Randomized Trial of Rate-Control Versus Rhythm-Control in Persistent Atrial Fibrillation

The Strategies of Treatment of Atrial Fibrillation (STAF) Study

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OBJECTIVES   This study was designed to compare two treatment strategies in patients with atrial fibrillation (AF): rhythm-control (restoration and maintenance of sinus rhythm) and rate-control (pharmacologic or invasive rate-control and anticoagulation).

BACKGROUND   Atrial fibrillation is the most common arrhythmia. It is unclear whether a strategy of rhythm- or rate-control is better in terms of mortality, morbidity, and quality of life.

METHODS   The Strategies of Treatment of Atrial Fibrillation (STAF) multicenter pilot trial randomized 200 patients (100 per group) with persistent AF to rhythm- or rate-control. The combined primary end point was a combination of death, cardiopulmonary resuscitation, cerebrovascular event, and systemic embolism.

RESULTS   After 19.6 ± 8.9 months (range 0 to 36 months) there was no difference in the primary end point between rhythm-control (9/100; 5.54%/year) and rate-control (10/100; 6.09%/year; p = 0.99). The percentage of patients in sinus rhythm in the rhythm-control group after up to four cardioversions during the follow-up period (rate-control group) was 23% (0%) at 36 months. Eighteen primary end points occurred in atrial fibrillation; only one occurred in sinus rhythm (p = 0.049).

CONCLUSIONS The STAF pilot study showed no differences between the two treatment strategies in all end points except hospitalizations. These data suggest that there was no benefit in attempting rhythm-control in these patients with a high risk of arrhythmia recurrence. It remains unclear whether the results in the rhythm-control group would have been better if sinus rhythm had been maintained in a higher proportion of patients, as all but one end point occurred during AF. (J Am Coll Cardiol 2003;41:1690–6) © 2003 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common arrhythmia, with an overall prevalence of at least 0.5% in the general population (1). Because AF is an age-related arrhythmia, it has been called a "new epidemic" of cardiovascular disease in Western societies, attributable to a steadily growing proportion of elderly people (2). Currently, about 70% of patients with AF are between 65 and 85 years old (1).

Atrial fibrillation is strongly related to congestive heart failure and stroke. The expected increased burden of stroke is illustrated by the fact that the attributable risk of stroke in AF increases by two- to threefold with each decade, from 1.5% in the 50 to 59 years group to 23.5% in the 80 to 89 years group (3). These data demonstrate that AF is and will continue to be a major health problem.

In any given patient presenting with persistent AF (according to the definition of Gallager and Camm [4]), the basic therapeutic question is whether to try to reestablish sinus rhythm or to leave the patient in AF and control the rate. Most physicians opt for rhythm-control with cardioversion and antiarrhythmic drug therapy (5), although there is a paucity of investigations dealing with treatment strategies in AF (6). Moreover, long-term maintenance of sinus rhythm is poor and there are serious side effects of antiarrhythmic treatment to consider when comparing rhythm-control with rate-control.

At present, the only published study data concerning treatment strategies stem from the Pharmacological Intervention in Atrial Fibrillation (PIAF) trial (7). The PIAF trial used an end point of symptoms related to AF and could not find a clinically meaningful difference between the two treatment strategies (7).

METHODS

Study design. The Strategies of Treatment of Atrial Fibrillation (STAF) study was an open, randomized, controlled pilot trial to compare the strategy of rhythm-control with the strategy of rate-control in patients with persistent AF (4) in terms of mortality, quality of life, and complications of therapy and disease.

Patients were randomized to one of two treatment strategies (randomization codes computer generated per

Abbreviations and Acronyms	
AF	= atrial fibrillation
AFFIRM	= Atrial Fibrillation Follow-up Investigation of Rhythm Management
AV	= atrioventricular
INR	= international normalized ratio
LV	= left ventricular
LVEF	= left ventricular ejection fraction
NYHA	= New York Heart Association
PIAF	= Pharmacological Intervention in Atrial Fibrillation
SPAF	= Stroke Prevention in Atrial Fibrillation
STAF	= Strategies of Treatment of Atrial Fibrillation

study center, blocks of 10 patients, randomization by calling the study center). The study protocol was approved by the local ethics committees of all participating centers.

Patients randomized to rhythm-control were to be cardioverted by external or internal cardioversion. The recommendations for prophylaxis of AF recurrence were class I antiarrhythmic agents or sotalol in the absence of coronary heart disease and in patients with a normal left ventricular (LV) function. Patients with coronary heart disease or an impaired LV function should receive a beta-blocker and/or amiodarone. In case of a recurrence, repeated cardioversion was to be performed.

In patients randomized to rate-control, beta-blockers, digitalis, calcium antagonists, or atrioventricular (AV)-node ablation/modification with or without pacemaker implantation were used.

Oral anticoagulation was prescribed in both treatment strategies according to the guidelines of the American College of Chest Physicians (8).

Inclusion/exclusion criteria. The STAF trial was aimed at patients with a moderate to high risk of arrhythmia recurrence. The inclusion/exclusion criteria were selected to exclude patients with a low risk of recurrence on one side of the spectrum of patients with AF, and patients with a very high risk of arrhythmia recurrence on the other side. Patients were eligible if they could give informed consent, were 18 years or older, and had *one or more* of the following criteria: AF for >4 weeks; left atrial size >45 mm; congestive heart failure, New York Heart Association (NYHA) functional class II or greater; left ventricular ejection fraction (LVEF) <45%; or ≥1 prior cardioversion with arrhythmia recurrence.

Patients were excluded from the study if they had permanent AF >2 years, a history of paroxysmal AF, left atrial size >70 mm, LVEF <20%, Wolff-Parksinon-White syndrome, history of AV-node ablation or modification, absolute contraindications against oral anticoagulation, primarily success-less cardioversion within 4 weeks before randomization, pregnancy, or malignant or other concomitant disease that would most likely limit the patient's life expectancy to <3 years.

Follow-up and study procedures. At baseline and at follow-up visits (3, 6, 12, 18, 24, and 36 months), patients underwent physical examination, transthoracic echocardiography, resting electrocardiogram, blood pressure measurement, and assessment of quality of life (Medical Outcomes Study Short-Form health survey [SF-36] questionnaire [9,10]) and symptoms.

Study end points. The primary end point of the study was the combination of death, stroke or transient ischemic attack, systemic embolism, and cardiopulmonary resuscitation. Secondary end points were syncope, bleeding (requiring hospitalization, transfusion, or both), quality of life (assessed by SF-36), echocardiographic parameters (LV end-diastolic diameter, LV end-systolic diameter, LVEF, left atrial diameter), resting heart rate, and maintenance of sinus rhythm at follow-up.

Statistical analysis. Primary and secondary end point analyses were done on an intention-to-treat basis. Another end point analysis was performed, stratified by the actual heart rhythm at follow-up or during the event of an end point.

All tests were two-tailed; $p < 0.05$ was considered significant. Comparisons of the end points between treatment groups were performed by Fisher exact test. Other data were compared by the Student t test when dealing with normally distributed variables or by the Wilcoxon test otherwise. Survival curves (survival without a primary end point) were determined according to the method of Kaplan and Meier (11). A two-sample t test was used to analyze changes from baseline in the SF-36 scores.

The hypothesis of the STAF study was that rhythm-control would reduce the incidence of the combined primary end point (death, cardiopulmonary resuscitation, cerebrovascular event, and systemic embolism) within two years of follow-up from 15% in the rate-control group to 10% (33% relative risk reduction). The number of patients, based on these assumptions, was calculated to be 2,000 (80% power).

Because of the magnitude of the sample size and the paucity of reliable mortality and morbidity data for such a patient cohort, it was decided to do an interim analysis (pilot phase of the study). To test the assumed event rates this interim analysis was planned after the first 200 patients (100 per group) with a minimum follow-up of 12 months, or a primary end point. Data were analyzed with STATISTICA 5.0 software (StatSoft Inc., Tulsa, Oklahoma).

Role of funding source. The funding source had no role in the study design, data collection, analysis, and interpretation, or the writing of the report.

RESULTS

Characteristics of patients. Between January 1997 and August 1999, 200 patients were included; baseline clinical characteristics of patients are shown in Table 1. A total of 44.5% of patients were between 60 and 69 years old, and 34.5% were ≥70 years old. Most patients (79%) had more than one inclusion criterion: 77.5% had a duration of AF of

Table 1. Baseline Characteristics

	Rhythm-Control (n = 100)	Rate-Control (n = 100)
Age, mean, yrs (SD)	65.3 (9.4)	66.2 (7.6)
Age, range, yrs	37–80	40–88
Age, mean, yrs	67	67
Women	41	32
Underlying cardiovascular disease		
Coronary artery disease	34	53
Previous myocardial infarction	6	12
Valvular heart disease	10	16
Dilated cardiomyopathy	9	16
Hypertension	63	62
None	12	9
LA, mean, cm (SD)	4.6 (0.6)	4.6 (0.5)
LVEDD, mean, cm (SD)	5.1 (0.8)	5.1 (0.8)
AF duration,* mean, months (SD)	6 (2)	6 (3)
Previous antiarrhythmic treatment	22	19
Previous cardioversion	31	33

*Duration of current AF episode.
AF = atrial fibrillation; LA = diameter of left atrium; LVEDD = left ventricular end-diastolic diameter.

Table 2. Study End Points

	Rhythm-Control (n = 100)	Rate-Control (n = 100)
Follow-up, mean, months (SD)	19.5 (8.9)	19.7 (8.9)
Follow-up, range, months	0–36	1–36
Follow-up, median, months	18	18
Primary end point*	9	10
Death	4	8
Cardiovascular	3†	8†
Noncardiovascular	1	0
Stroke/TIA	5	1
Systemic embolism	0	1
Secondary end points		
Syncope	0	1
Bleeding	11	8
Sinus rhythm at last follow-up‡	38	9
Hospitalization for cardiovascular disease†		
Number	54	26
Duration, total, days	449	314

*p = 0.99; †two were sudden deaths in the rhythm-control group and four were sudden deaths in the rate-control group; ‡p < 0.001.
TIA = transient ischemic attack.

more than 4 weeks, 52.5% had a left atrial diameter of more than 4.5 cm, 55.5% were in a NYHA functional class ≥II, 13.5% had a LVEF below 45%, and 32% had had ≥1 cardioversion with AF recurrence in the past. In patients who had been cardioverted in the past, the number of previous cardioversion was between 1 and 6, with a median of 2. The total duration of the AF history was 13.7 ± 29.8 months (range 0 to 240 months) in patients randomized to rhythm-control, compared with 10.4 ± 19.8 months (range 1 to 132 months) in rate-control patients (p = 0.38). The duration of the current AF episode was <6 months in 37 patients in the rhythm-control group and 39 in the rate-control group, ≥6 months in 63 patients in the rhythm-control group and 61 in the rate-control group (p = 0.77). Of the patients, 4% had been in AF for more than a year (five in rhythm-control and three in rate-control; p = 0.7).
Primary study end point. There was no difference in the occurrence of the combined primary end point between rhythm-control (9/100; 5.54%/year) and rate-control (10/100; 6.09%/year; p = 0.99; Table 2, Fig. 1).

Total mortality was 2.5% in the rhythm-control group and 4.9% per year in patients randomized to rate-control. Three of four deaths in the rhythm-control group were cardiovascular (two sudden deaths); one was due to kidney failure in a patient who refused dialysis. All deaths in the rate-control group were due to cardiovascular causes, four of which were sudden deaths. None of the cases of cardiovascular death was related to the prescription of class I or III antiarrhythmic agents.

Cerebrovascular events occurred with a frequency of 3.1% per year (rhythm-control) and 0.6% per year (rate-control). Of the five cerebrovascular events in the rhythm-control group, three occurred under full anticoagulation (international normalized ratio [INR] >2), and two at an INR of <2. In the rate-control group both embolic complications (stroke and renal artery embolism) occurred under full

coagulation with an INR >2. In all these events occurring under full anticoagulation, a level of INR >2 had been achieved and had been stable for at least one month before the event. Systemic embolism was rare, with no events in rhythm-control and 0.6% per year in rate-control. Cardiovascular resuscitation with survival, the fourth part of the combined primary end point, was not reported in either group.

Eighteen of 19 primary end points occurred in AF; only one occurred in sinus rhythm (p = 0.049) as shown in Table 2 and Figure 2. The one end point in sinus rhythm was a stroke with complete hemiparesis of the left side two days after successful external cardioversion at an INR of 2.0.
Secondary study end points. There was no difference in the occurrence of the secondary end points syncope (0 in rhythm-control vs. 1 [0.6%/year] in rate-control; p = 0.99) and bleeding complications (11 [6.8%/year] in rhythm-control vs. 8 [4.9%/year] in rate-control; p = 0.99).

In the rhythm-control group a total of 54 hospitalizations for cardiovascular disease occurred (449 days of hospital stay) versus 26 hospitalizations in the rate-control group (314 days; p < 0.001).

In both treatment groups quality of life as assessed by the SF-36 questionnaire was significantly lower at baseline in study patients than in an age-matched German norm population (10) with sinus rhythm (Table 3). At follow-up two measures of quality of life had improved in the rhythm-control group, whereas five measures had improved in the rate-control group. However, there was a tendency to lower quality of life at baseline in the rate-control group.

There were no significant changes in AF-related symptoms (dyspnea, palpitations, and dizziness) during the study period and no significant differences between the two groups.

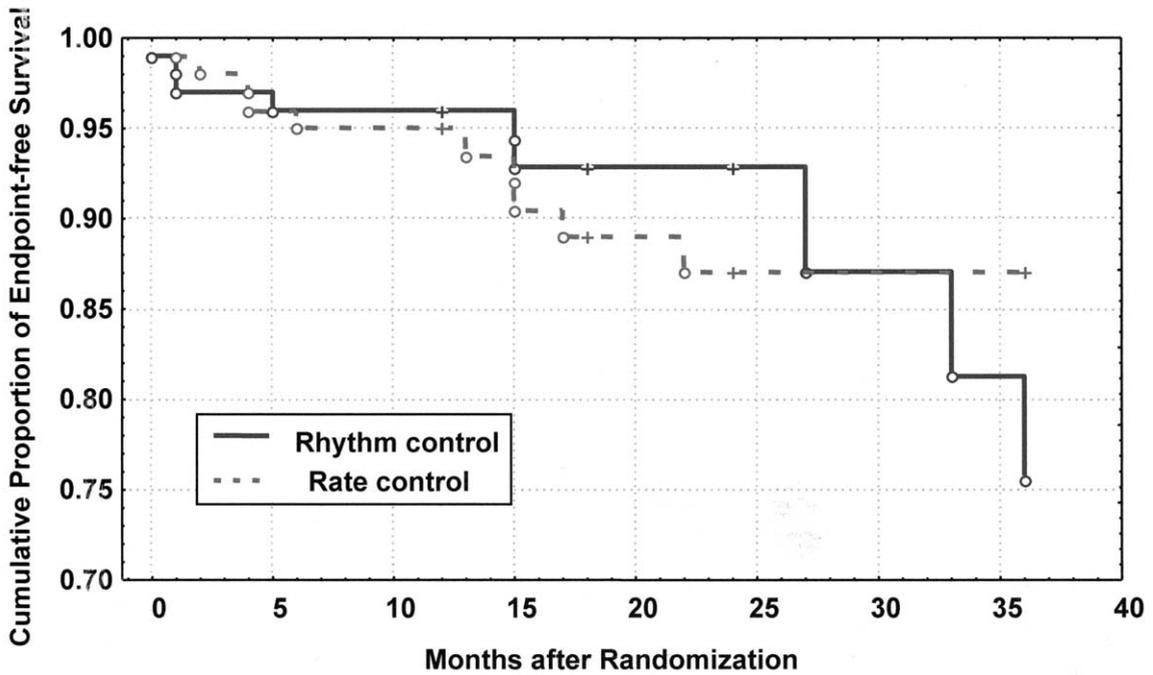The NYHA functional classification was recorded for

Figure 1. Kaplan-Meier estimates of the probability of end-point-free survival in the rhythm-control group and the rate-control group (treatment strategies).

each patient at baseline and during follow-up. Whereas 16 patients in the group of rhythm-control improved their NYHA functional class, 26 patients did so in the rate-control group. Forty-five patients in both groups remained unchanged, and 39 in the rhythm-control group compared with 29 patients in the rate-control group got worse in their NYHA functional class (p = 0.18).

The echocardiographic parameters LV diameter, LV function, and left atrial size did not show significant changes when both strategy groups were compared.

The resting heart rate in the rhythm-control group dropped from 81 ± 15 beats/min at baseline to 69 ± 14 beats/min at 12 months follow-up, and went up again to 79 beats/min at 36 months follow-up. In the rate-control
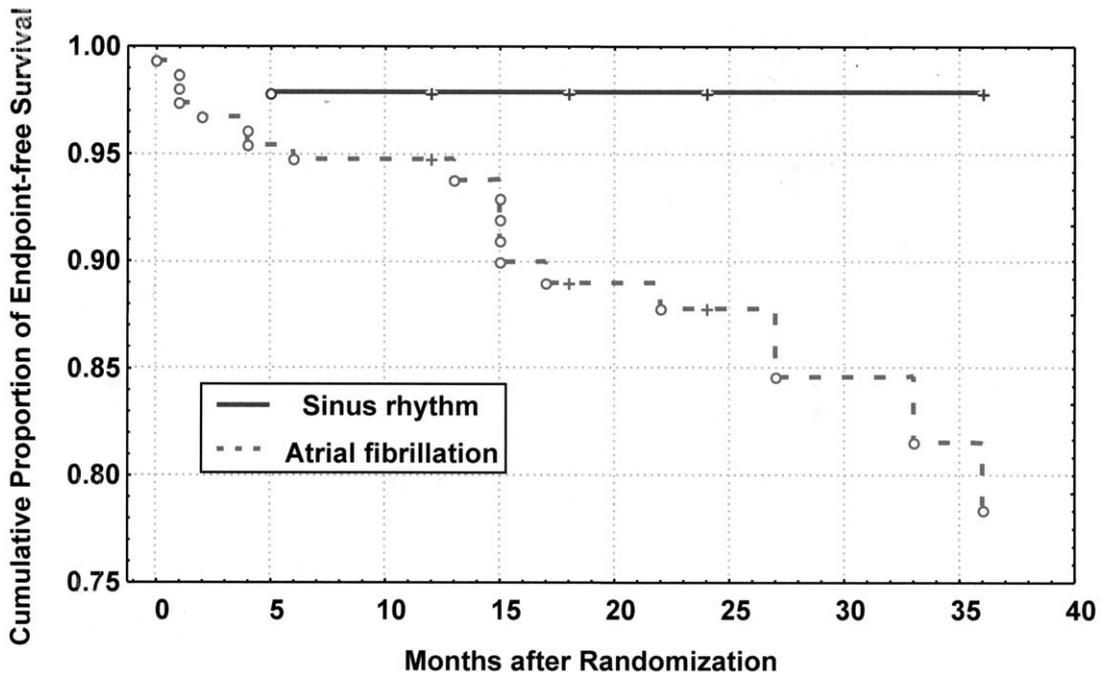

Figure 2. Kaplan-Meier estimates of the probability of end-point-free survival in the sinus rhythm group and the atrial fibrillation group (actual heart rhythm).

Table 3. Quality of Life (Assessed by SF-36)

	Rhythm-Control (n = 100)	Rate-Control (n = 100)	German Age-Matched Norm* (n = 433)
Physical functioning			
Baseline	68 ± 19	58 ± 21	76 ± 23
Follow-up	69 ± 12	62 ± 15†	
Physical role function			
Baseline	56 ± 22	50 ± 24	73 ± 35
Follow-up	62 ± 19†	55 ± 21†	
Bodily pain			
Baseline	75 ± 22	66 ± 23	71 ± 27
Follow-up	74 ± 15	72 ± 17‡	
General health			
Baseline	56 ± 15	51 ± 16	59 ± 18
Follow-up	56 ± 8	53 ± 12	
Vitality			
Baseline	53 ± 15	46 ± 17	61 ± 18
Follow-up	53 ± 10	49 ± 12	
Social functioning			
Baseline	81 ± 16	74 ± 20	87 ± 18
Follow-up	83 ± 13	79 ± 13†	
Emotional role function			
Baseline	74 ± 21	72 ± 22	89 ± 26
Follow-up	71 ± 17	75 ± 18	
Mental health			
Baseline	67 ± 16	63 ± 16	76 ± 17
Follow-up	72 ± 10‡	69 ± 10‡	

*Data from reference 10. All differences between study population and German norm population are significant (p < 0.01) except bodily pain. †p < 0.05 for within-group differences from baseline. ‡p < 0.01 for within-group differences from baseline.

group, the resting heart rate never showed significant changes during follow-up compared to 81 ± 15 beats/min at baseline.

The percentage of patients being in sinus rhythm in the rhythm-control group (rate-control group) after up to four cardioversions (255 primarily successful cardioversions during the total follow-up period) during the follow-up period was 70% after randomization (2%), 53% (13%) at one month, 46% (16%) at three months, 49% (11%) at six months, 40% (12%) at 12 months, 34% (8%) at 18 months, 26% (11%) at 24 months, and 23% (0) at 36 months. Initial cardioversion had been successful in 84% of patients, whereas 70% of patients maintained sinus rhythm after the initial treatment period of one to seven days. In the rhythm-control group 86% of patients received some kind of antiarrhythmic treatment, with 42% receiving amiodarone according to the study protocol. In the rate-control group, all patients received a beta-blocker, verapamil/diltiazem, or digitalis. Two underwent AV node ablation with pacemaker therapy.

DISCUSSION

The total mortality rate of 3.7%/year was lower than expected and was lower than the 4.2% mortality rate calculated as the basis of the North-American Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial (12–15). The cerebrovascular event rate

was also lower than expected, with 1.8%/year in the entire patient cohort. The only comparable and published data concerning event rates stem from anticoagulation trials in patients with AF. However, in these trials the mortality showed a wide range between 1.8% (16) and 9.3% a year (17). The rate of cerebrovascular events of 1.8%/year in STAF compares well with the data of the Stroke Prevention in Atrial Fibrillation (SPAF) II study, with 1.8% in patients ≤75 years of age and 4.1% in patients >75 years of age (16). Systemic embolism was a rare event with a rate of 0.31%/year. Data on systemic embolism from the literature are as rare as the event and vary between 0.09% and 0.25%/year (16).

Within a total of 162.6 patient-years of follow-up in the rhythm-control group and 164.3 years in the rate-control group no difference in the primary combined end point was found between the two treatment strategies. Because of the obvious statistical limitations of a pilot trial, these data can only serve as first evidence of equality of the two treatment strategies. The relevance of the tendency to a lower mortality but higher rate of cerebrovascular events in the rhythm-control group is obviously unclear at the moment.

Concerning the primary end point, the STAF study cannot be compared to the PIAF study, which used a symptomatic end point (7). There were no significant differences detected in mortality between the two groups with a follow-up of only one year and a mortality rate of 1.7% (7).

Secondary end points in the STAF study also did not show significant differences between the two treatment arms except hospitalizations for cardiovascular reasons. Hospitalizations, mainly for repeated cardioversions and initiation of antiarrhythmic treatment, were more frequently necessary in the rhythm-control group. This probably led to higher costs of treatment in this group, although a formal cost analysis has not been performed. This is in agreement with the PIAF study, which also found significantly more hospital admissions in rhythm-control patients than in the rate-control group. Also in agreement with the PIAF study are the results concerning quality of life. First, quality of life in patients with AF was expectedly (18) lower than in an age-matched control group (10). Furthermore, although quality of life improved somewhat during the trial in both strategies, it was still lower than in control patients.

The other main secondary end points were bleeding and syncope, which also did not show any significant differences between the two treatment strategies (Table 2). The total rate of bleeding in the STAF study was 5.8%/year and somewhat higher than in anticoagulation trials such as SPAF II, where the rate of "major bleeding" was between 1.7% and 4.2% per year (16). Because the definition of bleeding in the STAF study included some "minor bleeding" of the anticoagulation trials, the total rate seems to be in an acceptable range. Another difference, of course, is that the STAF study was a strategy trial, with less control of the anticoagulation level than in anticoagulation trials and,

therefore, the STAF study more resembles daily clinical practice. The incidence of syncope was 0.3% per year, rather low, although no clinical data exist in this patient cohort for comparison. The end point was chosen because of expected side effects of antiarrhythmic drugs in addition to the cardiopulmonary resuscitation end point. The strict guidelines for use of antiarrhythmic drugs might have prevented these events.

Another important secondary end point was maintenance of sinus rhythm. The fact that all but one end point (p = 0.049) occurred during AF (Fig. 2) and that maintenance of sinus rhythm was low, with 23% after three years, may suggest that rhythm-control failed to demonstrate superiority over rate-control because maintenance of sinus rhythm could not be achieved in the long term. However, this seems not to be the case because preliminary AFFIRM study data show a long-term maintenance of sinus rhythm of 60% in the rhythm-control group, and the AFFIRM study still failed to show any difference between the two treatment strategies (15). In the STAF study, the low percentage of patients in sinus rhythm was observed despite up to four cardioversions per patient during follow-up and antiarrhythmic therapy. Compared with the AFFIRM trial, however, the STAF study population somewhat represented a negative selection of patients in terms of probability of maintenance of sinus rhythm. For example, it was possible to cardiovert patients in the AFFIRM trial before randomization. Patients who could then not maintain sinus rhythm for at least 24 h were not eligible for the trial. At the time of randomization 54% of patients in the AFFIRM trial were in sinus rhythm compared with none in the STAF study (14). Also, patients with paroxysmal AF were excluded from the STAF study while being eligible for the AFFIRM trial.

It seems to be a limitation that the STAF study was a trial of treatment strategies and not of specific therapies, which led to a nonsystematic approach to the choice of antiarrhythmics. The physician could decide on the specifics of therapy within certain limits, which probably led to a lower use of class I antiarrhythmics and amiodarone than desirable. The available literature on long-term maintenance of sinus rhythm is sparse. The PIAF data are of no help because of short follow-up (7). The data of the Canadian Trial of Atrial Fibrillation (19) are not comparable because of inclusion of patients with a low risk of arrhythmia recurrence. The only comparable data come from Van Gelder et al. (20). In a report of 236 patients with AF undergoing serial cardioversion therapy with prophylactic antiarrhythmic drug treatment, only 27% maintained sinus rhythm after four years. That investigation used a systematic approach to antiarrhythmic treatment, starting with no prophylaxis, then sotalol, then flecainide, and after a fourth (or fifth) recurrence/cardioversion, amiodarone (20). So even amiodarone as fourth-line treatment did not really improve these results, which are comparable to the STAF study. Therefore, it is unlikely that the more frequent prescription of amiodarone would have improved the STAF

study results. Moreover, it is not only the limited effectiveness of amiodarone that limits its use, but also the frequent side effects that lead to discontinuation of treatment. In the PIAF study, treatment was discontinued in 25% in the amiodarone group within one year (7). Many problems with amiodarone develop only after prolonged therapy and may not be seen in this time (21). Because of the limited number of patients and the nonrandomized approach to antiarrhythmic treatment, it is not possible to compare specific antiarrhythmics in their ability to maintain sinus rhythm in the STAF study.

Several limitations of the study need to be mentioned. It would have been interesting to do a multivariate analysis with the primary end point as the dependent variable and clinical variables including the actual heart rhythm, NYHA functional classification, and LV function, with others as the independent variables. Unfortunately, such an analysis was not possible because there was only one event during sinus rhythm, and such a distribution makes this analysis undependable.

The so-called silent (22) or asymptomatic AF has not been systematically assessed in the STAF study by techniques such as transtelefonic electrogram monitoring. However, this would be a relevant argument if patients with paroxysmal AF were been included. Paroxysmal AF was an exclusion criterion in the STAF study and persistent AF even if asymptomatic would have been detected by the follow-up procedures.

It should be mentioned again that the STAF study population somewhat represented a negative selection of patients in terms of probability of maintenance of sinus rhythm, not least because of the relatively long duration of AF before randomization.

Conclusions. Under the conditions of this study and with the statistical limitations that have been discussed, the STAF study could not detect any differences between rhythm-control and rate-control regarding the combined primary end point and all secondary end points except hospitalizations. These data suggest that there was no benefit in attempting rhythm-control in this group of patients with a high risk of arrhythmia recurrence. It remains unclear whether the results in the rhythm-control group would have been better if sinus rhythm had been maintained in a higher proportion of patients because all but one end point occurred during AF.

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APPENDIX

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