group. A total of 70.8 percent of the patients had hypertension, which was the predominant cardiac diagnosis in 50.8 percent; 38.2 percent of the patients had coronary artery disease (which was the predominant cardiac diagnosis in 26.1 percent). More than one third were enrolled after having had a first episode of atrial fibrillation; more than 90 percent had had the qualifying episode within the previous six weeks; and in more than two thirds the qualifying episode lasted at least two days. The rate-control and rhythm-control groups were balanced according to base-line characteristics.

Therapy

Table 2 outlines the drugs used in the two study groups. The use of combinations of two or more agents was common.

In the rate-control group, beta-blocking drugs were used initially in nearly one half of the patients, and of the calcium-channel blockers, diltiazem was used more commonly than verapamil. However, changes in therapy were frequent. At the five-year visit, 34.6 percent

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	OVERALL (N=4060)	RATE-CONTROL GROUP (N=2027)	RHYTHM-CONTROL GROUP (N=2033)	P VALUE
Age — yr	69.7±9.0	69.8±8.9	69.7±9.0	0.82
Female sex — no. (%)	1594 (39.3)	823 (40.6)	771 (37.9)	0.08
Ethnic minority group — no. (%)	461 (11.4)	241 (11.9)	220 (10.8)	0.28
Predominant cardiac diagnosis — no. (%)				0.29
Coronary artery disease	1059 (26.1)	497 (24.5)	562 (27.6)	
Cardiomyopathy	194 (4.8)	99 (4.9)	95 (4.7)	
Hypertension	2063 (50.8)	1045 (51.6)	1018 (50.1)	
Valvular disease	198 (4.9)	98 (4.8)	100 (4.9)	
Other	42 (1.0)	23 (1.1)	19 (0.9)	
No apparent heart disease	504 (12.4)	265 (13.1)	239 (11.8)	
History of congestive heart failure — no. (%)	939 (23.1)	475 (23.4)	464 (22.8)	0.64
Duration of qualifying atrial fibrillation ≥2 days — no. (%)	2808 (69.2)	1406 (69.4)	1402 (69.0)	0.80
First episode of atrial fibrillation (vs. recurrent episode) — no. (%)†	1391 (35.5)	700 (35.8)	691 (35.3)	0.74
Any prerandomization failure of an antiarrhythmic drug — no. (%)	713 (17.6)	364 (18.0)	349 (17.2)	0.51
Size of left atrium normal — no. (%)‡	1103 (35.3)	549 (35.3)	554 (35.3)	0.98
Left ventricular ejection fraction — %§	54.7±13.5	54.9±13.1	54.6±13.8	0.74
Normal left ventricular ejection fraction — no. (%)‡	2244 (74.0)	1131 (74.9)	1113 (73.2)	0.29

*Plus–minus values are means ±SD.

†This information was not collected on the initial version of the data form and therefore is missing for 143 patients (70 in the rate-control group and 73 in the rhythm-control group).

‡Echocardiograms were obtained in 3311 patients (1650 in the rate-control group and 1661 in the rhythm-control group). The size of the left atrium was unknown in 185 cases, and left ventricular function (where normal function was defined as a left ventricular ejection fraction ≥0.50) was unknown in 279.

§A quantitative measurement of left ventricular ejection fraction was available for 894 echocardiograms.

of the patients were in sinus rhythm, and over 80 percent of those in atrial fibrillation had adequate heart-rate control. Radiofrequency ablation to modify or eliminate atrioventricular conduction was used in 105 (5.2 percent) of the patients in the rate-control group after drug failure. During the course of the study, 248 patients crossed over from the rate-control group to the rhythm-control group (actuarial rate of crossover, 7.8 percent, 11.6 percent, and 14.9 percent after one, three, and five years, respectively). Eighty-six of these patients had crossed back to the rate-control group by the end of the study. Uncontrolled symptoms due to atrial fibrillation and congestive heart failure were the most common reasons for the initial crossover to rhythm control in this group.

In the rhythm-control group, more than two thirds of patients started therapy with amiodarone or sotalol, and by the end of the study almost two thirds of the patients in this group had undergone at least one trial of amiodarone. Maintenance of sinus rhythm was not itself a primary end point. Patients with intermittent, self-terminating episodes of atrial fibrillation could have been enrolled in the study. The prevalence of sinus rhythm in the rhythm-control group at follow-up was 82.4 percent, 73.3 percent, and 62.6 percent at one, three, and five years, respectively. Electrical cardioversion was attempted once during follow-up in 368 patients, twice in 214 patients, and three or more times in 187 patients in this group. Fourteen patients underwent radiofrequency ablation for atrial flutter or fibrillation; three received an implantable atrial cardioverter (a protocol violation); three underwent a surgical maze procedure[32]; and one underwent a catheter-based maze procedure. During the course of the study, 594 patients assigned to the rhythm-control group crossed over to the rate-control group (actuarial rate of crossover, 16.7 percent, 27.3 percent, and 37.5 percent after one, three, and five years, respectively; $P<0.001$ for the comparison with the rate-control group). Sixty-one of these patients had crossed back to the

TABLE 2. DRUGS USED IN THE RATE-CONTROL GROUP AND THE RHYTHM-CONTROL GROUP.*

DRUG	RATE-CONTROL GROUP		RHYTHM-CONTROL GROUP	
	USED DRUG FOR INITIAL THERAPY	USED DRUG AT ANY TIME	USED DRUG FOR INITIAL THERAPY	USED DRUG AT ANY TIME
	no. of patients (%)			
Rate control				
Data available	1957	2027	1266	2033
Digoxin	949 (48.5)	1432 (70.6)	417 (32.9)	1106 (54.4)
Beta-blocker	915 (46.8)	1380 (68.1)	276 (21.8)	1008 (49.6)
Diltiazem	583 (29.8)	935 (46.1)	198 (15.6)	610 (30.0)
Verapamil	187 (9.6)	340 (16.8)	56 (4.4)	204 (10.0)
Rhythm control				
Data available	1265	2027	1960	2033
Amiodarone	2 (0.2)†	207 (10.2)	735 (37.5)	1277 (62.8)
Sotalol	1 (0.1)†	84 (4.1)	612 (31.2)	841 (41.4)
Propafenone	2 (0.2)†	45 (2.2)	183 (9.3)	294 (14.5)
Procainamide	0	30 (1.5)	103 (5.3)	173 (8.5)
Quinidine	2 (0.2)†	14 (0.7)	92 (4.7)	151 (7.4)
Flecainide	0	29 (1.4)	88 (4.5)	169 (8.3)
Disopyramide	0	7 (0.3)	42 (2.1)	87 (4.3)
Moricizine	0	2 (0.1)	14 (0.7)	35 (1.7)
Dofetilide	0	5 (0.2)	0	13 (0.6)

*Because of changes in the data forms during the study, information on initial therapy was not recorded for some patients; the denominators therefore vary. Percentages do not total 100 because more than one drug could have been tried at the beginning of treatment and because combination therapies were allowed.

†These patients immediately crossed over to the rhythm-control group, a crossover considered to be a protocol violation.

rhythm-control group by the end of the study. Inability to maintain sinus rhythm and drug intolerance were the chief reasons for abandonment of a rhythm-control strategy.

At each assessment during the study, more than 85 percent of patients in the rate-control group were taking warfarin. After the first four months of the trial, there was a decline in the use of warfarin in the rhythm-control group, but the overall proportion of patients receiving warfarin remained approximately 70 percent throughout the trial. A total of 62.3 percent of INR values measured at follow-up visits were within the recommended range (2.0 to 3.0).

Mortality

The primary end point of overall mortality is summarized in Figure 1, and major adverse events are summarized in Table 3. More deaths occurred in the rhythm-control group than in the rate-control group, but the difference in mortality between the two groups was not statistically significant ($P=0.08$; hazard ratio, 1.15 [95 percent confidence interval, 0.99 to 1.34]; both adjusted for interim monitoring but not for base-line covariates). The rates of the composite end point of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest were also similar in the two groups ($P=0.33$).

Central Nervous System Events

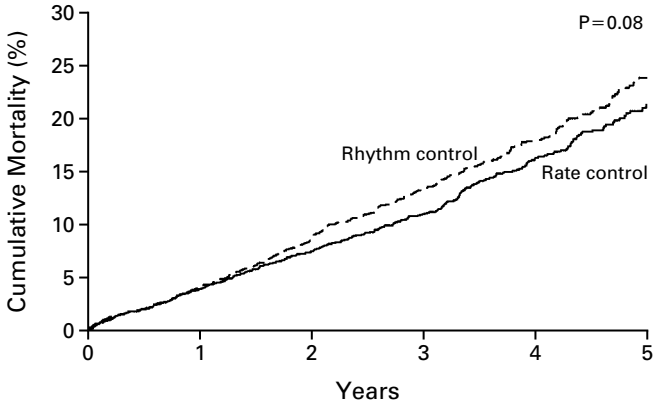
Ischemic strokes occurred in 77 and 80 patients in the rate-control and rhythm-control groups, respectively (Table 3), for an annual rate of approximately 1 percent per year in each group. Most occurred in patients in whom warfarin had been stopped or in whom the INR was subtherapeutic. The proportions of patients with ischemic stroke, primary intracerebral hemorrhage, subdural or subarachnoid hemorrhage, or disabling anoxic encephalopathy were similar in the two treatment groups.

Other Adverse Events

Other adverse events noted during the trial are listed in Tables 3 and 4. Hemorrhage not involving the central nervous system was uncommon. Most of these patients were taking warfarin at the time of their event and had an INR of 4.3 ± 4.9 (after the exclusion of three extreme values) near the time of the event. Other cardiac arrhythmias occurred, but only rarely, in the two groups (Table 3).

Other Observations

Scores on the Mini–Mental State Examination, a test of cognitive ability,[33] and selected measures of quality of life were similar in the two groups at all time points. The number of patients needing hospitalization



No. of Deaths		number (percent)				
Rhythm control	0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
Rate control	0	78 (4)	148 (7)	210 (11)	275 (16)	306 (21)

Figure 1. Cumulative Mortality from Any Cause in the Rhythm-Control Group and the Rate-Control Group.

Time zero is the day of randomization. Data have been truncated at five years.

during follow-up was greater in the rhythm-control group than in the rate-control group (1374 [80.1 percent] vs. 1220 [73.0 percent], $P<0.001$).

The hazard ratios for death in each of the prespecified subgroups are shown in Figure 2. The rhythm-control strategy was associated with a higher risk of death than the rate-control strategy among older patients, those without congestive heart failure, and those with coronary artery disease. After adjustment for the prespecified covariates that were statistically significant in a Cox proportional-hazards model (age, coronary artery disease, congestive heart failure, left ventricular ejection fraction, and hypertension), the trend toward a higher risk of death in the rhythm-control group than in the rate-control group persisted (hazard ratio, 1.18 [95 percent confidence interval, 0.99 to 1.41]; $P=0.07$).

DISCUSSION

In this study, we compared rate-control and rhythm-control strategies for the treatment of atrial fibrillation. The population in this study is representative of the majority of patients with atrial fibrillation. Patients who are elderly (65 years of age or older) have the highest incidence and prevalence of this common tachyarrhythmia[34-38] and are increasing in number.[1,39] To allow patients to remain in their assigned treatment groups, the protocol permitted the use of multiple drugs and nonpharmacologic therapies that the investigators considered effective in patients with atrial fibrillation.[22] The crossover rate was significantly greater among the patients initially assigned to rhythm control than among those assigned to rate control, in keeping with the fact that antiarrhythmic drug therapies frequently fail.[2,3,15,18] However, crossover rates were within the ranges predicted by the protocol.[22] Only a small number of patients in the study were treated with nonpharmacologic therapies. Indeed, many nonpharmacologic therapies may not be applicable to elderly patients with atrial fibrillation.[40,41]

In this study of patients with atrial fibrillation and risk factors for stroke, the strategy of restoring and maintaining sinus rhythm had no clear advantage over the strategy of controlling the ventricular rate and allowing atrial fibrillation to persist. There was a trend toward increased mortality in association with the rhythm-control strategy ($P=0.08$). In a multivariate analysis with adjustment for prespecified covariates, the trend toward a survival advantage with the rate-control strategy was essentially unchanged ($P=0.07$). Follow-up was relatively long (3.5 years, on average), and the trend toward a difference in mortality did not begin to emerge until near the second year of follow-up. All comparisons of subgroups according to the prespecified covariates either showed nonsignificant differences or showed a benefit with rate control. Thus, we did not find any benefit in association with the rhythm-control strategy. Analysis of death according to specific causes is ongoing.

Stroke is probably the most serious direct clinical consequence of atrial fibrillation.[34-36] The rates of ischemic stroke were low, at approximately 1 percent per year in both groups. The majority of strokes in both groups occurred in patients who had stopped taking

TABLE 3. ADVERSE EVENTS.*

EVENT	OVERALL (N=4060)	RATE-CONTROL GROUP (N=2027)	RHYTHM-CONTROL GROUP (N=2033)	P VALUE
	no. of patients (%)			
Primary end point (death)	666 (26.3)	310 (25.9)	356 (26.7)	0.08†
Secondary end point (composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest)	861 (32.3)	416 (32.7)	445 (32.0)	0.33
Torsade de pointes	14 (0.5)	2 (0.2)‡	12 (0.8)	0.007
Sustained ventricular tachycardia	15 (0.6)	9 (0.7)	6 (0.6)	0.44
Cardiac arrest followed by resuscitation				
Ventricular fibrillation or ventricular tachycardia	19 (0.6)	10 (0.7)	9 (0.5)	0.83
Pulseless electrical activity, bradycardia, or other rhythm	10 (0.3)	1 (<0.1)	9 (0.6)	0.01
Central nervous system event				
Total	211 (8.2)	105 (7.4)	106 (8.9)	0.93
Ischemic stroke§	157 (6.3)	77 (5.5)	80 (7.1)	0.79
After discontinuation of warfarin	69	25	44	
During warfarin but with INR <2.0	44	27	17	
Concurrent atrial fibrillation	67	42	25	
Primary intracerebral hemorrhage	34 (1.2)	18 (1.1)	16 (1.3)	0.73
Subdural or subarachnoid hemorrhage	24 (0.8)	11 (0.8)	13 (0.8)	0.68
Disabling anoxic encephalopathy	9 (0.3)	4 (0.2)	5 (0.4)	0.74
Myocardial infarction	140 (5.5)	67 (4.9)	73 (6.1)	0.60
Hemorrhage not involving the central nervous system	203 (7.3)	107 (7.7)	96 (6.9)	0.44
Systemic embolism	16 (0.5)	9 (0.5)	7 (0.4)	0.62
Pulmonary embolism	8 (0.3)	2 (0.1)	6 (0.5)	0.16
Hospitalization after base line	2594 (76.6)	1220 (73.0)	1374 (80.1)	<0.001

*Percentages were derived from a Kaplan–Meier analysis. P values were derived from the log-rank statistic.

†The P value in the case of death was based on the square root of the log-rank statistic, adjusted for 10 interim monitoring analyses.

‡One patient had crossed over to the rhythm-control group and was taking quinidine, and one patient had torsade de pointes 72 hours after mitral-valve replacement.

§Information on warfarin therapy was missing for two patients in the rate-control group and three patients in the rhythm-control group. Information on the presence of atrial fibrillation with the event was missing for 16 patients in the rate-control group and 13 patients in the rhythm-control group.

TABLE 4. ADDITIONAL ADVERSE EVENTS OR CLINICAL FINDINGS PROMPTING DISCONTINUATION OF A DRUG.*

EVENT	OVERALL (N=4060)	RATE-CONTROL GROUP (N=2027)	RHYTHM-CONTROL GROUP (N=2033)	P VALUE†
	no. of patients (%)			
Congestive heart failure	79 (2.4)	37 (2.1)	42 (2.7)	0.58
Pulmonary event	132 (4.6)	24 (1.7)	108 (7.3)	<0.001
Gastrointestinal event	162 (5.0)	35 (2.1)	127 (8.0)	<0.001
Bradycardia	169 (5.1)	64 (4.2)	105 (6.0)	0.001
Prolongation of the corrected QT interval (>520 msec)	35 (1.1)	4 (0.3)	31 (1.9)	<0.001
Other	590 (19.8)	176 (14.0)	414 (25.4)	<0.001

*Percentages were derived from a Kaplan–Meier analysis.

†P values were based on the log-rank statistic.

warfarin or whose INR was subtherapeutic at the time of the stroke, in general agreement with previously reported observations.[42]

Proarrhythmia (i.e., the presumed induction of ventricular arrhythmia by antiarrhythmic drugs) was uncommon in this study, and the restricted use of many antiarrhythmic drugs (particularly class I drugs) imposed by the protocol may explain this finding. However, torsade de pointes or bradycardic arrest occurred more often in the rhythm-control group than in the rate-control group. The cardiac rhythm in some of the patients in the rate-control group was sinus rhythm at times during follow-up. The cardiac rhythm was classified only on the day of the follow-up visit, and atrial fibrillation could have been present at other times. The high prevalence of sinus rhythm may be due to the inclusion of patients with paroxysmal atrial fibrillation,[16] adequate control of blood pressure in pa-

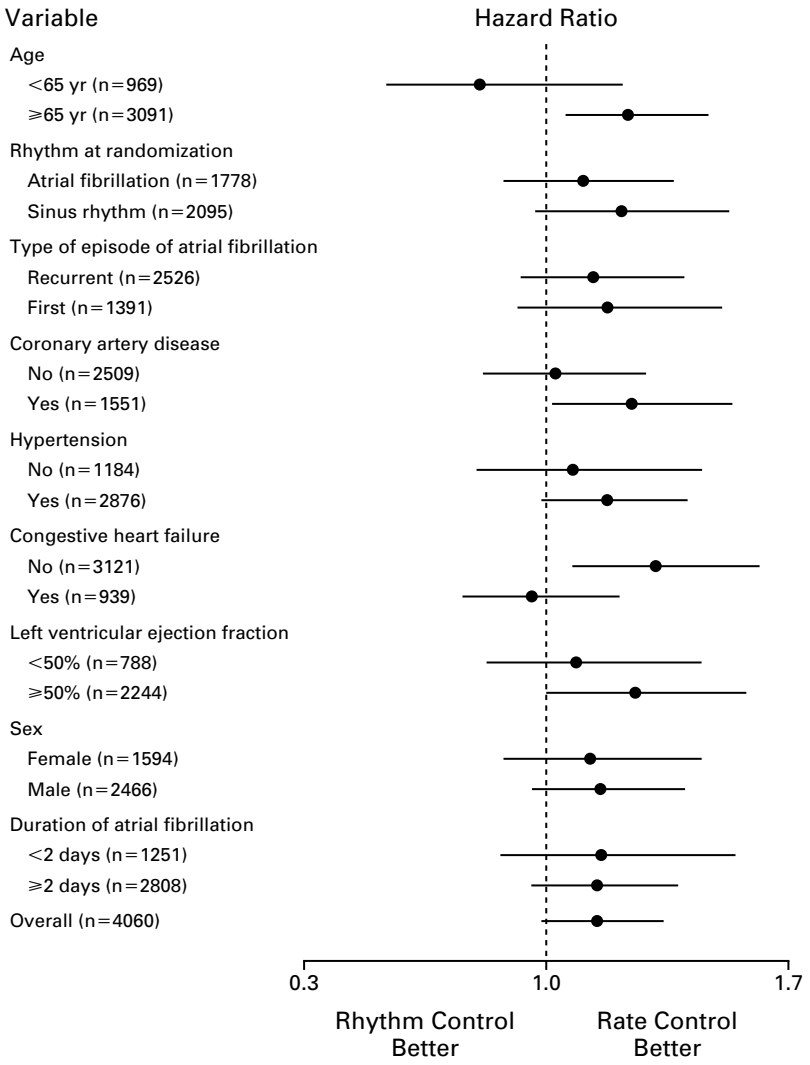


Figure 2. Hazard Ratios for Death in Prespecified Subgroups.

The numbers in the groups do not total 4060 for all variables because of incomplete reporting. The ratios shown are for the rhythm-control group as compared with the rate-control group.

tients with hypertension, and the antiarrhythmic effects of beta-blockers and calcium-channel blockers.

The patients in the rhythm-control group were significantly more likely to be hospitalized and have adverse drug effects than those in the rate-control group, in general agreement with findings previously reported.[43] These findings probably have important cost implications.

Our study tested a treatment strategy to maintain sinus rhythm. Use of a single drug could have yielded a different result (either better or worse), but the ability to use multiple drugs increased the chance that any individual patient would maintain sinus rhythm. Patients with frequent or severe symptoms might have been considered unsuitable for a rate-control strategy and therefore may not have been enrolled by some investigators. Moreover, the results probably cannot be generalized to younger patients without risk factors for stroke (i.e., patients with primary, or "lone," atrial fibrillation), particularly those with paroxysmal atrial fibrillation. Nevertheless, our results apply to the majority of patients with atrial fibrillation. Finally, some of the patients in each of the two groups had paroxysmal atrial fibrillation, and thus, the prevalence of sinus rhythm at any time was high, even in the rate-control group.

Patients with atrial fibrillation often need treatment for decades, not years. However, the survival curves appear to be diverging, not converging, later in follow-up. Furthermore, the adverse effects due to the most commonly used drug, amiodarone, might be reasonably expected to increase with longer use.

None of the presumed benefits of rhythm control noted above were confirmed in this study. The implication is that rate control should be considered a primary approach to therapy and that rhythm control, if used, may be abandoned early if it is not fully satisfactory. Our data also suggest that continuous anticoagulation is warranted in all patients with atrial fibrillation and risk factors for stroke, even when sinus rhythm appears to be restored and maintained.

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Dr. Wyse has reported that he receives research support from Medtronic and Cardiome Pharma, is a consultant for AstraZeneca and Cardiome Pharma, is a speaker for Guidant, and is a member of the data and safety monitoring boards of Procter & Gamble, Cardiome Pharma, Orion Pharma, and Bristol-Myers Squibb/Sanofi–Synthelabo. Dr. Waldo has reported that he receives research support from AstraZeneca and Guidant, is on the speakers' bureaus of many companies, and is a consultant to Procter & Gamble, 3-M Pharmaceuticals, AstraZeneca, Pfizer, Solvay, and CryoCor. Dr. DiMarco has reported that he receives research support from Medtronic, Guidant, and Procter & Gamble and that he is a consultant to Bayer, Novartis, and Pfizer. Dr. Greene has reported that he is a member of the data and safety monitoring board for Procter & Gamble and CryoCor.

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