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Rhythm Control versus Rate Control for Atrial Fibrillation and Heart Failure

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ABSTRACT

BACKGROUND

It is common practice to restore and maintain sinus rhythm in patients with atrial fibrillation and heart failure. This approach is based in part on data indicating that atrial fibrillation is a predictor of death in patients with heart failure and suggesting that the suppression of atrial fibrillation may favorably affect the outcome. However, the benefits and risks of this approach have not been adequately studied.

METHODS

We conducted a multicenter, randomized trial comparing the maintenance of sinus rhythm (rhythm control) with control of the ventricular rate (rate control) in patients with a left ventricular ejection fraction of 35% or less, symptoms of congestive heart failure, and a history of atrial fibrillation. The primary outcome was the time to death from cardiovascular causes.

RESULTS

A total of 1376 patients were enrolled (682 in the rhythm-control group and 694 in the rate-control group) and were followed for a mean of 37 months. Of these patients, 182 (27%) in the rhythm-control group died from cardiovascular causes, as compared with 175 (25%) in the rate-control group (hazard ratio in the rhythm-control group, 1.06; 95% confidence interval, 0.86 to 1.30; $P=0.59$ by the log-rank test). Secondary outcomes were similar in the two groups, including death from any cause (32% in the rhythm-control group and 33% in the rate-control group), stroke (3% and 4%, respectively), worsening heart failure (28% and 31%), and the composite of death from cardiovascular causes, stroke, or worsening heart failure (43% and 46%). There were also no significant differences favoring either strategy in any predefined subgroup.

CONCLUSIONS

In patients with atrial fibrillation and congestive heart failure, a routine strategy of rhythm control does not reduce the rate of death from cardiovascular causes, as compared with a rate-control strategy. (ClinicalTrials.gov number, NCT00597077.)

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ATRIAL FIBRILLATION AND CONGESTIVE heart failure are common cardiac disorders associated with substantial morbidity and mortality.¹⁻⁷ Atrial fibrillation can lead to heart failure, and heart failure can lead to atrial fibrillation, which is present in 10 to 50% of patients with heart failure.⁸⁻¹⁴ An excessive ventricular rate, a loss of atrial contraction, and an irregular ventricular filling time that is associated with atrial fibrillation may all have negative clinical consequences in patients with heart failure. Most of the available evidence suggests that such patients with atrial fibrillation have a worse prognosis than those in whom sinus rhythm is maintained and that the presence of atrial fibrillation is an independent risk factor for death.^{8,9,11,14-20}

The treatment of patients with heart failure and atrial fibrillation presents specific challenges. In view of the prognostic importance of atrial fibrillation in patients with heart failure, the restoration

and maintenance of sinus rhythm with electrical cardioversion and antiarrhythmic drugs are often attempted.^{5,21-24} However, patients with impaired left ventricular function have an increased risk of adverse effects from antiarrhythmic drugs.²⁵⁻²⁷ Data from six trials do not support a routine strategy of rhythm control in patients with atrial fibrillation.²⁸⁻³³ However, only a small minority of patients who were enrolled in these trials had left ventricular dysfunction, and the lack of benefit from the maintenance of sinus rhythm in such patients may not apply to the general population of patients with heart failure.³⁴

We wanted to determine, in an adequately powered, prospective clinical trial, whether the prevention of atrial fibrillation would improve survival in patients with heart failure. Therefore, we conducted a multicenter, prospective, randomized trial to test the hypothesis that a rhythm-control strategy would reduce the rate of death from car-

Table 1. Baseline Characteristics of the Patients.*

| Variable | Rhythm-Control Group (N = 682) | Rate-Control Group (N = 694) |
|--|-----------------------------------|---------------------------------|
| Male sex (%) | 78 | 85 |
| Age (yr) | 66±11 | 67±11 |
| Body-mass index† | 27.8±5.4 | 28.0±5.1 |
| Nonwhite race (%)‡ | 16 | 13 |
| NYHA class III or IV (%) | | |
| At baseline | 32 | 31 |
| During previous 6 mo | 76 | 76 |
| Predominant cardiac diagnosis (%)§ | | |
| Coronary artery disease | 48 | 48 |
| Valvular heart disease | 5 | 5 |
| Nonischemic cardiomyopathy | 36 | 39 |
| Congenital heart disease | 1 | 1 |
| Hypertensive heart disease | 10 | 7 |
| Coexisting conditions (%) | | |
| Hypertension | 49 | 46 |
| Diabetes | 22 | 20 |
| Previous stroke or transient ischemic attack | 11 | 8 |
| Left ventricular ejection fraction (%) | 27±6 | 27±6 |
| Primary classification of atrial fibrillation (%) | | |
| Paroxysmal | 33 | 30 |
| Persistent¶ | 67 | 70 |
| ≥6 Mo since first diagnosis of atrial fibrillation (%) | 41 | 46 |
| Atrial fibrillation on electrocardiography (%) | 54 | 61 |

Table 1. (Continued.)

| Variable | Rhythm-Control Group (N = 682) | Rate-Control Group (N = 694) |
|---|-----------------------------------|---------------------------------|
| QRS duration (msec) | 112±30 | 115±30 |
| Previous electrical cardioversion (%) | 34 | 37 |
| Left atrial dimension (mm) | 49±7 | 49±7 |
| Previous hospitalization (%) | | |
| For atrial fibrillation | 51 | 55 |
| For congestive heart failure (during previous 6 mo) | 54 | 56 |
| Concomitant drug therapy (%) | | |
| Digoxin | 64 | 65 |
| Beta-blocker | 80 | 78 |
| Long-acting nitrate | 17 | 17 |
| Angiotensin-converting-enzyme inhibitor | 86 | 86 |
| Angiotensin-receptor blocker | 11 | 11 |
| Aldosterone antagonist | 43 | 46 |
| Oral anticoagulant | 86 | 90 |
| Aspirin | 40 | 37 |
| Lipid-lowering drug | 44 | 42 |
| Previous antiarrhythmic agent (%) | 43 | 44 |
| Implantable cardioverter-defibrillator (%) | 7 | 7 |

* Plus-minus values are means ±SD. NYHA denotes New York Heart Association.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Race was self-reported.

§ Conditions in this category were determined by the investigator to be the predominant underlying cause of left ventricular systolic dysfunction.

¶ Atrial fibrillation was defined as persistent if the termination of most episodes required drug therapy or electrical cardioversion.

diovascular causes, as compared with a rate-control strategy, among patients with atrial fibrillation and congestive heart failure.

METHODS

STUDY DESIGN

The details of the protocol have been reported previously.¹⁵ The Atrial Fibrillation and Congestive Heart Failure trial was conducted in 123 centers in Canada, United States, Brazil, Argentina, Europe, and Israel. The institutional review board at each center approved the study, and all patients gave written informed consent. Recruitment began in May 2001 and was concluded in June 2005; the follow-up period ended on June 30, 2007. The steering committee designed the study. Data management and analyses were performed at the Montreal Heart Institute Coordinating Center. All authors reviewed and edited the manuscript and vouch for the completeness and accuracy of the data.

All patients purchased their own cardiac medications, except in cases of inadequate financial resources. In these cases, the manufacturers provided the medications at no cost to the patients.

PATIENTS

To be eligible, patients had to meet all of the following criteria: a left ventricular ejection fraction of 35% or less, as measured by nuclear imaging, echocardiography, or cardiac angiography, with testing performed 6 months or less before enrollment; a history of congestive heart failure, which was defined as symptomatic New York Heart Association (NYHA) class II or IV heart failure within the previous 6 months, an asymptomatic condition for which the patient had been hospitalized for heart failure during the previous 6 months, or a left ventricular ejection fraction of 25% or less; a history of atrial fibrillation (with electrocardiographic documentation), which was defined as one episode lasting for at least 6 hours or requiring

Table 2. Medical Therapy at 12 Months.*

| Drug | Rhythm-Control Group (N=682) | Rate-Control Group (N=694) | P Value |
|------------------------|---------------------------------|-------------------------------|---------|
| | percent | | |
| Amiodarone | 82 | 7 | <0.001 |
| Sotalol | 2 | <1 | 0.02 |
| Dofetilide | <1 | <1 | 0.62 |
| Beta-blocker | 80 | 88 | <0.001 |
| Digoxin | 51 | 75 | <0.001 |
| Verapamil or diltiazem | 2 | 3 | 0.10 |
| ACE inhibitor | 81 | 82 | 0.41 |
| ARB | 16 | 13 | 0.09 |
| ACE inhibitor or ARB | 94 | 94 | 0.57 |
| Diuretic | 80 | 82 | 0.37 |
| Aldosterone antagonist | 47 | 49 | 0.51 |
| Oral anticoagulant | 88 | 92 | 0.03 |
| Aspirin | 34 | 31 | 0.31 |
| Lipid-lowering drug | 44 | 46 | 0.61 |

* ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

cardioversion within the previous 6 months or an episode lasting for at least 10 minutes within the previous 6 months and previous electrical cardioversion for atrial fibrillation; and eligibility for long-term therapy in either of the two study groups.

Exclusion criteria were persistent atrial fibrillation for more than 12 months, a reversible cause of atrial fibrillation or heart failure, decompensated heart failure within 48 hours before intended randomization, the use of antiarrhythmic drugs for other arrhythmias, second-degree or third-degree atrioventricular block (bradycardia of <50 beats per minute), a history of the long-QT syndrome, previous ablation of an atrioventricular node, anticipated cardiac transplantation within 6 months, renal failure requiring dialysis, lack of birth control in women of child-bearing potential, an estimated life expectancy of less than 1 year, and an age of less than 18 years.

Patients were randomly assigned to either the rhythm-control group or the rate-control group in an unblinded fashion. Randomization was performed with permuted blocks of various sizes and was stratified according to the study center.

THERAPIES

Rhythm Control

Aggressive therapy to prevent atrial fibrillation was recommended for patients in the rhythm-control group. Electrical cardioversion was recommended within 6 weeks after randomization in patients who did not have conversion to sinus rhythm after antiarrhythmic drug therapy. If necessary, a second cardioversion was recommended within 3 months after enrollment. Additional cardioversions were recommended for subsequent recurrences of atrial fibrillation. Amiodarone was the drug of choice for the maintenance of sinus rhythm, and either sotalol or dofetilide was used if required.¹⁵ The installation of a permanent pacemaker was recommended if bradycardia prevented the use of antiarrhythmic drugs. Patients who did not have a response to antiarrhythmic drug therapy could be referred for nonpharmacologic therapy.

Rate Control

Therapies for rate control included adjusted doses of beta-blockers with digitalis to achieve the targeted heart rate, which was defined as a ventricular rate of less than 80 beats per minute during resting 12-lead electrocardiography and of less than 110 beats per minute during a 6-minute walk test; both tests were performed at 4 and 12 months and yearly thereafter. Atrioventricular nodal ablation and pacemaker therapy were recommended for patients who did not meet the rate-control targets with drug therapy.

Therapies for Heart Failure

Treatment with an angiotensin-converting-enzyme inhibitor or an angiotensin-receptor antagonist was recommended for all patients. Maximum tolerated doses of beta-blockers were recommended for patients in both groups. Anticoagulation was recommended for all patients.³⁵ The use of an implantable defibrillator and ventricular-resynchronization therapy was recommended according to guidelines reported previously.³⁶

PRIMARY AND SECONDARY OUTCOMES

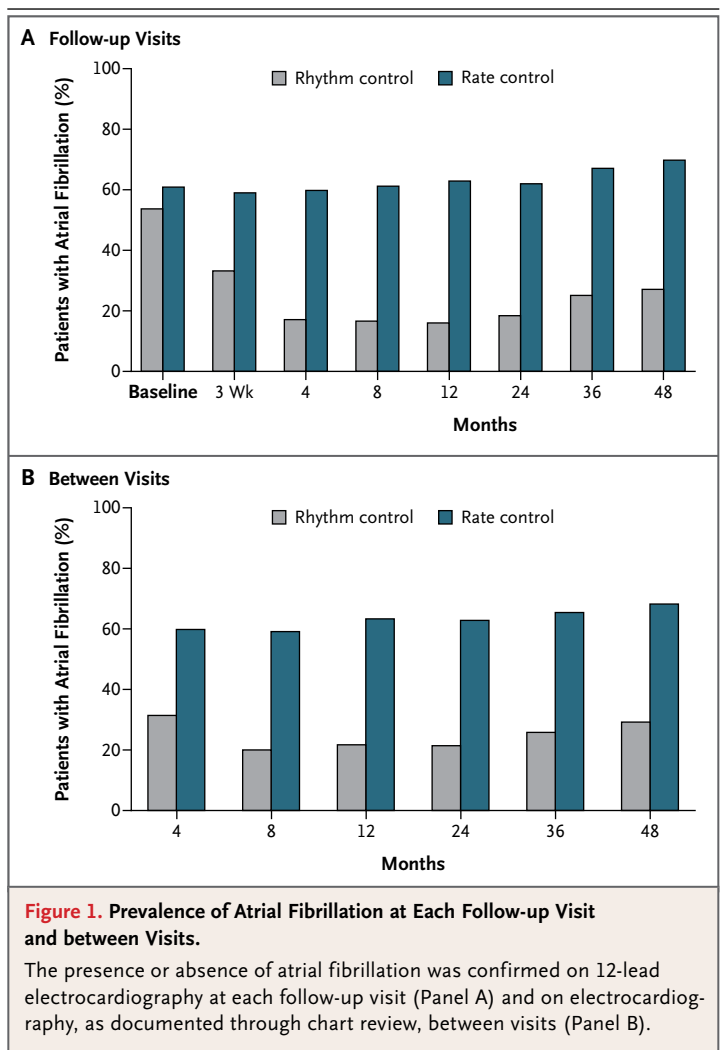
Patients were evaluated at 3 weeks, at 4 months and every 4 months thereafter until 48 months, and subsequently every 6 months. The primary outcome was death from cardiovascular causes. Secondary outcomes were death from any cause, stroke, worsening congestive heart failure, hospi-

talization, quality of life, cost of therapy, and a composite of death from cardiovascular causes, stroke, or worsening congestive heart failure. Major clinical events were adjudicated by an events committee whose members were unaware of the patients' study-group assignments.

STATISTICAL ANALYSIS

Prespecified analyses were performed according to the intention-to-treat principle. Event rates for death from cardiovascular causes and secondary outcomes were estimated by the Kaplan–Meier method and compared by the log-rank test. The primary analysis was adjusted for the following baseline variables: age, sex, left ventricular ejection fraction, NYHA functional class, the presence or absence of diabetes or hypertension, the use or nonuse of an internal defibrillator, the time since the diagnosis of atrial fibrillation, the creatinine level, and the use or nonuse of a beta-blocker, angiotensin-converting–enzyme inhibitor, or oral anticoagulant. The level of statistical significance that was required for the primary analysis was adjusted to account for six interim analyses, each performed at an alpha level of 0.00014, resulting in a final significance level of 0.04998. Follow-up data were censored at the time of the patient's last contact with a study investigator or withdrawal from the study or, if the patient underwent heart transplantation, at the time of surgery. Univariate and multivariate Cox logistic-regression models were used to generate hazard ratios. All reported P values are two-tailed. A data and safety monitoring board reviewed the study twice yearly.

The original estimate that 1450 patients would be needed for the study was based on a 2-year rate of death from cardiovascular causes of 19% in the rate-control group, a power of 80% to detect a reduction of 25% in the rate of death from cardiovascular causes in the rhythm-control group, an accrual period of 2 years, a total study duration of 4 years, a rate of loss to follow-up of 2% per year, and a two-sided alpha level of 0.05.¹⁵ As a result of the extended period of recruitment, sample-size calculations were revised in 2005. It was estimated that with the increased follow-up time, 1374 patients would be needed to demonstrate with equal statistical power the same reduction in the number of deaths from cardiovascular causes.



RESULTS

PATIENTS

A total of 1376 patients were enrolled: 557 (40%) in Canada, 123 (9%) in the United States, 453 (33%) in Brazil and Argentina, 166 (12%) in Europe, and 77 (6%) in Israel (Fig. 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org). Of these patients, 682 were assigned to the rhythm-control group, and 694 were assigned to the rate-control group; 647 (95%) in the rhythm-control group and 650 (94%) in the rate-control group either completed follow-up or died. The mean (\pm SD) follow-up was 37 \pm 19 months; the longest period of follow-up was 74 months,

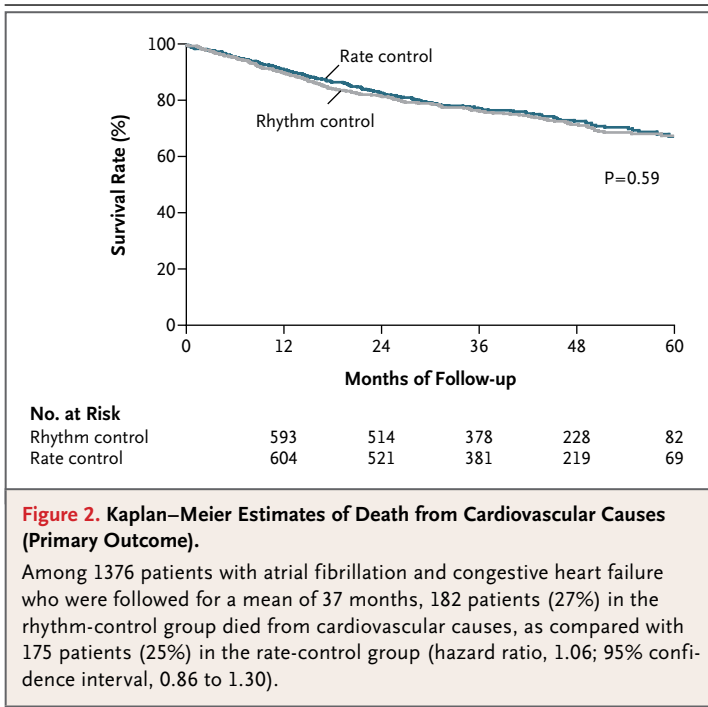


Figure 2. Kaplan–Meier Estimates of Death from Cardiovascular Causes (Primary Outcome).

Among 1376 patients with atrial fibrillation and congestive heart failure who were followed for a mean of 37 months, 182 patients (27%) in the rhythm-control group died from cardiovascular causes, as compared with 175 patients (25%) in the rate-control group (hazard ratio, 1.06; 95% confidence interval, 0.86 to 1.30).

and the median follow-up for all surviving patients was 47 months.

BASELINE CHARACTERISTICS

The two groups were generally well matched with respect to baseline characteristics (Table 1). Overall, the mean age was 67 years, and 82% of the patients were men. Thirty-one percent of the patients were in NYHA class III or IV, and coronary artery disease was the predominant cardiac diagnosis in 48% of the patients; 48% had systemic hypertension, and 21% had diabetes. The mean left ventricular ejection fraction was $27 \pm 6\%$. More than two thirds of the patients had persistent atrial fibrillation, and more than 50% had previously been hospitalized for atrial fibrillation or heart failure.

THERAPY

At 12 months of follow-up, 82% of patients in the rhythm-control group were receiving amiodarone (Table 2). That percentage dropped to 76% at 24 months and to 73% at 36 months. A higher proportion of patients in the rate-control group than in the rhythm-control group received beta-blockers and digoxin. More than 90% of the patients were treated with an angiotensin-converting-enzyme

inhibitor or an angiotensin-receptor blocker, and 90% received an oral anticoagulant.

During the study, 142 patients (21%) in the rhythm-control group crossed over to the rate-control group. The most common reason for the switch was an inability to maintain sinus rhythm. Of the 66 patients (10%) in the rate-control group who crossed over to the rhythm-control group, the most common reason was worsening heart failure.

As documented on 12-lead electrocardiography, the prevalence of atrial fibrillation in the rhythm-control group was 54% at baseline and then declined to 33% at 3 weeks and to 17% at 4 months (Fig. 1A). The rate remained under 20% until the 24-month visit and was 27% at 4 years of follow-up. In the rate-control group, the prevalence of atrial fibrillation ranged from 59 to 70% during follow-up. The proportion of patients in whom electrocardiographically confirmed atrial fibrillation occurred between visits, as documented through chart review, paralleled trends documented on electrocardiography performed at scheduled visits (Fig. 1B). During follow-up, 58% of patients in the rhythm-control group had at least one recurrence of atrial fibrillation.

In the rate-control group, the baseline ventricular rate was within the range specified by the guidelines in 72% of patients who underwent a 6-minute walk test, and targets for the management of atrial fibrillation and for heart rate were subsequently achieved in 82 to 88% of patients during the first 3 years of follow-up.

PRIMARY OUTCOME

The mean actuarial annual rate of death from cardiovascular causes for all patients was 8%. Death from cardiovascular causes, the primary outcome, occurred in 182 patients (27%) in the rhythm-control group and 175 patients (25%) in the rate-control group (Fig. 2). The two curves overlapped throughout the study ($P=0.59$ by the log-rank test). The unadjusted hazard ratio for the rhythm-control group, as compared with the rate-control group, was 1.06 (95% confidence interval [CI], 0.86 to 1.30). This confidence interval was consistent with a maximum reduction of 14% and a maximum increase of 30% in the primary outcome in the rhythm-control group. After adjustment for baseline measures, the hazard ratio was 1.05 (95% CI, 0.85 to 1.29; $P=0.67$).

SECONDARY OUTCOMES

Overall, 445 patients (32%) died during the study, at a rate of nearly 10% per year. Of these deaths, 80% were from cardiovascular causes (Table 3). Overall survival and the risks of stroke, worsening heart failure, and the composite of death from cardiovascular causes, stroke, or worsening heart failure were similar in the two groups (Fig. 3).

HOSPITALIZATIONS, PROCEDURES, AND OTHER EVENTS

The proportion of patients who required hospitalization was higher in the rhythm-control group than in the rate-control group (64% vs. 59%, $P=0.06$), particularly during the first year (46% vs. 39%, $P=0.001$). Also more frequent in the rhythm-control group were hospitalization for atrial fibrillation (14% vs. 9%, $P=0.001$) and hospitalization for bradyarrhythmia (6% vs. 3%, $P=0.02$) (Table A in the Supplementary Appendix). A higher proportion of patients in the rhythm-control than in the rate-control group required electrical cardioversion (59% vs. 9%, $P<0.001$). The rates of sustained ventricular tachyarrhythmias and major hemorrhage that did not involve the central nervous system were similar in the two groups (Table B in the Supplementary Appendix). No significant differences favoring either strategy were noted in any of 10 prespecified subgroups (Fig. 2 in the Supplementary Appendix).

DISCUSSION

In this multicenter, randomized trial involving patients with atrial fibrillation and congestive heart failure, the routine use of a rhythm-control strategy did not reduce the rate of death from cardiovascular causes, as compared with a rate-control strategy. In addition, there was no evidence of a reduction in the rate of death from cardiovascular causes in key prespecified subgroups, and there were no significant differences in important secondary outcomes (death from any cause, worsening heart failure, or stroke).

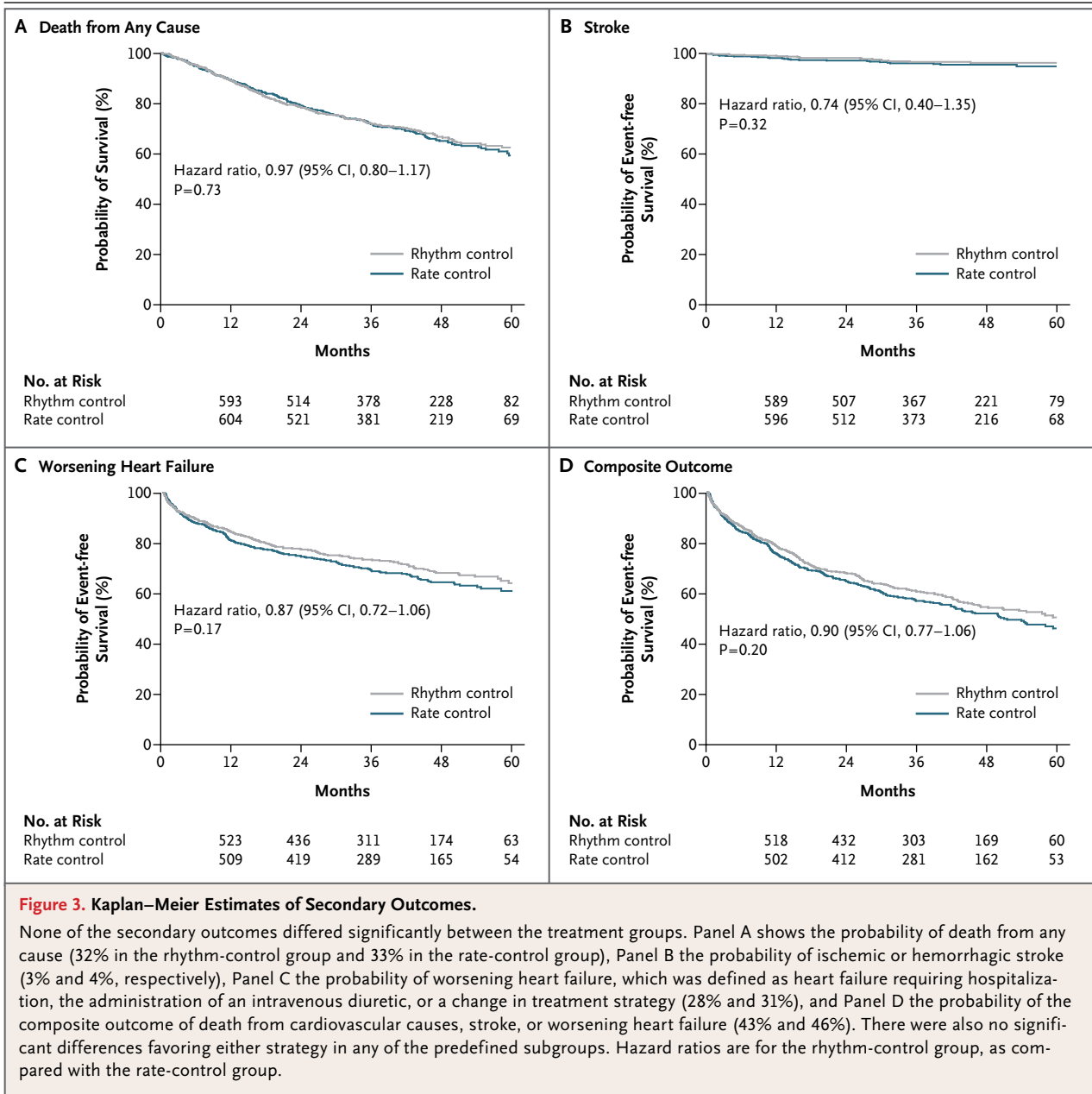
The study population is representative of an international population of patients with atrial fibrillation and congestive heart failure. Compliance with the assigned therapeutic strategy was high, and 75 to 80% of patients in the rhythm-control group were in sinus rhythm at repeated assessments during a relatively long follow-up period (3 years on average).

Table 3. Cause of Death.

| Cause | Rhythm-Control Group (N = 682) | Rate-Control Group (N = 694) | P Value |
|---------------------------|-----------------------------------|---------------------------------|---------|
| | no. (%) | | |
| Total deaths | 217 (32) | 228 (33) | 0.68 |
| Cardiovascular | 182 (27) | 175 (25) | 0.53 |
| Presumed arrhythmic cause | 71 (10) | 88 (13) | 0.19 |
| Congestive heart failure | 73 (11) | 57 (8) | 0.11 |
| Myocardial infarction | 15 (2) | 9 (1) | 0.20 |
| Stroke | 9 (1) | 11 (2) | 0.68 |
| Other | 14 (2) | 10 (1) | 0.39 |
| Noncardiovascular | 35 (5) | 53 (8) | 0.06 |
| Cancer | 14 (2) | 20 (3) | 0.32 |
| Renal failure | 1 (<1) | 2 (<1) | 1.0 |
| Trauma | 0 | 1 (<1) | 1.0 |
| Sepsis | 11 (2) | 26 (4) | 0.01 |
| Other | 9 (1) | 4 (1) | 0.15 |

The importance of this trial is that it compared a rhythm-control strategy with a rate-control strategy specifically in patients with heart failure. Our findings are consistent with studies that did not show a benefit of rhythm control on mortality or morbidity in patients with atrial fibrillation, most of whom did not have heart failure.²⁸⁻³³ As compared with some previous trials involving patients who had atrial fibrillation without heart failure,^{30,31} our study showed no trend toward an increased rate of death or stroke associated with rhythm control, possibly because we excluded patients who were using class I antiarrhythmic agents and because our patients had a higher rate of use of warfarin than those in the previous trials.

Our results cannot be generalized to patients with heart failure and preserved left ventricular function. Atrial fibrillation is common in such patients, particularly in the elderly, but little is known about the prognostic effect and treatment of atrial fibrillation in patients who have heart failure with preserved systolic function.^{20,37} The therapies we used to maintain sinus rhythm were predominantly pharmacologic, which reflects current general practice for patients with heart failure. Although some data suggest that ablation can improve ventricular function in patients with abnormal systolic function,^{38,39} the effects of these



procedures on ventricular function and outcome in patients with heart failure remain to be established in prospective, randomized clinical trials.

In our study, the actuarial annual rate of death (10%) was somewhat higher than the rate that has been reported in contemporary trials involving patients with heart failure. In the Sudden Cardiac Death in Heart Failure trial (ClinicalTrials.gov number, NCT00000609), which enrolled patients similar to those in our trial with respect to left ventricular dysfunction, the annual mortality was

approximately 9% for medically treated patients and 7% for those who received an implantable defibrillator.⁴⁰ However, in that trial, the average age of the patients was 60 years, and only 15% had a history of atrial fibrillation, as compared with our trial, in which the average age was 67 years and all patients had atrial fibrillation. The proportion of patients with implantable defibrillators was low in our trial (7% of patients at baseline and an additional 9% during follow-up), reflecting international practice over the course of

the trial, and 36% of all deaths were presumed to be associated with arrhythmia. Therefore, wider use of implantable defibrillators might have decreased the mortality in our study.

Patients in the rhythm-control group were more likely to be hospitalized than were those in the rate-control group, particularly during the first year after enrollment. This finding probably reflects the need for repeated cardioversion and adjustment of antiarrhythmic therapy, which is consistent with the results of previous studies.^{28,30,32}

Several factors may explain why the rhythm-control strategy did not reduce mortality among patients with heart failure. The predictive value of atrial fibrillation in patients with heart failure may be due to the negative prognostic features that make atrial fibrillation more likely (e.g., worse ventricular function, increased neurohormonal activation, and the presence of an underlying inflammatory state) rather than an independent effect of atrial fibrillation on the outcome. Although most patients in the rhythm-control group were free of atrial fibrillation at repeated assessments, not all patients were in sinus rhythm at all times. In addition, some patients in the rate-control group were free of atrial fibrillation during follow-up. If atrial fibrillation has a truly independent effect on prognosis, then a greater decrease in the prevalence of atrial fibrillation may be needed to show a reduction in mortality. Finally, the potential benefit of sinus-rhythm maintenance with respect to mortality may have been neutralized by harmful effects of currently available antiarrhythmic therapies.

Our clinical trial provided important new information concerning two widely used treatment

strategies for atrial fibrillation in patients with heart failure. The study hypothesis was not borne out, and none of the postulated benefits of a rhythm-control strategy were confirmed. The rate-control strategy eliminated the need for repeated cardioversion and reduced rates of hospitalization. In conclusion, our results suggest that rate control should be considered a primary approach for patients with atrial fibrillation and congestive heart failure.

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APPENDIX

The following persons participated in this trial: **Executive Committee:** D. Roy (chair), M. Talajic, S. Nattel, D.G. Wyse, P. Dorian, M.G. Bourassa, J. Lambert, J.L. Rouleau; **Steering Committee:** J.M.O. Arnold, A.E. Buxton, A.J. Camm, S.S. Connolly, M. Dubuc, A. Ducharme, P.G. Guerra, S. Hohnloser, J.Y. Le Heuzey, K.L. Lee, G. O'Hara, O.D. Pedersen, I. Schmid, B.N. Singh, L.W. Stevenson, W.G. Stevenson, B. Thibault, A.L. Waldo; **Data and Safety Monitoring Board:** G. Dagenais (chair), D. Johnstone, R. Nadeau, R. Roberts, D. Roden, S. Shapiro, D.P. Zipes; **External Events Committee:** N. Racine (chair), J. Brophy, I. Dyrda, L.-H. Lebrun, G. Lalonde, A. Roussin, M. Sturmer; **Montreal Heart Institute Coordinating Center:** D. Johnson (director), M.C. Guertin (biostatistician), S. Levesque, C. Alcide, F. Desgagné, M.C. Tremblay; **Study Management:** M. Morello (coordinator), C. Bossy, M. Provencher; **Investigators:** **Argentina** — Instituto Argentino de Diagnóstico y Tratamiento: J. Gonzalez-Zuelgaray; *Centre Privado de Cardiología de Tucuman:* L. Aguinaga; *Instituto de Cardiología de Corrientes:* D.L. Pozzer; *Hospital General de Agudos J.M. Mejía:* M.V. Elizari, J. Galperin; *Clinica y Maternidad Sulzo Argentina:* S. Dubner; *Sanatorio Británico Rosario:* R. Lanzotti; *Fundación Ruscalleda:* J.L. Serra; *Instituto Modelo de Cardiología:* D. Boccardo; *Instituto Cardiovascular de Buenos Aires:* A. Giniger; *Hospital Privado—Centro Médico de Córdoba:* A. Caeiro; *Sanatorio Guemes:* A. Peralta, B. Sansalone. **Belgium** — *Clinique Sud Luxembourg:* G.H. Mairesse; *Cliniques Universitaires UCL de Mont-Godinne:* L. De Roy. **Brazil** — *Hospital São Lucas Da Pontifícia Universidade Católica do Rio Grande do Sul:* C. Kalil; *Hospital Italiano de Garibaldi:* J.L. Ramos; *Instituto de Cardiologia DO RS:* G. Glotz De Lima; *Instituto de Molestias Cardiovasculares:* A. Menezes Lorga; *Hospital Pro-Cardiaco:* E.T. Mesquita; *Barra d'Or Hospital:* O. Ferreira de Souza; *Hospital da PUC—Curitiba:* J.C. Moura Jorge; *Hospital de Clinicas de Porto Alegre:* L. Zimmerman; *Federal University of Sao Paulo:* A.A.V. de Paola. **Canada** — *Institut de Cardiologie de Montréal:* D. Roy; *Institut de Cardiologie de Québec:* G. O'Hara; *Port Arthur Clinic:* F. Nigro; *Recherche Medicale St-Jérôme:* D. Ouimet; *Libin Cardiovascular Institute of Alberta:* D.G. Wyse; *Hamilton General Hospital:* C. Demers; *Cité de La Santé de Laval:* H. Mayrand; *London Health Sciences Centre:* J.M.O. Arnold; *CH Pierre Le Gardeur:* G. Gosselin; *Keary Medical Centre:* D. Rupka; *Centre Hospitalier de l'Université de Mon-*

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