Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

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הדסה מאסטי – סטודנטית שנה ו'
פנימית ב' תל השומר

Background

- Atrial fibrillation is not a benign condition.
- 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.
- Rate control has become front-line therapy in the management of atrial fibrillation.

Background (2)

- The optimal level of heart-rate control is unknown.
- Guidelines are empirical, they recommend the use of strict rate control to:
  - Reduce symptoms
  - Improve the quality of life and exercise tolerance
  - Reduce heart failure (and hence bleeding and stroke)
  - Improve survival
- Strict rate control could cause drug-related adverse effects, including:
  - Bradycardia / A need for pacemaker implantation
  - Syncope

The problem

The balance between benefit and risk in terms of cardiovascular morbidity and mortality, quality of life, exercise tolerance, and disease burden remains unknown.

Is there another way?

- A multicenter, prospective, randomized trial tested 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 Participants

- The study was conducted in 33 centers in the Netherlands.
- A total of 614 patients were enrolled in the study:
  - 311 in the lenient-control group
  - 303 in the strict-control group
- Eligibility criteria were as follows:
  1. Permanent atrial fibrillation for up to 12 months
  2. Age ≤ 80 years
  3. Mean resting heart rate > 80 beats per minute (bpm)
  4. Current use of oral anticoagulation therapy (or aspirin, if no risk factors for thromboembolic complications were present)
  5. Physically active patients

Randomization

- 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.

Treatment

- During the dose-adjustment phase, patients were administered one or more drugs:
  - Beta-blockers (Atenolol, Metoprolol)
  - Nondihydropyridine calcium-channel blockers (Dilitiazem, Verapamil)
  - Digoxin
- The drugs were used alone or in combination and at various doses, until the heart-rate target was achieved.
- Lenient-control strategy:
  - Resting heart rate < 110 bpm
- Strict-control strategy :
  - Resting heart rate < 80 bpm
  - Heart rate < 110 bpm during moderate exercise.

Treatment (2)

- 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 position.
- In the strict-control group only:
  - The heart rate was measured during moderate exercise 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

- Follow-up outpatient visits occurred every 2 weeks until the heart-rate target was 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,
- During the follow-up period, the resting/exercise heart rate 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 couldn't 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.

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)

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)

Outcomes

Primary outcomes

The primary outcome was a composite of:

- Death from cardiovascular causes

Primary outcomes

The primary outcome was a composite of:

- Death from cardiovascular causes
- Heart failure:
  - Hospitalization
  - Increase in dose of diuretics

Primary outcomes

The primary outcome was a composite of:

- Death from cardiovascular causes
- Heart failure
- Stroke:
  - A 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.

Primary outcomes

The primary outcome was a composite of:

- Death from cardiovascular causes
- Heart failure
- Stroke
- Systemic embolism:
  - An acute vascular occlusion of an extremity or organ as documented with the use of imaging, surgery or autopsy.

Primary outcomes

The primary outcome was a composite of:

- Death from cardiovascular causes
- Heart failure
- Stroke
- Systemic embolism
- Major bleeding:
  - A reduction in the hemoglobin level by at least 20g per liter.
  - Transfusion of at least 2 units of blood.
  - Symptomatic bleeding in a critical area or organ.

Primary outcomes

The primary outcome was a composite of:

- Death from cardiovascular causes
- Heart failure
- Stroke
- Systemic embolism
- Major bleeding
- Syncope:
  - A transient loss of consciousness that may have been caused by a rhythm disorder.

Primary outcomes

The primary outcome was a composite of:

- Death from cardiovascular causes
- Heart failure
- Stroke
- Systemic embolism
- Major bleeding
- Syncope
- Sustained ventricular tachycardia:
  - Ventricular tachycardia lasting more than 30 seconds.
  - Requiring electrical termination owing to hemodynamic compromise.

Primary outcomes

The primary outcome was a composite of:

- Death from cardiovascular causes
- Heart failure
- Stroke
- Systemic embolism
- Major bleeding
- Syncope
- Sustained ventricular tachycardia
- Cardiac arrest:
  - Circulatory arrest necessitating resuscitation and hospitalization.

Primary outcomes

The primary outcome was a composite of:

- Death from cardiovascular causes
- Heart failure
- Stroke
- Systemic embolism
- Major bleeding
- Syncope
- Sustained ventricular tachycardia
- Cardiac arrest
- Life-threatening adverse effects of rate-control drugs:
  - Digitalis intoxication.
  - Conduction disturbances necessitating hospitalization.

Primary outcomes

The primary outcome was a composite of:

- Death from cardiovascular causes
- Heart failure
- Stroke
- Systemic embolism
- Major bleeding
- Syncope
- Sustained ventricular tachycardia
- Cardiac arrest
- Life-threatening adverse effects of rate-control drugs
- Pacemaker implantations for clinically significant bradycardia
- Cardioverter-defibrillator implantations for sustained ventricular arrhythmias

Primary outcomes

All reported primary-outcome events were adjudicated by an independent adjudication committee that was unaware of the randomized treatment assignments.

Statistical Analysis

- 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.
  - 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 Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial.
- The noninferiority boundary in the present study was similar to that in the previous RACE trial.

Statistical Analysis (2)

- A sample size of 250 patients in each group with a median follow-up of 2.5 years satisfied the statistical requirements.
- In the course of the trial it was discovered that the primary outcome occurred less frequently than anticipated.
- The number of patients was increased to 300 in each group and the follow-up period was extended to June 30, 2009, with a maximum duration of 3 years.

Statistical Analysis (3)

- The primary analysis for efficacy 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.
  - Had been followed through June 30, 2009.

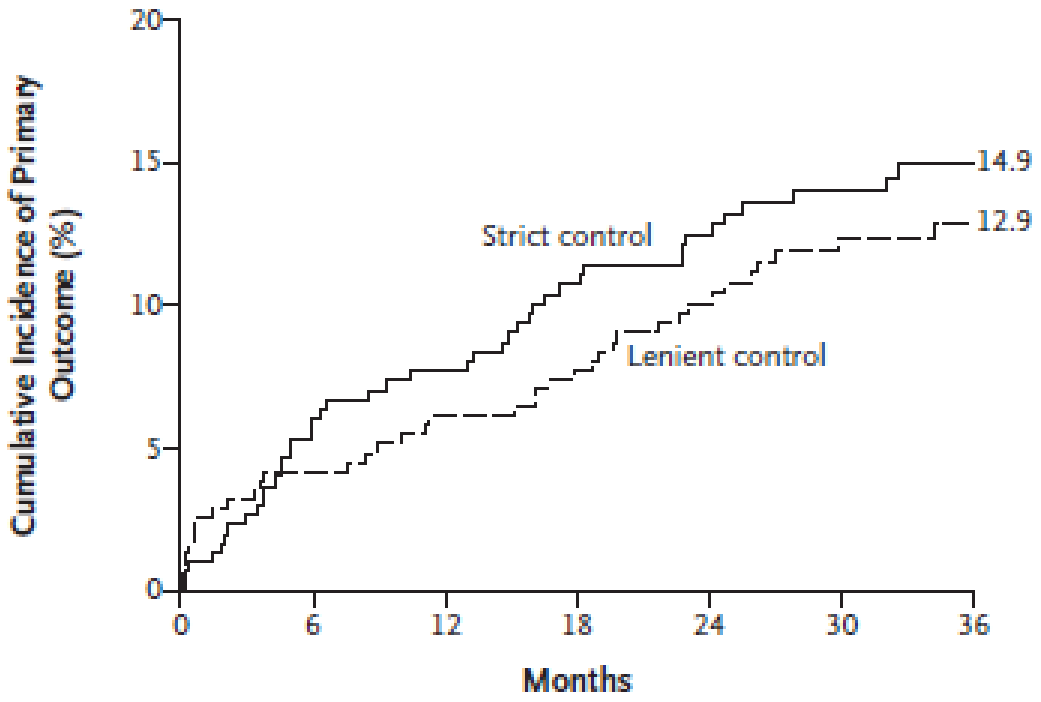

Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of the Primary Outcome, According to Treatment Group.

The numbers at the end of the Kaplan–Meier curves are the estimated cumulative incidence of the primary outcome at 3 years.

Results

Follow up of Rate control in the lenient and the strict control groups:

	At the end of the dose-adjustment phase	After 1 year	After 2 year	At the end of the follow up
The lenient control group	93±9 bpm	86±15 bpm	84±14 bpm	85±14 bpm
The strict control group	76±12 bpm	75±12 bpm	75±12 bpm	76±14 bpm

Results

Primary Outcome

- A total of 81 patients reached the primary outcome.
  - In the lenient-control group: 38 (12%)
  - In the strict-control group: 43 (14%)
- 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.

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.

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

Results - Other Outcomes

	The lenient control group	The strict control group	
Symptoms associated with atrial fibrillation	129/283 (45.6%)	126/274 (46.0%)	P=0.96
Dyspnea	30%	29%	P=0.90
Fatigue	24.4%	22.6%	P=0.63
Palpitations	10.6%	9.5%	P=0.66
New York Heart Association functional class — no. (%)			P=0.74
1	70%	70.4%	
2	23.3%	23.4%	
3	6.7%	6.2%	
Death from any cause	17/283 (5.6% at 3 years)	18/274 (6.6% at 3 years)	hazard ratio, 0.91 90% CI, 0.52 to 1.59
Death from noncardiovascular causes	8/283	7/274	
Death from cardiovascular causes	9/283 3.2% at 3 years	11/274 4% at 3 years	

Results
Subgroup Analyses

Occurrence of primary outcome according to CHADS2 score:

	The lenient control group	The strict control group	
CHADS2 ≥ 2	**17/133** (12.7%)	**25/108** (23.1%)	**P<0.001** for noninferiority
CHADS2 < 2	**21/178** (11.8%)	**18/195** (9.2%)	**P=0.02** for noninferiority

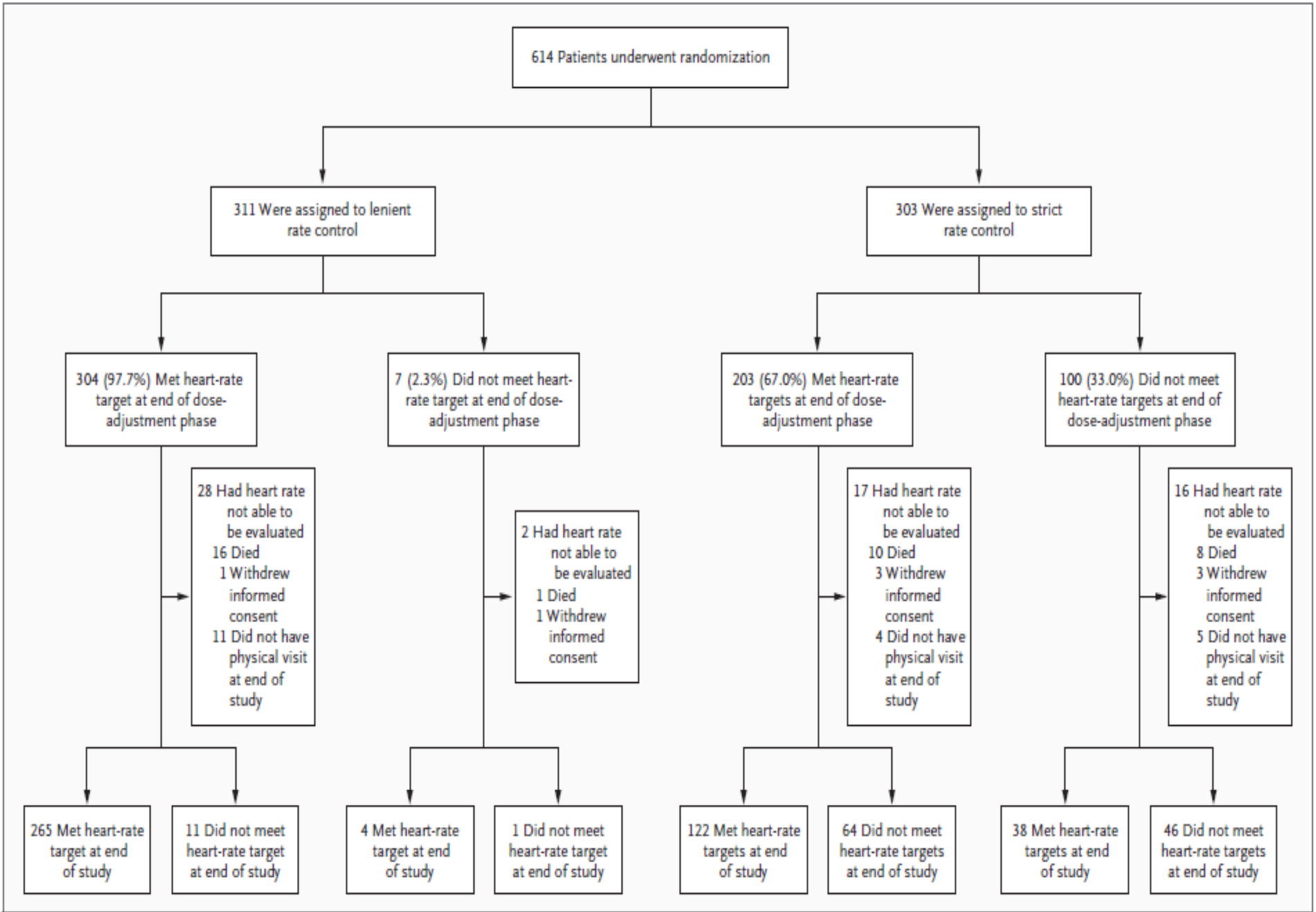

Figure 1. Randomization and Follow-up of the Study Patients.

Discussion

- 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.
  - 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.
- 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.

Discussion (2)

Why was lenient rate control not associated with more cardiovascular morbidity and mortality?

- Apparently, a resting heart rate below 110 bpm was low enough to prevent an increased number of hospitalizations for heart failure.
- The incidence of death from cardiovascular causes was similar between the two groups.
- The rate of adverse effects of drugs, syncope and pacemaker implantation was similar between the two groups.
- There aren't any significant differences in the prevalence of symptoms associated with atrial fibrillation.

Limitation

- Although the prevalence of symptoms associated with AF were similar in the two groups, we cannot rule out potential differences in the severity of symptoms.
- In order to assess the rate control in the strict-control group by means of exercise testing, one of the Eligibility criteria was physically active patients:
  - Patients with a previous stroke were excluded resulting in a low-risk study population.
  - These choices may have resulted in the lower-than-expected primary outcome event rate.

Limitation (2)

- Although the increase in number of patients in each treatment group, the overall frequency of the primary outcome events remained relatively low.
- There is a possibility that we would have found more significant differences between the two groups by:
  - Using a more effective means of strict rate control - the resting and exercise targets were achieved in only 67.0% of the patients where as in the lenient control group the target rate was virtually always reached, without much change in therapy.
  - Keeping a heart rates just below 110 bpm in the lenient-control group.
  - Patient's follow up beyond 3 years.

Summary

- Lenient rate control is as effective as strict rate control and is easier to achieve.
- Furthermore, for both patients and health care providers, lenient rate control is more convenient, since fewer outpatient visits and examinations are needed.

The End

Thank you…