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Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Rate control is often the therapy of choice for atrial fibrillation. Guidelines recommend strict rate control, but this is not based on clinical evidence. We hypothesized that lenient rate control is not inferior to strict rate control for preventing cardiovascular morbidity and mortality in patients with permanent atrial fibrillation.

METHODS

We randomly assigned 614 patients with permanent atrial fibrillation to undergo a lenient rate-control strategy (resting heart rate <110 beats per minute) or a strict rate-control strategy (resting heart rate <80 beats per minute and heart rate during moderate exercise <110 beats per minute). The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. The duration of follow-up was at least 2 years, with a maximum of 3 years.

RESULTS

The estimated cumulative incidence of the primary outcome at 3 years was 12.9% in the lenient-control group and 14.9% in the strict-control group, with an absolute difference with respect to the lenient-control group of –2.0 percentage points (90% confidence interval, –7.6 to 3.5; P<0.001 for the prespecified noninferiority margin). The frequencies of the components of the primary outcome were similar in the two groups. More patients in the lenient-control group met the heart-rate target or targets (304 [97.7%], vs. 203 [67.0%] in the strict-control group; P<0.001) with fewer total visits (75 [median, 0], vs. 684 [median, 2]; P<0.001). The frequencies of symptoms and adverse events were similar in the two groups.

CONCLUSIONS

In patients with permanent atrial fibrillation, lenient rate control is as effective as strict rate control and is easier to achieve. (ClinicalTrials.gov number, NCT00392613.)

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*Investigators and committees of the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II) study are listed in the Appendix.

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Atrial fibrillation is not a benign condition.[1] It may cause symptoms and is associated with stroke and heart failure. Previous studies have established that the rates of complications and death were similar in patients with atrial fibrillation receiving rate-control therapy and in those receiving rhythm-control therapy.[2,3] Therefore, rate control has become front-line therapy in the management of atrial fibrillation. The optimal level of heart-rate control, however, is unknown, as is whether strict rate control is associated with an improved prognosis as compared with a more lenient approach.[2-6] Guidelines, though empirical and not evidence-based, recommend the use of strict rate control[1] to reduce symptoms, improve the quality of life and exercise tolerance, reduce heart failure (and hence bleeding[7] and stroke[8]), and improve survival. On the other hand, strict rate control could cause drug-related adverse effects, including bradycardia, syncope, and a need for pacemaker implantation. Thus, the balance between benefit and risk in terms of cardiovascular morbidity and mortality, quality of life, exercise tolerance, and disease burden remains unknown. Therefore, we conducted a multicenter, prospective, randomized trial to test the hypothesis that lenient rate control is not inferior to strict rate control in preventing cardiovascular events in patients with permanent atrial fibrillation.

Methods

Study Design

The Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II (RACE II) study was a prospective, multicenter, randomized, open-label, noninferiority trial designed to compare two rate-control strategies in patients with permanent atrial fibrillation. The design of the study has been described previously.[6] Recruitment started in January 2005 and ended in June 2007.

The study was initiated and coordinated by the Interuniversity Cardiology Institute of the Netherlands, the University Medical Center Groningen, and the Working Group on Cardiovascular Research the Netherlands. The study was funded by a major grant from the Netherlands Heart Foundation and by unrestricted educational grants from pharmaceutical and device companies. None of the sponsors were involved in the study design, data collection, data analysis, or manuscript preparation. The steering committee was responsible for the design and conduct of the study, the data analysis and reporting, and manuscript preparation. Study monitoring, data management, and validation were independently performed at the Trial Coordination Center (University Medical Center Groningen, the Netherlands). The study was approved by the institutional review boards of all participating centers. All authors reviewed a previous version of the manuscript and vouch for the accuracy and completeness of the data and analyses.

Study Participants

The study was conducted in 33 centers in the Netherlands. Eligibility criteria were as follows: permanent atrial fibrillation for up to 12 months, age of 80 years or younger, mean resting heart rate above 80 beats per minute, and current use of oral anticoagulation therapy (or aspirin, if no risk factors for thromboembolic complications were present). Reasons for exclusion were described previously.[6]

Randomization and Treatment

After providing written informed consent, all trial participants were randomly assigned, in an open-label fashion, to undergo either a lenient rate-control strategy or a strict rate-control strategy. Randomization was accomplished by means of a central, interactive, automated telephone system, with the use of permuted blocks of various sizes.

During the dose-adjustment phase, patients were administered one or more negative dromotropic drugs (i.e., beta-blockers, nondihydropyridine calcium-channel blockers, and digoxin), used alone or in combination and at various doses, until the heart-rate target or targets were achieved. Patients assigned to undergo the lenient-control strategy (which allowed for a higher heart-rate target than strict control) had a target resting heart rate of below 110 beats per minute. Patients assigned to undergo the strict-control strategy had a target resting heart rate of below 80 beats per minute — lower than the target in the lenient-control group — and a target heart rate of below 110 beats per minute during moderate exercise. The resting heart rate was measured in both groups by means of 12-lead electrocardiography after 2 to 3 minutes of rest in the supine posi-

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tion. In the strict-control group only, the heart rate during exercise was measured during moderate exercise performed for a duration corresponding to 25% of the maximal time achieved on bicycle exercise testing. After the heart-rate targets were reached, 24-hour Holter monitoring was performed to check for bradycardia, in the strict-control group only.

Follow-up outpatient visits occurred every 2 weeks until the heart-rate target or targets were achieved and in all patients after 1, 2, and 3 years. Follow-up was terminated after a maximum follow-up period of 3 years or on June 30, 2009, whichever came first.

During the follow-up period, the resting heart rate (and the exercise heart rate, in the strict-control group) was assessed by the attending physician at each visit. If rate-control drugs had to be adjusted, 24-hour Holter monitoring was repeated to check for bradycardia, in the strict-control group only. If the heart-rate target or targets could not be achieved or patients remained symptomatic, the study protocol permitted further adjustment of rate-control drugs or doses, electrical cardioversion, or ablation at the discretion of the attending physician.

OUTCOMES

The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, major bleeding, and arrhythmic events including syncope, sustained ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate-control drugs, and implantation of a pacemaker or cardioverter–defibrillator. Secondary outcomes included the components of the primary outcome, death from any cause, symptoms, and functional status. All reported primary-outcome events were adjudicated by an independent adjudication committee that was unaware of the randomized treatment assignments. Only deaths classified as having a cardiac arrhythmic, cardiac nonarrhythmic, or noncardiac vascular cause were included in the analysis of the primary end point.[9,10]

Heart failure was defined as heart failure necessitating hospitalization and the start of or increase in dose of diuretics. Stroke was defined as the sudden onset of a focal deficit consistent with occlusion of a major cerebral artery (documented by means of imaging) and categorized as ischemic, hemorrhagic, or indeterminate. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ as documented with the use of imaging, surgery, or autopsy. Major bleeding was defined as a reduction in the hemoglobin level by at least 20 g per liter, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. Syncope was defined as a transient loss of consciousness that may have been caused by a rhythm disorder. Sustained ventricular tachycardia was defined as ventricular tachycardia lasting more than 30 seconds or requiring electrical termination owing to hemodynamic compromise. Cardiac arrest was defined as circulatory arrest necessitating resuscitation and hospitalization. Life-threatening adverse effects of rate-control drugs included digitalis intoxication and conduction disturbances necessitating hospitalization. Pacemaker implantations for clinically significant bradycardia and cardioverter–defibrillator implantations for sustained ventricular arrhythmias were the only types of implantations included in the primary analysis.

STATISTICAL ANALYSIS

The trial was designed to determine whether a strategy of lenient rate control was as effective as (i.e., noninferior to) a strategy of strict rate control. The study size was determined on the basis of an expected rate of the primary outcome of 25% at 2.5 years in both treatment groups and a requirement that the study had 80% power to rule out an absolute increase of 10 percentage points in the rate of the primary outcome at 2.5 years in the lenient-control group, with a one-sided alpha level of 0.05. Pretrial estimates of the expected event rates were based on the observed event rate in the (lenient) rate-control group of the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial.[3] The noninferiority boundary in the present study was similar to that in the previous RACE trial, which implied that noninferiority of lenient rate control to strict rate control was to be determined by the same criteria by which we had previously shown the noninferiority of (lenient) rate control to rhythm control. A sample size of 250 patients in each group with a median follow-up of 2.5 years satisfied the statistical requirements, allowing for an attrition rate of less than 5% of patients. In the course of the trial, we found that the primary outcome occurred

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less frequently than anticipated. We increased the number of patients to 300 in each group and extended the follow-up period to June 30, 2009, with a maximum duration of 3 years.

The primary analysis for efficacy (in the intention-to-treat population) consisted of a comparison between the lenient-control group and the strict-control group of the time to the first occurrence of the composite primary outcome as assessed by Kaplan–Meier curves. The follow-up data were censored for patients who had a first occurrence of one of the primary-outcome events, had informed consent withdrawn, had died from a noncardiovascular cause, were lost to follow-up, had been in the trial for 3 years, or had been followed through June 30, 2009 — whichever event

Table 1. Baseline Characteristics of the Study Patients, According to Treatment Group.*

Characteristic	Lenient Rate Control (N=311)	Strict Rate Control (N=303)	Total Population (N=614)
Age — yr	69±8	67±9	68±8
Male sex — no. (%)	205 (65.9)	198 (65.3)	403 (65.6)
Duration of any atrial fibrillation — mo			
Median	16	20	18
Interquartile range	6–54	6–64	6–60
Duration of permanent atrial fibrillation — mo			
Median	3	2	3
Interquartile range	1–6	1–5	1–6
Previous electrical cardioversion — no. (%)	221 (71.1)	220 (72.6)	441 (71.8)
Hypertension — no. (%)	200 (64.3)	175 (57.8)	375 (61.1)
Coronary artery disease — no. (%)	67 (21.5)	44 (14.5)	111 (18.1)
Valvular heart disease — no. (%)	64 (20.6)	60 (19.8)	124 (20.2)
Chronic obstructive pulmonary disease — no. (%)	36 (11.6)	43 (14.2)	79 (12.9)
Diabetes mellitus — no. (%)	36 (11.6)	32 (10.6)	68 (11.1)
Lone atrial fibrillation — no. (%)†	5 (1.6)	6 (2.0)	11 (1.8)
Previous hospitalization for heart failure — no. (%)	28 (9.0)	32 (10.6)	60 (9.8)
$CHADS_2$ score — no. (%)‡	1.4±1.0	1.4±1.2	1.4±1.1
0 or 1	178 (57.2)	195 (64.4)	373 (60.7)
2	94 (30.2)	65 (21.5)	159 (25.9)
3–6	39 (12.5)	43 (14.2)	82 (13.4)
Symptoms — no. (%)	173 (55.6)	175 (57.8)	348 (56.7)
Palpitations	62 (19.9)	83 (27.4)	145 (23.6)
Dyspnea	105 (33.8)	109 (36.0)	214 (34.9)
Fatigue	86 (27.7)	97 (32.0)	183 (29.8)
Body-mass index§	29±5	29±5	29±5
Blood pressure — mm Hg			
Systolic	137±19	135±16	136±18
Diastolic	85±11	82±11	83±11
Heart rate at rest — beats/min	96±14	96±12	96±13
New York Heart Association functional class — no. (%)			
I	206 (66.2)	194 (64.0)	400 (65.1)
II	89 (28.6)	96 (31.7)	185 (30.1)
III	16 (5.1)	13 (4.3)	29 (4.7)

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Table 1. (Continued.)

Characteristic	Lenient Rate Control (N=311)	Strict Rate Control (N=303)	Total Population (N=614)
Rate-control medications in use — no. (%)			
None	36 (11.6)	27 (8.9)	63 (10.3)
Beta-blocker alone	140 (45.0)	136 (44.9)	276 (45.0)
Verapamil or diltiazem alone	18 (5.8)	19 (6.3)	37 (6.0)
Digoxin alone	20 (6.4)	24 (7.9)	44 (7.2)
Beta-blocker and either verapamil or diltiazem	7 (2.3)	11 (3.6)	18 (2.9)
Beta-blocker and digoxin	53 (17.0)	49 (16.2)	102 (16.6)
Digoxin and either verapamil or diltiazem	14 (4.5)	14 (4.6)	28 (4.6)
Beta-blocker, digoxin, and either verapamil or diltiazem	2 (0.6)	5 (1.7)	7 (1.1)
Sotalol	18 (5.8)	13 (4.3)	31 (5.0)
Amiodarone	3 (1.0)	5 (1.7)	8 (1.3)
Other medications in use at baseline — no. (%)			
ARB or ACE inhibitor	166 (53.4)	140 (46.2)	306 (49.8)
Diuretic	134 (43.1)	113 (37.3)	247 (40.2)
Statin¶	103 (33.1)	74 (24.4)	177 (28.8)
Vitamin K antagonist	308 (99.0)	298 (98.3)	606 (98.7)
Aspirin	4 (1.3)	6 (2.0)	10 (1.6)
Echocardiographic variables			
Left atrial size, long axis — mm	46±6	46±7	46±7
Left ventricular end-diastolic diameter — mm	51±7	51±8	51±7
Left ventricular end-systolic diameter — mm	36±8	36±9	36±8
Left ventricular ejection fraction — %	52±11	52±12	52±12
Left ventricular ejection fraction ≤40% — no. (%)	45 (14.5)	48 (15.8)	93 (15.1)

* Plus–minus values are means ±SD. ARB denotes angiotensin-receptor blocker, and ACE angiotensin-converting enzyme.
† Lone atrial fibrillation was defined as atrial fibrillation in the absence of cardiovascular disease and extracardiac precipitating causes of atrial fibrillation.
‡ The $CHADS_2$ score is a measure of the risk of stroke in patients with atrial fibrillation, with scores ranging from 0 to 6 and higher scores indicating a greater risk.[8] Congestive heart failure, hypertension, an age of 75 years or older, and diabetes are each assigned 1 point, and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ Statins were defined as 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors.

came first. The observation time was calculated as the time from randomization until either the occurrence of the primary outcome or the moment of censoring.

To satisfy the criterion for noninferiority, the upper bound of the 90% confidence interval for the absolute difference between the two treatment groups in the estimated rate of the primary outcome needed to be less than 10 percentage points (erroneously specified in our design paper as a relative 10% difference, when in fact it is a 10-percentage-point absolute difference[6]). Because the treatment period had been extended, we eventually used the estimated cumulative incidences at 3 years to assess noninferiority.

The difference between the two groups in the 3-year cumulative incidence was calculated by subtracting the Kaplan–Meier estimated event rate in the lenient-control group from that in the strict-control group. The 90% confidence interval for the difference was calculated with the use of the standard errors from the Kaplan–Meier curves. We

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also tested for noninferiority by comparing the upper bound of the 90% confidence interval for the hazard ratio (calculated from the Cox proportional-hazards model) for the primary outcome in the lenient-control group as compared with the strict-control group with a margin of 1.40, which was derived (post hoc) as 25% divided by (25% + 10%). There were no prespecified subgroup analyses. The results of post hoc subgroup analyses are presented for descriptive purposes. No formal interim analyses were planned or performed. The data and safety monitoring board monitored the occurrence of clinical events from the standpoint of safety.

RESULTS

PATIENTS

A total of 614 patients were enrolled in the study: 311 in the lenient-control group and 303 in the strict-control group (Table 1 and Fig. 1). The groups were well matched, with the exception of a higher prevalence of coronary artery disease and statin use, and a slightly higher diastolic pressure, in the lenient-control group.

HEART RATES

Data recorded at the end of the dose-adjustment phase are reported in Table 2. The mean (±SD) resting heart rate at the end of the dose-adjustment phase was 93±9 beats per minute in the lenient-control group, as compared with 76±12 beats per minute in the strict-control group (P<0.001). After 1 and 2 years and at the end of the follow-up period, the resting heart rates in the lenient-control group were 86±15, 84±14, and 85±14 beats per minute, respectively, as compared with 75±12, 75±12, and 76±14 beats per minute, respectively, in the strict-control group (P<0.001 for all comparisons between the two groups). During the follow-up period, 18 patients in the lenient-control group and 22 patients in the strict-control group had conversion to sinus rhythm (P=0.60). Nine patients in both groups were in sinus rhythm at the end of follow-up (P=0.96). There was no difference between the two groups in the mean percentage of the study period during which the international normalized ratio was within the target range.

PRIMARY OUTCOME

A total of 81 patients (38 in the lenient-control group and 43 in the strict-control group) reached the primary outcome. Kaplan–Meier curves for the primary outcome are shown in Figure 2. The 3-year estimated cumulative incidence was 12.9% in the lenient-control group and 14.9% in the strict-control group (Table 3), with an absolute difference between lenient control and strict control of –2.0 percentage points (90% confidence interval [CI], –7.6 to 3.5) and a hazard ratio of 0.84 (90% CI, 0.58 to 1.21). As compared with strict rate control, lenient rate control was noninferior with regard to the prevention of the primary outcome, for both the criteria of the difference in risk (P<0.001) and the hazard ratio (P=0.001). The hazard ratio was 0.80 (90% CI, 0.55 to 1.17) after statistical adjustment for the unbalanced distribution of the presence of coronary artery disease, the use of statins, and the diastolic blood pressure. The cumulative incidences of components of the primary outcome are shown in Table 3.

OTHER OUTCOMES

Death from any cause occurred in 17 patients in the lenient-control group (5.6% at 3 years), as compared with 18 (6.6% at 3 years) in the strict-control group (hazard ratio, 0.91; 90% CI, 0.52 to 1.59). Death from noncardiovascular causes occurred in 8 patients in the lenient-control group as compared with 7 in the strict-control group.

At the end of the follow-up period, 129 of 283 patients (45.6%) in the lenient-control group and 126 of 274 patients (46.0%) in the strict-control group had symptoms associated with atrial fibrillation (P=0.92): dyspnea (30.0% vs. 29.6%, P=0.90), fatigue (24.4% vs. 22.6%, P=0.63), and palpitations (10.6% vs. 9.5%, P=0.66). In addition, at the end of the follow-up period, in the lenient-control group and the strict-control group, 70.0% and 70.4% of patients, respectively, were in New York Heart Association functional class I, 23.3% and 23.4% were in class II, and 6.7% and 6.2% were in class III (P=0.74 for all comparisons).

Frequencies of hospitalizations and adverse events were similar in the two groups (Table A in the Supplementary Appendix, available with the full text of this article at NEJM.org).

SUBGROUP ANALYSES

Among the 241 patients with a $CHADS_2$ score of 2 or more, the primary outcome occurred in 17 of the 133 patients in the lenient-control group and in 25 of the 108 patients in the strict-control group (P<0.001 for noninferiority). Among the 373 patients with a $CHADS_2$ score below 2, the primary

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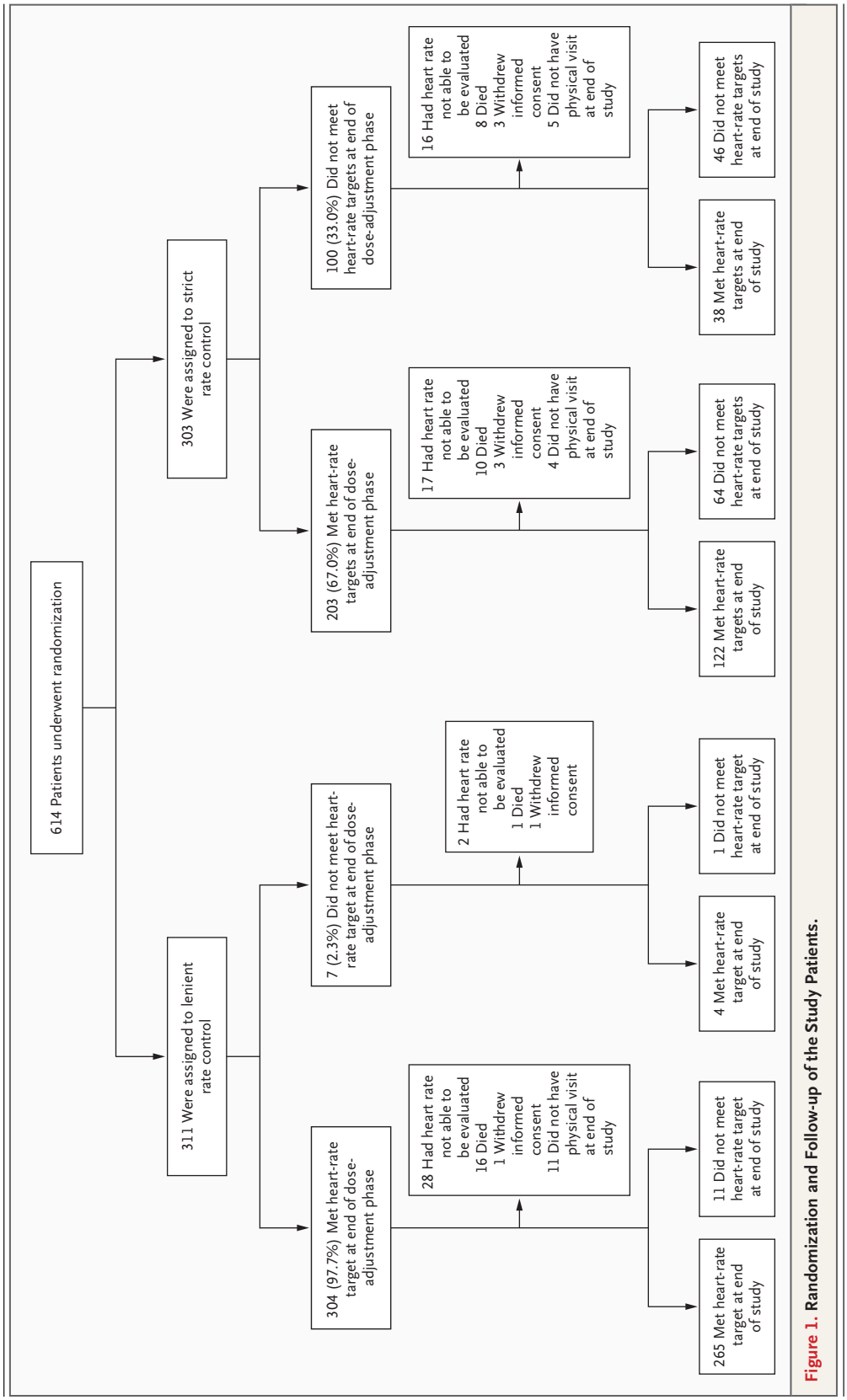

Figure 1. Randomization and Follow-up of the Study Patients.

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Table 2. Rate-Control Targets and Drug Therapy at the End of the Dose-Adjustment Phase, According to Treatment Group.*

Variable	Lenient Rate Control (N=311)	Strict Rate Control (N=303)	P Value
Rate-control target or targets achieved — no. (%)	304 (97.7)	203 (67.0)	<0.001
Resting heart rate — no. (%)			
<70 beats/min	1 (0.3)	67 (22.1)	<0.001
70–80 beats/min	5 (1.6)	161 (53.1)	<0.001
81–90 beats/min	112 (36.0)	39 (12.9)	<0.001
91–100 beats/min	123 (39.5)	20 (6.6)	<0.001
>100 beats/min	70 (22.5)	16 (5.3)	<0.001
Resting heart-rate target achieved — no. (%)	304 (97.7)	228 (75.2)	<0.001
Exercise heart-rate target achieved — no. (%)		220 (72.6)	
Mean heart rate — beats/min		99±16	
Mean duration of exercise with target achieved — sec		94±44	
Holter monitoring†			
Mean heart rate — beats/min		78±11	
Maximal RR interval — sec		2.3±0.6	
Visits to achieve rate-control target or targets — total no.	75	684	<0.001
Median	0	2	
Interquartile range	0–0	1–3	
Reasons for failure to achieve rate-control target or targets — no./total no. (%)			<0.001
Drug-related adverse events	0/7	25/100 (25.0)	
No symptoms or symptoms tolerated	7/7 (100)	53/100 (53.0)	
Target impossible to achieve with drugs	0/7	22/100 (22.0)	
Rate-control medication — no. (%)			
None	32 (10.3)	3 (1.0)	<0.001
Beta-blocker alone	132 (42.4)	61 (20.1)	<0.001
Verapamil or diltiazem alone	18 (5.8)	16 (5.3)	0.78
Digoxin alone	21 (6.8)	5 (1.7)	0.002
Beta-blocker and either verapamil or diltiazem	12 (3.9)	38 (12.5)	<0.001
Beta-blocker and digoxin	60 (19.3)	113 (37.3)	<0.001
Digoxin and either verapamil or diltiazem	18 (5.8)	29 (9.6)	0.08
Beta-blocker, digoxin, and either verapamil or diltiazem	3 (1.0)	27 (8.9)	<0.001
Dose — mg (no. of patients)			
Beta-blocker (normalized to metoprolol-equivalent doses)	120±78 (210)	162±85 (243)	<0.001
Verapamil	166±60 (46)	217±97 (105)	<0.001
Diltiazem	232±74 (5)	217±64 (7)	0.72
Digoxin	0.19±0.8 (109)	0.21±0.8 (180)	0.06

* Plus–minus values are means ±SD. The strict-control group had two heart-rate targets (resting and exercise), whereas the lenient-control group had only one (resting). In addition, exercise testing and 24-hour Holter monitoring were performed in the strict-control group only.

† Holter monitoring was performed in the strict-control group to check for bradycardia (defined as symptomatic bradycardia, asystole for >3 seconds, or an escape rhythm of <40 beats per minute in patients who were awake and free of symptoms). The results led to a reduction in the dose of rate-control medication in eight patients; in three of these, pacemaker implantation was eventually unavoidable.

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outcome occurred in 21 of the 178 patients in the lenient-control group and in 18 of the 195 patients in the strict-control group (P=0.02 for noninferiority). The primary outcome event rates were similar across heart-rate categories at the end of the dose-adjustment phase (Table B in the Supplementary Appendix).

DISCUSSION

We found that lenient rate control was noninferior to strict rate control in the prevention of major cardiovascular events in patients with permanent atrial fibrillation. The primary outcome occurred in 12.9% of patients in the lenient-control group, as compared with 14.9% of patients in the strict-control group. The heart rates achieved in the strict-control group were similar to those observed in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.[11] We confirmed a post hoc comparison of data from the AFFIRM study and the first RACE trial, demonstrating that the stringency of rate control was not associated with significant differences in outcome.[2,3,5]

Why was lenient rate control not associated with more cardiovascular morbidity and mortality? First, the incidence of heart failure was similar between the two groups. A major concern with lenient rate control is the induction or worsening of heart failure.[12-15] This concern was not confirmed by our observations. Apparently, a resting heart rate below 110 beats per minute was low enough to prevent an increased number of hospitalizations for heart failure. This observation is consistent with the notion that beta-blockers do not improve the prognosis of patients with heart failure with atrial fibrillation.[16,17]

Second, the incidence of death from cardiovascular causes was similar between the two groups. Approximately half the deaths in our study were of vascular origin, rather than arrhythmia or heart failure. Third, the rate of adverse effects of drugs, syncope, and pacemaker implantation was similar between the two groups. This observation is inconsistent with data from the AFFIRM trial.[5,11] In that trial, the rate of pacemaker implantation was 7.3% over 3.5 years, as compared with 1.4% over 3 years in the strict-control group in our trial. Reasons for this discrepancy may be that we administered rate-control drugs rather gradually. Alternatively, the thresholds for pacemaker implantation may have varied.

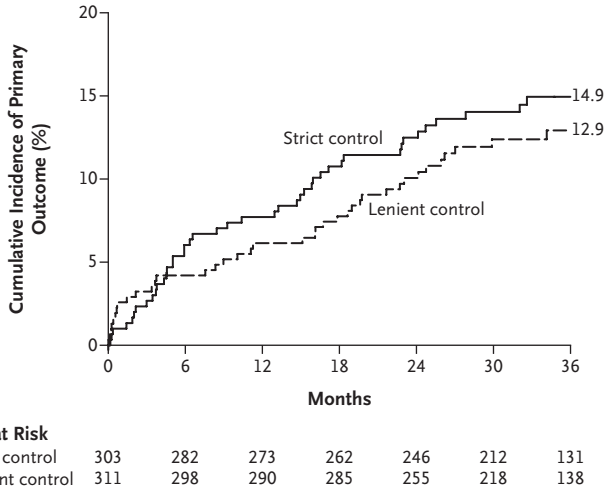

Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of the Primary Outcome, According to Treatment Group.
The numbers at the end of the Kaplan–Meier curves are the estimated cumulative incidence of the primary outcome at 3 years.

Finally, we did not find significant differences in the prevalence of symptoms associated with atrial fibrillation. Almost 60% of the patients in both groups were symptomatic at baseline; this fraction decreased to 46% by the end of the follow-up period, a decline that may be related to underlying disease rather than to the heart rate driving symptoms.[18] Although the prevalence of symptoms was similar in the two groups in our study, we cannot rule out potential differences in the severity of symptoms between the groups.

We included physically active patients, rather than sedentary patients, in our trial, because we chose to assess rate control by means of exercise testing in the strict-control group. Thus, we excluded patients with a previous stroke, resulting in a low-risk study population. These choices may have resulted in the lower-than-expected primary outcome event rate. Although we increased the number of patients from 250 to more than 300 in each treatment group, the overall frequency of the primary outcome events remained relatively low.

A trial evaluating high and low resting heart rates in patients with atrial fibrillation would ideally ensure that the relevant rate targets were met in all patients. In our strict-control group, the resting and exercise targets were achieved in 67.0% of the patients, whereas in the lenient-control group the target rate was virtually always

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Table 3. Cumulative Incidence of the Composite Primary Outcome and Its Components during the 3-Year Follow-up Period, According to Treatment Group.*

Outcome	Lenient Rate Control (N=311)	Strict Rate Control (N=303)	Hazard Ratio (90% CI)
	no. of patients (%)		
Composite primary outcome	38 (12.9)	43 (14.9)	0.84 (0.58–1.21)
Individual components			
Death from cardiovascular cause	9 (2.9)	11 (3.9)	0.79 (0.38–1.65)
From cardiac arrhythmia	3 (1.0)	4 (1.4)	
From cardiac cause other than arrhythmia	1 (0.3)	2 (0.8)	
From noncardiac vascular cause	5 (1.7)	5 (1.9)	
Heart failure	11 (3.8)	11 (4.1)	0.97 (0.48–1.96)
Stroke	4 (1.6)	11 (3.9)	0.35 (0.13–0.92)
Ischemic	3 (1.3)	8 (2.9)	
Hemorrhagic	1 (0.3)	4 (1.5)	
Systemic embolism	1 (0.3)	0	
Bleeding	15 (5.3)	13 (4.5)	1.12 (0.60–2.08)
Intracranial	0	3 (1.0)	
Extracranial	15 (5.3)	10 (3.5)	
Syncope	3 (1.0)	3 (1.0)	
Life-threatening adverse effect of rate-control drugs	3 (1.1)	2 (0.7)	
Sustained ventricular tachycardia or ventricular fibrillation	0	1 (0.3)	
Cardioverter–defibrillator implantation	0	1 (0.3)	
Pacemaker implantation	2 (0.8)	4 (1.4)	

* The tabulations of the composite primary outcome include the first event for each patient. In contrast, the tabulations of component events include all such events. The cumulative incidences were determined with use of Kaplan–Meier analysis.

reached, without much change in therapy. We cannot rule out the possibility that we would have found significant differences between the two groups had we used a more effective means of strict rate control and had we kept heart rates just below 110 beats per minute in the lenient-control group or if we had followed patients beyond 3 years. Although we enrolled relatively low-risk patients, the subgroup analysis revealed that our results also apply to higher-risk patients (i.e., those with a $CHADS_2$ score[8] of 2 or more).

In conclusion, as compared with strict rate control, lenient rate control was noninferior in terms of major clinical events. Furthermore, for both patients and health care providers, lenient rate control is more convenient, since fewer outpatient visits and examinations are needed.

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APPENDIX

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