

ORIGINAL ARTICLE

Amiodarone versus Sotalol for Atrial Fibrillation

Bramah N. Singh, M.D., D.Sc., Steven N. Singh, M.D., Domenic J. Reda, Ph.D., X. Charlene Tang, M.D., Ph.D., Becky Lopez, R.N., Crystal L. Harris, Pharm.D., Ross D. Fletcher, M.D., Satish C. Sharma, M.D., J. Edwin Atwood, M.D., Alan K. Jacobson, M.D., H. Daniel Lewis, Jr., M.D., Dennis W. Raisch, Ph.D., and Michael D. Ezekowitz, M.B., Ch.B., Ph.D.,
for the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) Investigators*

ABSTRACT

BACKGROUND

The optimal pharmacologic means to restore and maintain sinus rhythm in patients with atrial fibrillation remains controversial.

METHODS

In this double-blind, placebo-controlled trial, we randomly assigned 665 patients who were receiving anticoagulants and had persistent atrial fibrillation to receive amiodarone (267 patients), sotalol (261 patients), or placebo (137 patients) and monitored them for 1 to 4.5 years. The primary end point was the time to recurrence of atrial fibrillation beginning on day 28, determined by means of weekly transtelephonic monitoring.

RESULTS

Spontaneous conversion occurred in 27.1 percent of the amiodarone group, 24.2 percent of the sotalol group, and 0.8 percent of the placebo group, and direct-current cardioversion failed in 27.7 percent, 26.5 percent, and 32.1 percent, respectively. The median times to a recurrence of atrial fibrillation were 487 days in the amiodarone group, 74 days in the sotalol group, and 6 days in the placebo group according to intention to treat and 809, 209, and 13 days, respectively, according to treatment received. Amiodarone was superior to sotalol ($P < 0.001$) and to placebo ($P < 0.001$), and sotalol was superior to placebo ($P < 0.001$). In patients with ischemic heart disease, the median time to a recurrence of atrial fibrillation was 569 days with amiodarone therapy and 428 days with sotalol therapy ($P = 0.53$). Restoration and maintenance of sinus rhythm significantly improved the quality of life and exercise capacity. There were no significant differences in major adverse events among the three groups.

CONCLUSIONS

Amiodarone and sotalol are equally efficacious in converting atrial fibrillation to sinus rhythm. Amiodarone is superior for maintaining sinus rhythm, but both drugs have similar efficacy in patients with ischemic heart disease. Sustained sinus rhythm is associated with an improved quality of life and improved exercise performance.

From the Department of Veterans Affairs Medical Center, West Los Angeles, Calif. (B.N.S., B.L.); the Department of Veterans Affairs Medical Center, Washington, D.C. (S.N.S., R.D.F.); the Department of Veterans Affairs Hospital, Hines, Ill. (D.J.R., X.C.T.); the Department of Veterans Affairs Medical Center, Albuquerque, N.M. (C.L.H., D.W.R.); the Department of Veterans Affairs Medical Center, Providence, R.I. (S.C.S.); Walter Reed Army Medical Center, Washington, D.C. (J.E.A.); the Department of Veterans Affairs Medical Center, Loma Linda, Calif. (A.K.J.); the Department of Veterans Affairs Medical Center, Kansas City, Mo. (H.D.L.); and Hahnemann University and the Department of Veterans Affairs Medical Center Philadelphia — both in Philadelphia (M.D.E.). Address reprint requests to Dr. Singh at the Veterans Affairs Medical Center of West Los Angeles, 11301 Wilshire Blvd., Los Angeles, CA 90073, or at bsingh@ucla.edu.

*Other participants in SAFE-T are listed in the Appendix.

N Engl J Med 2005;352:1861-72.

Copyright © 2005 Massachusetts Medical Society.

ATRIAL FIBRILLATION IS THE MOST common arrhythmia requiring continuous therapy.¹⁻⁴ Conversion to and maintenance of sinus rhythm remain the cornerstones of therapy, but the optimal long-term drug strategy is controversial. Unblinded trials found that rhythm control did not offer a survival advantage over rate control with anticoagulation,⁵⁻⁷ but they did not compare standardized drug regimens for maintaining sinus rhythm or regularly monitor for atrial fibrillation. Thus, if the best approach to maintaining sinus rhythm had been used, the outcomes might have differed.⁸

The double-blind Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) compared the ability of sotalol and amiodarone⁹⁻¹² to restore and maintain sinus rhythm in patients with atrial fibrillation. Our objective was to determine whether amiodarone was superior to sotalol and whether both were superior to placebo in maintaining sinus rhythm in patients with persistent atrial fibrillation.

METHODS

CONDUCT OF THE STUDY

This Veterans Affairs Cooperative Study was designed, executed, and analyzed by an executive committee under the surveillance of an end-points committee, a data and safety monitoring board, a pharmacy coordinating center, and a biostatistical and research coordinating center, which monitored and stored the data in a computerized database in conjunction with the offices of the cochairs of the trial. All investigators had full access to all the data and performed the data analysis. The members of the executive committee wrote the article and assume overall responsibility for the data and the analysis.

SAFE-T was monitored independently by the human rights committee of the Cooperative Studies Program Coordinating Center of the Veterans Affairs Medical Center in Hines, Illinois, and the data and safety monitoring board. The site-monitoring and review team of the Cooperative Studies Program conducted limited on-site examination of study data. An end-points committee reviewed all events defined as serious and possibly related to treatment.

PATIENTS

Eligible patients had had electrocardiographically documented atrial fibrillation for at least 72 hours, still had atrial fibrillation at randomization, and

were receiving anticoagulants. Patients with atrial flutter or paroxysmal atrial fibrillation were excluded. Other exclusion criteria included New York Heart Association class III or IV heart failure, a calculated creatinine clearance below 60 ml per minute,¹³ intolerance of beta-blockers, and a history of the long-QT syndrome. Originally, patients who had had atrial fibrillation for more than 12 months were excluded. Subsequently, this restriction was eliminated. All patients provided written informed consent, and the protocol was approved by the human-research review board at each site.

PROTOCOL DESIGN

The trial design has been described previously.¹⁴ Eligibility screening spanned three or four visits at seven-day intervals. The baseline evaluation included chest radiography, 12-lead electrocardiography (ECG), a complete blood count, urinalysis, thyroid-function tests, hepatic panel, and measurement of serum chemical values and serum digoxin levels. The international normalized ratio (INR) had to be stable and between 2.0 and 3.0 before cardioversion was attempted. The ventricular response was controlled by treatment with diltiazem, verapamil, and digoxin,¹⁴ in order to achieve a rate of 60 to 90 beats per minute. The left ventricular ejection fraction and the size of the left atrium were measured by two-dimensional echocardiography. Health-related quality of life was measured with the use of the Medical Outcomes Study 36-item Short Form General Health Survey (SF-36), which assesses eight aspects of health status: general and mental health, physical and social functioning, physical and emotional role, pain, and vitality.¹⁵ Scores on each scale can range from 0 (worst) to 100 (best). Exercise treadmill testing was conducted according to a modified Naughton protocol.¹⁶

RANDOMIZATION, THERAPY, AND FOLLOW-UP

Permuted-block randomization was performed, with stratification according to participating hospital, patient's symptoms, and the presence or absence of ischemic heart disease. Eligible patients were randomly assigned to receive amiodarone, sotalol, or placebo on an outpatient basis. Both the investigators and the patients were unaware of the study-group assignments. The amiodarone regimen was 800 mg per day for the first 14 days, 600 mg per day for the next 14 days, 300 mg per day for the first year, and 200 mg per day thereafter. The sotalol regimen was 80 mg twice daily for the first

week and 160 mg twice daily thereafter. Berlex Laboratories and Wyeth–Ayerst Laboratories donated preparations of sotalol, amiodarone, and their respective placebos.

Follow-up visits were scheduled every four weeks and included a clinical evaluation, 12-lead ECG recordings, and measurements of digoxin levels and the INR; the patient's rhythm was monitored transtelephonically weekly. The presence of atrial fibrillation or atrial flutter was confirmed by the concordance of two transtelephonic measurements or of a 12-lead ECG and a transtelephonic measurement obtained less than 24 hours apart. If spontaneous conversion had not occurred by day 28 after randomization, direct-current (DC) cardioversion was performed with up to four standardized monophasic shocks (one at 100 J, one at 200 J, and two at 360 J). In the final year of the study, biphasic shocks (one at 150 J, one at 175 J, and two at 200 J) were also used.

Failed DC cardioversion was defined by either the absence of sinus rhythm or the presence of sinus rhythm for less than one minute after the highest-energy shock. Patients who initially converted to sinus rhythm but in whom atrial fibrillation recurred after day 28 received another dose of anticoagulants before again undergoing DC cardioversion; the study drug was withdrawn if atrial fibrillation recurred after the second attempt. Patients in whom DC cardioversion was unsuccessful on day 28 were not subjected to further attempts, the study drug was withdrawn, and the patients were followed for one year.

After conversion, patients were seen monthly to undergo ECG, review medications, and report adverse reactions. Physical examinations were performed quarterly, and an ECG was obtained if indicated. The dose of the study drug was reduced if QT intervals exceeded 550 msec,¹⁴ and treatment was stopped if the QT interval remained above 550 msec. Patients who required coronary surgery, a pacemaker, or therapy for hypothyroidism were treated conventionally; the study drug was continued. Patients in whom hyperthyroidism developed were withdrawn from the study. Doses of the study drug were reduced if intolerable adverse reactions occurred, and treatment was stopped if they persisted. Temporary discontinuation of the study drug was permitted for 30 days, but treatment was permanently discontinued in the event of treatment-related torsades de pointes, adverse pulmonary effects, persistent liver-function abnormalities, heart failure, or bronchospasm. The patient's participation was ter-

minated in the event of death, withdrawal of consent, loss to follow-up, or recurrence of atrial fibrillation after the one-year follow-up visit.

Treadmill testing and echocardiography were performed at 8 weeks and 6 and 12 months during the first year, annually thereafter, and at the completion of the study. Three months after randomization, thyroid-function tests and serum chemical measurements were obtained, and a complete blood count, urinalysis, thyroid-function tests, hepatic panel, and serum chemical measurements were obtained semiannually thereafter; digoxin levels and INR were measured as required, and chest radiography was performed annually. Health-related quality of life was assessed by means of the SF-36 at 8 weeks and 6 and 12 months after randomization and annually thereafter.

STATISTICAL ANALYSIS

The primary outcome was the time to the first recurrence of atrial fibrillation after sinus rhythm had been restored. Failed conversion was defined as the persistence of atrial fibrillation on day 28 (considered time 0). The expected rates of sustained sinus rhythm at one year were 60 percent in the amiodarone group, 50 percent in the sotalol group, and 35 percent in the placebo group. On the basis of these assumptions, the study had a statistical power of 85 percent to identify a significant difference in the Kaplan–Meier time-to-event distributions between amiodarone and sotalol (two-sided alpha, 0.04), amiodarone and placebo (alpha, 0.005), and sotalol and placebo (alpha, 0.005), given the enrollment of 706 patients (279 patients in both the amiodarone and sotalol groups and 148 patients in the placebo group). The log-rank test was used to compare the three groups in a pairwise manner. Changes in the quality of life and exercise ability were compared in patients with sustained sinus rhythm and those with persistent atrial fibrillation by means of the two-sample t-test. All statistical tests were two-sided, and a P value of 0.05 or less was considered to indicate statistical significance in the secondary analysis.

Enrollment lasted 42 months, and follow-up lasted a minimum of 12 and a maximum of 54 months. Supporting analyses included the time to the first recurrence of atrial fibrillation among patients with conversion on or before day 28 and among predefined subgroups based on the duration of atrial fibrillation and the presence or absence of symptoms or ischemic heart disease.

To account for differences in the duration of follow-up among the study groups, the rates of adverse events were calculated as the number of patients who had a particular adverse event at least once per 100 patient-years of follow-up. Logistic regression was used to compare the rates of adverse events among the study groups after adjustment for the duration of follow-up.

A total of 6582 patients were screened at 20 sites, 665 of whom underwent randomization: 267 to amiodarone, 261 to sotalol, and 137 to placebo (Fig. 1). The adherence rate was significantly higher ($P=0.01$) among those given active amiodarone (98.1 percent) than among those given active sotalol (95.8 percent) or those given placebo (94.9 percent). A total of 81 patients withdrew their consent, and 28 were lost to follow-up.

The baseline characteristics of the patients are shown in Table 1; 98.9 percent were men, and 89.3 percent were white. The mean (\pm SD) age was 67.1 ± 9.3 years.

RESULTS

CHARACTERISTICS OF THE PATIENTS

The study was conducted in an outpatient setting between April 1, 1998, and October 31, 2002; 28 sites participated initially and 8 discontinued participation early. Renal impairment, inability to provide written informed consent or to participate in the study, treatment with amiodarone during the previous 12 months, and cessation of atrial fibrillation after the first screening visit were the most frequent reasons for the failure to enroll screened pa-

RESTORATION OF SINUS RHYTHM

Between randomization and day 28, 70 of 258 patients in the amiodarone group (27.1 percent) had spontaneous conversion, as compared with 59 of 244 patients in the sotalol group (24.2 percent, $P=0.45$) and 1 of 132 patients in the placebo group (0.8 percent, $P<0.001$ for the comparison with

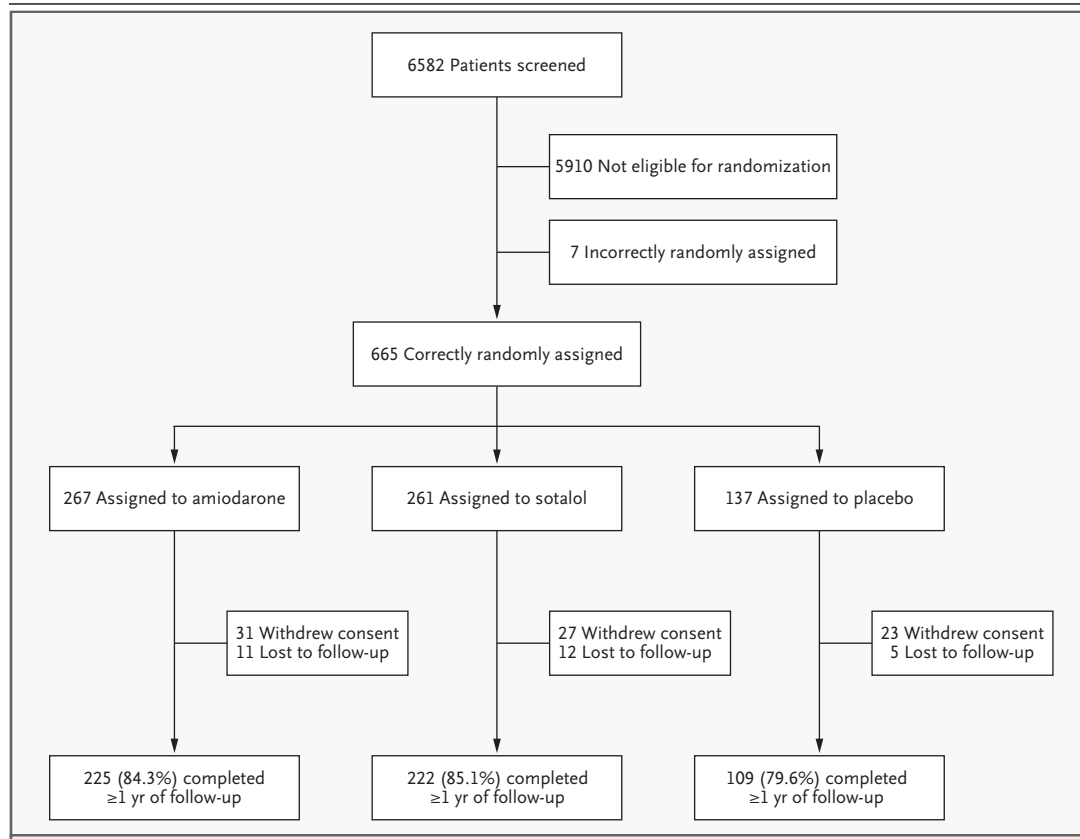


Figure 1. Selection Process, Randomization, and Outcome.
The regimens were administered in a double-dummy manner.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Amiodarone Group (N=267)	Sotalol Group (N=261)	Placebo Group (N=137)	P Value†
Age — yr	67.1±9.4	66.8±8.9	67.7±9.8	0.68
Male sex — no. (%)	265 (99.3)	257 (98.5)	136 (99.3)	0.27
Race or ethnic group — no. (%)‡				
White	235 (88.0)	230 (88.1)	129 (94.2)	0.38
Black	20 (7.5)	15 (5.7)	4 (2.9)	
Hispanic	10 (3.7)	11 (4.2)	3 (2.2)	
Other	2 (0.7)	5 (1.9)	0	
Body-mass index§	31.5±6.1	31.6±6.2	30.7±4.9	0.44
Weight — lb.	220.6±42.8	226.9±48.1	212.3±37.8	0.01
Smoking status — no. (%)¶				
Current	37 (13.9)	38 (14.6)	28 (20.4)	0.14
Former	152 (56.9)	164 (62.8)	78 (56.9)	
Never	77 (28.8)	58 (22.2)	29 (21.2)	
Current alcohol use — drinks per mo	12.6±30.9	16.9±42.9	8.1±16.7	0.05
Hypertension — no. (%)	194 (72.7)	172 (65.9)	76 (55.5)	0.004
Documented ischemic heart disease — no. (%)**	71 (26.6)	66 (25.3)	31 (22.6)	0.69
Nonischemic cardiomyopathy — no. (%)	25 (9.4)	19 (7.3)	7 (5.1)	0.31
Diabetes mellitus — no. (%)	67 (25.1)	65 (24.9)	32 (23.4)	0.94
COPD without bronchospasm — no. (%)	36 (13.5)	31 (11.9)	15 (10.9)	0.75
NYHA class I or II congestive heart failure — no. (%)	67 (25.1)	72 (27.6)	33 (24.1)	0.72
Valvular heart disease — no. (%)	19 (7.1)	17 (6.5)	8 (5.8)	0.89
History of cerebrovascular disease — no. (%)	33 (12.4)	30 (11.5)	20 (14.6)	0.64
Duration of atrial fibrillation — no. (%)††				
≤1 yr	197 (73.8)	206 (78.9)	110 (80.3)	0.33
>1 yr	61 (22.8)	53 (20.3)	23 (16.8)	
Ventricular rate — beats/min	80.3±14.9	81.6±14.9	83.9±14.9	0.07
Pacemaker — no. (%)	11 (4.1)	7 (2.7)	4 (2.9)	0.63
Left ventricular ejection fraction	0.505±0.124	0.515±0.119	0.494±0.127	0.30
Left atrial dimension — mm	47.7±7.1	48.2±6.9	49.0±6.5	0.22
Symptomatic atrial fibrillation — no. (%)‡‡	167 (62.5)	164 (62.8)	83 (60.6)	0.90

* Plus-minus values are means ±SD. COPD denotes chronic obstructive pulmonary disease, and NYHA New York Heart Association.
† Significantly greater percentages of patients had hypertension in the amiodarone and sotalol groups than in the placebo group. The trend toward significant differences in current alcohol use (P=0.05) and the mean ventricular rate in atrial fibrillation (P=0.07) at baseline was deemed clinically insignificant. The differences in weight were significant (P=0.01) at baseline. Other baseline characteristics were well balanced among the groups.
‡ Race was determined by the investigators on the basis of hospital records. Data were missing for one patient in the placebo group.
§ Body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.
¶ Data were missing for one patient in the amiodarone group, one in the sotalol group, and two in the placebo group.
|| A drink was defined as 30 ml.
** Ischemic heart disease was diagnosed on the basis of history-taking and investigational findings; the 25.3 percent incidence of myocardial infarction was confirmed on the basis of history and ECG findings; 25.9 percent received the diagnosis of congestive heart failure on clinical grounds.
†† Data were missing for nine patients in the amiodarone group, two in the sotalol group, and four in the placebo group.
‡‡ The criteria for symptomatic atrial fibrillation included one or more of the following: palpitations, syncope, light-headedness or presyncope, shortness of breath, chest pain, and fatigue.

both amiodarone and sotalol). The remainder underwent DC cardioversion on or near day 28, which was unsuccessful in 27.7 percent of the patients in the amiodarone group, 26.5 percent in the sotalol group, and 32.1 percent in the placebo group ($P=0.54$). The total rate of conversion was 79.8 percent in the amiodarone group, as compared with 79.9 percent in the sotalol group ($P=0.98$) and 68.2 percent in the placebo group ($P=0.01$ for the comparison with both amiodarone and sotalol). The rate of DC cardioversion was higher with the use of biphasic shocks (42 given, 81 percent success rate) than monophasic shocks (427 given, 70 percent success rate; $P=0.14$). The rates of DC cardioversion did not differ significantly among the groups with respect to the duration of atrial fibrillation, but it was higher in the subgroup of patients in the placebo group who had had atrial fibrillation for no more than one year than in those who had had atrial fibrillation for more than one year (71 percent vs. 50 percent, $P=0.04$).

PRIMARY END POINT

The median times to the first recurrence of atrial fibrillation are shown in Table 2 according to the intention to treat and to the treatment actually received. Amiodarone and sotalol were both significantly more effective than placebo in increasing the time to a recurrence of atrial fibrillation ($P<0.001$). Amiodarone was six times as effective as sotalol in the intention-to-treat analysis ($P<0.001$) and four times as effective in the analysis according to the treatment actually received ($P<0.001$).

The Kaplan–Meier estimates of the distribution of times to a recurrence of atrial fibrillation among patients in whom sinus rhythm was restored on day 28 are shown in Figure 2. In subgroups defined according to the duration of atrial fibrillation (one year or less vs. more than one year), the presence or absence of ischemic heart disease, and the presence or absence of symptoms of arrhythmia, amiodarone and sotalol were superior to placebo (Table 2). Amiodarone was superior to sotalol in all subgroups except the subgroup of patients with ischemic heart disease, wherein the time to a recurrence of atrial fibrillation was 569 days in the amiodarone group and 428 days in the sotalol group ($P=0.53$). In the amiodarone group, the time to a recurrence of atrial fibrillation was longer in the subgroup without ischemic heart disease than in the group with ischemic heart disease (867 vs. 569

days, $P=0.09$). The corresponding values in the sotalol group demonstrated the converse trend (180 days in the subgroup without ischemic heart disease and 428 days in the subgroup with ischemic heart disease, $P=0.10$).

CHANGES IN QUALITY OF LIFE AND EXERCISE CAPACITY

Table 3 presents changes in quality-of-life scores and exercise capacity from baseline to one year of follow-up for patients remaining in sinus rhythm and those with persistent atrial fibrillation. Scores for physical functioning, general health, and social functioning on the SF-36 were significantly better in the group in sinus rhythm than in the group with persistent atrial fibrillation, and there was a trend toward an improvement in vitality scores in the former group ($P=0.08$). The differences in scores for physical-role limitations, pain, emotional-role limitations, and mental health between the two groups were not significant. For the comparison of all three randomized groups, there were no significant differences in quality-of-life scores from baseline to one year, except for a decrease in the mental health score in the amiodarone group ($P=0.005$ for the comparison with both the sotalol and placebo groups).

The reductions in heart rate at rest and during peak exercise at one year were greater among patients who remained in sinus rhythm than among those with persistent atrial fibrillation ($P<0.001$ for both comparisons). There was no discernible relationship between the quality-of-life scores and exercise capacity.

ADVERSE EVENTS

There were no significant differences in the rates of adverse events among the study groups except in the rates of minor bleeding episodes, which were significantly higher in the amiodarone group (8.33 per 100 patient-years of follow-up) than in the sotalol group (6.37 per 100 patient-years of follow-up) or the placebo group (6.71 per 100 patient-years of follow-up) ($P<0.04$ for the comparison among the three groups). The corresponding values for major bleeding episodes were 2.07, 3.10, and 3.97 per 100 patient-years of follow-up, respectively ($P=0.86$); those for minor strokes were 1.19, 0.68, and 0.96 per 100 patient-years of follow-up, respectively ($P=0.67$); and those for major strokes were 0.87, 2.03, and 0.95 per 100 patient-years of

Table 2. Time to First Recurrence of Atrial Fibrillation among Patients with Conversion at Baseline.

Subgroup	Amiodarone Group				Sotalol Group				Placebo Group				P Value		
	No. of Patients	Median Days to Recurrence	Recurrence Rate at 1 Yr %	No. of Patients	Median Days to Recurrence	Recurrence Rate at 1 Yr %	No. of Patients	Median Days to Recurrence	Recurrence Rate at 1 Yr %	No. of Patients	Median Days to Recurrence	Recurrence Rate at 1 Yr %	Amiodarone vs. Sotalol	Amiodarone vs. Placebo	Sotalol vs. Placebo
Intention-to-treat analysis	258	487	48	244	74	68	132	6	87	0.002	0.001	0.001	0.001	0.001	0.001
Treatment-received analysis	206	809	35	195	209	60	90	13	82	0.001	0.001	0.001	0.001	0.001	0.001
Duration of atrial fibrillation*															
≤1 Yr	148	832	31	150	238	56	75	14	79	0.004	0.001	0.001	0.001	0.001	0.001
>1 Yr	51	487	45	44	78	74	13	9	92	0.01	0.002	0.002	0.002	0.04	0.04
Ischemic heart disease†															
Present	51	569	40	47	428	50	22	16	83	0.53	0.001	0.001	0.001	0.001	0.001
Absent	155	867	34	148	180	63	68	13	83	0.001	0.001	0.001	0.001	0.001	0.001
Symptomatic atrial fibrillation‡															
Present	126	763	38	119	218	59	55	10	83	0.02	0.001	0.001	0.001	0.001	0.001
Absent	80	832	31	76	160	62	35	16	80	0.001	0.001	0.001	0.001	0.001	0.04

* A total of 373 patients had had atrial fibrillation for one year or less, and 108 had had atrial fibrillation for more than one year. The median times to a recurrence of atrial fibrillation among patients who had had atrial fibrillation for one year or less and those who had had atrial fibrillation for more than one year were 832 and 487 days (P<0.08), respectively, in the amiodarone group and 238 and 78 days (P=0.001), respectively, in the sotalol group.

† In the amiodarone group, the median time to recurrence of atrial fibrillation tended to be higher in the group without ischemic heart disease than in the group with ischemic heart disease (P=0.09). The corresponding figures for the sotalol group demonstrated a converse trend (P=0.10).

‡ There was no significant difference in the median time to recurrence of atrial fibrillation between patients with symptoms and those without symptoms in either the amiodarone group (P=0.15) or the sotalol group (P=0.14).

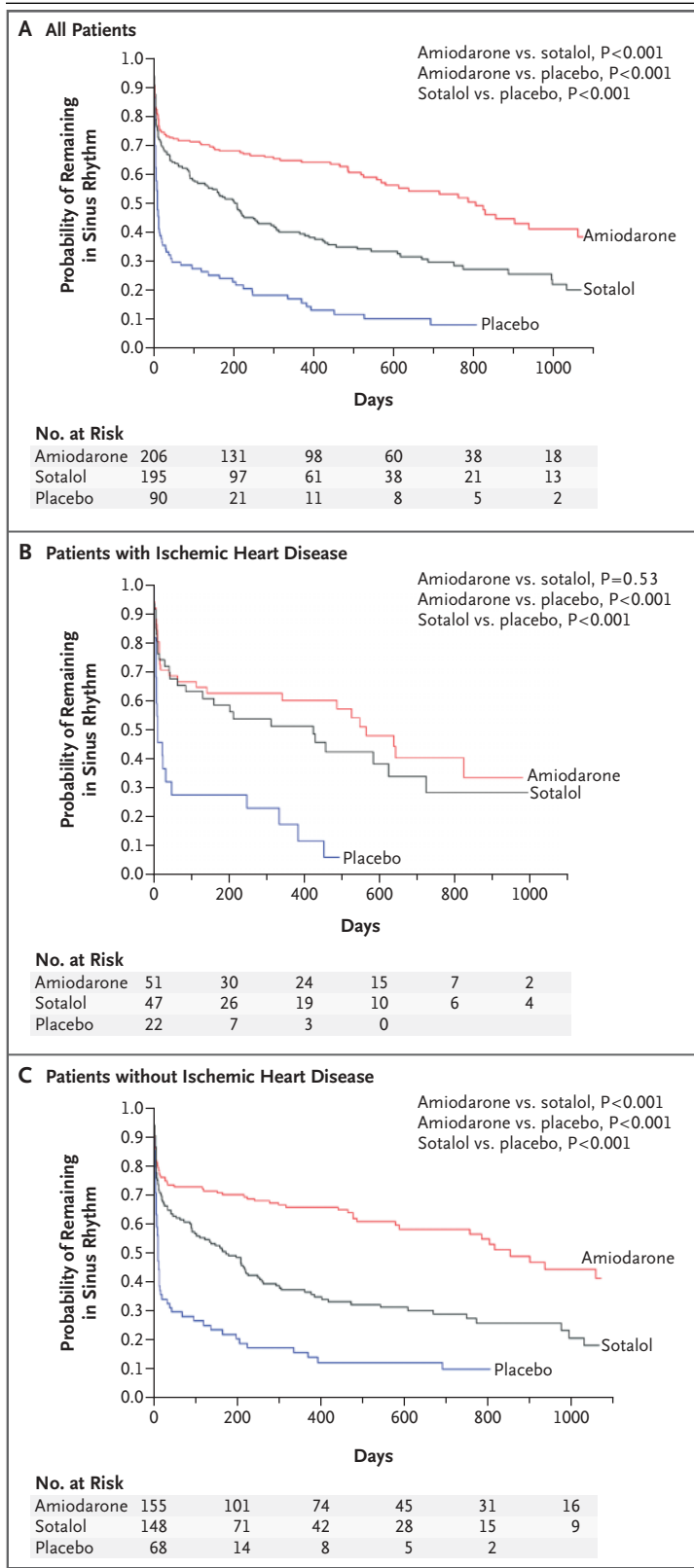


Figure 2. Kaplan–Meier Estimates of the Time to Recurrence of Atrial Fibrillation among Patients in Whom Sinus Rhythm Was Restored on Day 28.

Estimates of the time to recurrence of atrial fibrillation are shown for all patients with conversion to sinus rhythm (Panel A) and in subgroups of patients with conversion to sinus rhythm according to the presence or absence of ischemic heart disease (Panels B and C, respectively).

follow-up, respectively ($P = 0.36$). There were two cases of nonfatal adverse pulmonary effects in the amiodarone group and one in the placebo group. One case of nonfatal torsades de pointes occurred in the sotalol group.

There were 13 deaths (6 sudden) in the amiodarone group, 15 deaths (8 sudden) in the sotalol group, and 3 deaths (2 sudden) in the placebo group. After adjustment for the duration of follow-up (344.08 patient-years in the amiodarone group, 297.93 in the sotalol group, and 105.72 in the placebo group), the mortality ratios were 1.3 in the amiodarone group as compared with the placebo group ($P = 0.19$) and 1.8 in the sotalol group as compared with the placebo group ($P = 0.11$). Among the patients who actually received the assigned study drug, 13 died in the amiodarone group, 10 died in the sotalol group, and 2 died in the placebo group; the mortality ratios were 2.0 for the comparison of amiodarone with placebo ($P = 0.11$) and 1.8 for the comparison of sotalol with placebo ($P = 0.20$). The death rate was 4.36 per 100 person-years of follow-up in the amiodarone and sotalol groups combined, as compared with 2.84 per 100 person-years of follow-up in the placebo group ($P = 0.13$).

DISCUSSION

During steady-state therapy in SAFE-T, both amiodarone and sotalol induced similar rates of spontaneous and DC cardioversion, an effect greatly superior to that achieved by placebo. Thus, our results emphasize the importance of establishing steady-state antiarrhythmic therapy before DC cardioversion is performed if sustained sinus rhythm is the ultimate therapeutic goal in patients with atrial fibrillation. Previously, smaller trials found amiodarone and sotalol to be effective as single agents in atrial fibrillation,¹⁷⁻²¹ but only one of two comparative trials^{22,23} confined the analysis to patients

Table 3. Effects of Continued Sinus Rhythm and Persistent Atrial Fibrillation on the Quality of Life and Exercise Capacity at One Year.*

Measure	Sustained Sinus Rhythm		Persistent Atrial Fibrillation		P Value
	No. of Patients	Mean ±SD	No. of Patients	Mean ±SD	
SF-36 subscale					
Physical functioning score	290		156		
Before randomization		57.9±28.6		57.7±25.3	
At 1 yr		60.6±28.3		55.8±25.7	
Change		2.7±24.3		-1.9±22.1	0.05
General health score	278		152		
Before randomization		59.8±21.3		61.8±19.8	
At 1 yr		59.7±21.3		56.2±21.6	
Change		-0.1±17.6		-5.6±19.1†	0.003
Social functioning score	290		154		
Before randomization		76.6±25.4		79.4±25.2	
At 1 yr		77.5±26.4		74.1±25.4	
Change		1.0±23.7		-5.3±24.8‡	0.01
Vitality score	284		151		
Before randomization		49.8±24.8		48.8±21.8	
At 1 yr		53.7±23.1		49.1±23.7	
Change		3.8±20.4§		0.3±19.5	0.08
Treadmill exercise test					
Resting heart rate (beats/min)	204		104		
Before randomization		86.8±17.6		87.1±15.7	
At 1 yr		63.6±11.2		82.2±17.1	
Change		-23.2±18.0†		-4.9±18.1§	<0.001
Peak heart rate (beats/min)	204		102		
Before randomization		149.1±26.4		152.2±25.0	
At 1 yr		108.7±16.2		140.0±28.1	
Change		-40.4±26.7†		-12.3±27.2†	<0.001
Duration of exercise (sec)¶	205		104		
Before randomization		505.5±261.5		481.5±271.2	
At 1 yr		583.3±250.3		496.1±268.6	
Change		77.9±220.5†		14.6±227.4	0.02

* The data were derived from 478 patients (304 with sustained sinus rhythm and 174 with persistent atrial fibrillation) who were still taking study medications in a blinded fashion at one year; 465 of these patients completed quality-of-life questionnaires and 318 patients performed treadmill exercise before randomization and at one year.

† P<0.001 for the within-group comparison.

‡ P<0.05 for the within-group comparison.

§ P<0.01 for the within-group comparison.

¶ The mean increase in the duration of exercise was significantly greater among patients with sustained sinus rhythm than among those with persistent atrial fibrillation (15.4 percent vs. 3.0 percent, P<0.02) but was not significantly affected by sotalol or amiodarone.

with persistent atrial fibrillation. In the unblinded trial,²³ involving 400 patients with persistent and paroxysmal atrial fibrillation randomly assigned to amiodarone, sotalol, or propafenone without placebo control, amiodarone was superior to sotalol and propafenone. In our blinded, placebo-controlled

trial, the regimens of amiodarone and sotalol were standardized and rhythm was assessed by weekly transtelephonic monitoring for 4.5 years. The DC cardioversion protocol was standardized, with most patients receiving monophasic shocks. When the rates of spontaneous conversion during drug thera-

py were factored into the analysis, the overall conversion rates were consistent with recent data on the effects of monophasic shocks in patients with persistent atrial fibrillation.^{24,25}

An unexpected finding was that treatment with either sotalol or amiodarone resulted in similar times to a first recurrence of atrial fibrillation in patients with ischemic heart disease. There also was a trend toward a longer period of sustained sinus rhythm with sotalol therapy in patients with ischemic heart disease than in those without ischemic heart disease. The converse was true among patients who received amiodarone.

Despite the fact that our observations were not derived from the use of disease-specific instruments,²⁶ the restoration and maintenance of sinus rhythm in patients with atrial fibrillation significantly improved certain quality-of-life domains. In patients with chronic diseases, an improvement in SF-36 scores of three to five points is considered clinically significant.²⁷ The quality of life is impaired in patients with chronic atrial fibrillation,²⁶ but not all studies^{5,6,28,29} have reported improvements in quality of life after the restoration of sinus rhythm. The data from our relatively large, blinded study provide support for the superiority of sustained sinus rhythm over rate control with respect to quality-of-life measures in patients with atrial fibrillation. Although amiodarone was associated with a significant decrease in mental health function as compared with sotalol or placebo ($P=0.005$), mental health scores were higher in the amiodarone group at baseline but similar in all three groups at one year. Thus, the finding may represent regression to the mean effect. During the past 20 years,³⁰ there have been only two case reports of reversible amiodarone-induced acute delirium and one of acute depression. The clinical significance of these reports remains uncertain. However, since the quality-of-life data are not based on an intention-to-treat analysis, they tell us less about the advisability of the initial treatment strategies than about the functional consequences of the outcomes.

Increases in exercise capacity accompanied by decreases in the peak heart rate during exercise have been noted after cardioversion in small, unblinded studies of patients with atrial fibrillation. Our much larger placebo-controlled, blinded trial involving patients with persistent atrial fibrillation, which had a longer follow-up, confirms and extends these observations.^{31,32}

Another pertinent finding is the absence of sig-

nificant differences among the three groups in the incidence of major adverse events. There was only one case of torsades de pointes in a patient in the sotalol group, and three of adverse pulmonary effects, two in the amiodarone group and one in the placebo group. The incidence of minor bleeding episodes was higher ($P=0.04$) in the amiodarone group than in the sotalol or placebo groups, possibly owing to an interaction between amiodarone and warfarin.³³ We found no significant differences in mortality rates among the three groups, but the study was statistically underpowered to evaluate mortality differences. Therefore, the possibility cannot be excluded that the observed adverse mortality trends with sotalol or amiodarone may have reached statistical significance in a larger trial. However, this possibility appears unlikely, since relatively large mortality trials involving patients with myocardial infarction and heart failure, who have a higher risk of death from arrhythmia³⁴⁻³⁷ than do patients with atrial fibrillation, have reported similar or lower mortality rates with amiodarone or sotalol, as compared with placebo. In addition, smaller efficacy trials involving patients with atrial fibrillation who received amiodarone or sotalol^{17,22,23} have not revealed an excess risk of drug-induced mortality.

Our data on the comparative effectiveness of amiodarone and sotalol extend the results of previous studies^{17,19,23} and confirm that the drugs are equally efficacious in symptomatic and asymptomatic patients. In another blinded study, sotalol was more effective than placebo in maintaining sinus rhythm, and torsades de pointes did not develop if drug doses were adjusted to reflect renal function and the QT interval was monitored.¹⁷ The rare occurrence of torsades de pointes in our trial, which took similar precautions, may permit outpatient initiation of sotalol therapy, as is customary for amiodarone.

The unparalleled effectiveness of amiodarone in patients with persistent atrial fibrillation has not been explained mechanistically. However, a recent study suggested that its superior effectiveness may stem from a striking reversal of heart rate-related adverse atrial remodeling.³⁸ The side-effect profile of amiodarone did not differ from that of sotalol or placebo during the follow-up period. However, our finding that amiodarone was not superior to sotalol in patients with ischemic heart disease has important clinical implications. Both agents slow the ventricular response during recurrences

of atrial fibrillation by depressing atrioventricular conduction.^{20,39} Thus, the use of standardized regimens may provide the scope to differentiate the precise roles of rate control and rhythm control in patients with atrial fibrillation and to develop atrial antiarrhythmic compounds.

Supported by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development (Wash-

ington, D.C.) and by unrestricted grants-in-aid from Berlex Laboratories and Wyeth-Ayerst Laboratories.

Presented in part at the North American Society of Pacing and Electrophysiology meeting, Washington, D.C., May 14–16, 2003, and as an abstract at the American Heart Association Annual Meeting, Orlando, Fla., November 9–12, 2003.

Dr. Bramah Singh reports having acted in an advisory capacity and as a speaker for Wyeth-Ayerst Laboratories, Sanofi-Synthelabo Laboratories, and Berlex Laboratories. Dr. Reda reports having received grant support from Novartis Pharmaceuticals.

APPENDIX

The following persons contributed to SAFE-T: *Office of the Cochair, West Los Angeles, Calif.* — B.N. Singh (cochair), B. Lopez; *Office of the Cochair, Washington, D.C.* — S. N. Singh (cochair); *Transtelephonic Monitoring Laboratory, Washington, D.C.* — R. Fletcher, M. Platt, P. Paul, K. Crawford, D. Meza, R. Harrington; *Biostatistics and Research Data Processing* — D. Reda, W.G. Henderson, X.C. Tang, M. Abdellatif, D. Motyka, B. Mackay, M. Reinhard, L. Anfinson, N. Alvarado-Garcia, J. Jimenez, D.J. Semlow; *Pharmacy Coordinating Center, Albuquerque, N.M.* — M.R. Sather, S.L. Buchanan, C. Harris, C. Fye, W. Gagne, L. Gifford, L. Guidarelli; *Consultants* — H.D. Lewis, M. Ezekowitz, R. Falk, E. Antman; *Events Committee* — H.D. Lewis (chair), J.E. Atwood, A. Jacobson; *Executive Committee* — B.N. Singh, S.N. Singh, R. Fletcher, J.E. Atwood, A.K. Jacobson, S. Sharma, M. Ezekowitz, H.D. Lewis, C. Fye, D. Reda, W.G. Henderson; *Data and Safety Monitoring Board* — P.J. Podrid (chair), J.C. Torner, M.A. Brodsky, P.R. Kowey; *Cooperative Studies Program Administration* — J. Feussner, S. Berkowitz, J. Gough; *Veterans Affairs Medical Centers Investigative Groups* — Albuquerque, N.M.: C. Cadman, R. Cataldo, L. Beeman; Augusta, Ga.: R. Ahmed, S. Verma, J. Jordan; Bay Pines, Fla.: U.R. Shettigar, G. Appunn, R. Norvalis, D. Dove; Brooklyn, N.Y.: N. El-Sherif, S. Graham, A. Mohamed, E. Caref; Dallas: M. Hamdan, C. Willis, S. Mull, J. Nichols, M. Roesler; Fresno, Calif.: P. Deedwania, J. Barker, C. Frigon, R. Kanefield; Hines, Ill.: R. Hariman, M. O'Sullivan; Iowa City: J.B. Martins, H.C. Lee, J. Morse, L. Wolfe; Kansas City, Mo.: M. Liston, D. Lewis, Jr., B. Martin, W. Payne, B. Voshall, S. Keeton; Little Rock, Ark.: J. Bisett, B. Cotter; Loma Linda, Calif.: A.K. Jacobson, V. Simpson; Madison, Wis.: D.C. Russell, E. Luick, L.E. Williams; Memphis, Tenn.: K.B. Ramanathan, L. Johnson, Z. Qualls; Minneapolis: I. Anand, S. Berg; Palo Alto, Calif.: J.E. Atwood, B. Danabar, J. Myers, C. Zipp, C. Ferguson; Pittsburgh: A. Shalaby, E. Thompson, R. Weiss, K. Hickey, K. Zana, K. Jones, M. DiTommaso; Portland, Oreg.: M.H. Raitt, K. Martin; Providence, R.I.: S. Sharma, L. Marquis, M. Beliard; Richmond, Va.: R. Jesse, D. Gilligan, D. Dan, P. Mohanty, T. Spencer; St. Louis: A. Mark, H.G. Stratmann, H. Manns, C. Isenberg; Sepulveda, Calif.: M.K. Heng, G. Bitner-Burley, J. Rhee, S. Reynolds, D. Church, C. Lyu; Tampa, Fla.: R.G. Zoble, I. Dejesus, D. Garrett, A. Dellaportas; Tucson, Ariz.: S. Goldman, G. Pennock, B. Gregorio, J. Ohm, C. Bernheim, C. Quattlander; Washington, D.C.: P. Karasik, K.D. Vogel; West Haven, Conn.: B. Abbott, I.S. Cohen, M. Ezekowitz, L. Sheehan, K. Pace; West Los Angeles, Calif.: F.V. Mody, E.L. Ziff, T. Davidson; West Roxbury, Mass.: M. Orlov, M. Katcher, B.S. Stambler, J.A. Faber, C. Bogosh.

REFERENCES

1. Tsang TS, Gersh BJ. Atrial fibrillation: an old disease, a new epidemic. *Am J Med* 2002;113:432-5.
2. Prystowsky EN, Benson DW Jr, Woodrow M, et al. Management of patients with atrial fibrillation: a statement of healthcare professionals from the Subcommittee on Electrocardiography and Electrophysiology, American Heart Association. *Circulation* 1996;93:1262-77.
3. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;285:2370-5.
4. Singh BN. Atrial fibrillation: epidemiologic considerations and rationale for conversion and maintenance of sinus rhythm. *J Cardiovasc Pharmacol Ther* 2003;8:Suppl 1:S13-S26.
5. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825-33.
6. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation — Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet* 2000;356:1789-94.
7. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;347:1834-40.
8. Singh BN. Atrial fibrillation following investigation of rhythm management: AFFIRM trial outcomes: what might be their implications for arrhythmia control? *J Cardiovasc Pharmacol Ther* 2002;7:131-3.
9. Singh BN, Vaughan Williams EM. The effect of amiodarone, a new anti-anginal drug, on cardiac muscle. *Br J Pharmacol* 1970;39:657-67.
10. *Idem*. A third class of anti-arrhythmic action: effects on atrial and ventricular intracellular potentials, and other pharmacological actions on cardiac muscle, of MJ 1999 and AH 3474. *Br J Pharmacol* 1970;39:675-87.
11. Nattel S, Singh BN. Evolution, mechanisms, and classification of antiarrhythmic drugs: focus on class III actions. *Am J Cardiol* 1999;84:11R-19R.
12. Nattel S. The molecular and ionic specificity of antiarrhythmic drug actions. *J Cardiovasc Electrophysiol* 1999;10:272-82.
13. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
14. Singh SN, Singh BN, Reda DJ, et al. Comparison of sotalol versus amiodarone in maintaining stability of sinus rhythm in patients with atrial fibrillation (Sotalol-Amiodarone Fibrillation Efficacy Trial [SAFE-T]). *Am J Cardiol* 2003;92:468-72.
15. McHorney AC, Ware JE Jr, Raczek AE. The MOS 36-item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993;31:247-63.
16. Patterson JA, Naughton J, Pietras RJ, Gunnar RM. Treadmill exercise in assessment of the functional capacity of patients with cardiac disease. *Am J Cardiol* 1972;30:757-62.
17. Benditt DG, Williams JH, Jin J, et al. Maintenance of sinus rhythm with oral d,l-sotalol therapy in patients with symptomatic atrial fibrillation and/or atrial flutter. *Am J Cardiol* 1999;84:270-7.
18. Singh BN. Sotalol: current status and expanding indications. *J Cardiovasc Pharmacol Ther* 1999;4:49-65.
19. Chun SH, Sager PT, Stevenson WG, Nademanee K, Middlekauff HR, Singh BN. Long-term efficacy of amiodarone for the maintenance of normal sinus rhythm in patients with refractory atrial fibrillation or flutter. *Am J Cardiol* 1995;76:47-50.
20. Singh BN. Current antiarrhythmic drugs: an overview of mechanisms of action and

- potential clinical utility. *J Cardiovasc Electro-physiol* 1999;10:283-301.
21. McNamara RL, Tamariz LJ, Segal JB, Bass EB. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. *Ann Intern Med* 2003;139:1018-33.
22. Kochiadakis GE, Igoumenidis NE, Marketou ME, Solomou MC, Kanoupakis EM, Vardas PE. Low-dose amiodarone versus sotalol for suppression of recurrent symptomatic atrial fibrillation. *Am J Cardiol* 1998;81:995-8.
23. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. *N Engl J Med* 2000;342:913-20.
24. Lehto M, Kala K. Persistent atrial fibrillation: a population based study of patients with their first cardioversion. *Int J Cardiol* 2003;92:145-50.
25. Frick F, Frykman V, Jensen-Urstad M, Ostergren J, Rosenqvist M. Factors predicting success rate and recurrence of atrial fibrillation after first electrical cardioversion in patients with persistent atrial fibrillation. *Clin Cardiol* 2001;24:238-44.
26. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardiol* 2000;36:1303-09.
27. Stewart AL, Greenfield S, Hays RD, et al. Functional status and well-being of patients with chronic conditions: results from the Medical Outcomes Study. *JAMA* 1989;262:907-13. [Erratum, *JAMA* 1989;262:2542.]
28. Hagens VE, Rancho AV, Van Sonderen E, et al. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation: results from the Rate Control versus Electrical Cardioversion (RACE) Study. *J Am Coll Cardiol* 2004;43:241-7.
29. Dorian P, Paquette M, Newman D, et al. Quality of life improves with treatment in the Canadian Trial of Atrial Fibrillation. *Am Heart J* 2002;143:984-90.
30. Keller S, Frishman WH. Neuropsychiatric effects of cardiovascular drug therapy. *Cardiol Rev* 2003;11:73-93.
31. Van Gelder IC, Crijns HJ, Blanksma PK, et al. Time course of hemodynamic changes and improvement of exercise tolerance after cardioversion of chronic atrial fibrillation unassociated with cardiac valve disease. *Am J Cardiol* 1993;72:560-6.
32. Ueshima K, Myers J, Morris CK, Atwood JE, Kawaguchi T, Froelicher VE. The effect of cardioversion on exercise capacity in patients with atrial fibrillation. *Am Heart J* 1993;126:1021-4.
33. Singh BN. Amiodarone: the expanding antiarrhythmic role and how to follow a patient on chronic therapy. *Clin Cardiol* 1997;20:608-18.
34. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med* 1995;333:77-82.
35. Doval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R. Randomized trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994;344:493-8.
36. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. *Lancet* 1997;350:1417-24.
37. Julian DG, Prescott RJ, Jackson FS, Szekeley P. Controlled trial of sotalol for one year after myocardial infarction. *Lancet* 1982;1:1142-7.
38. Shinagawa K, Shiroshita-Takeshita A, Schram G, Nattel S. Effects of antiarrhythmic drugs on fibrillation in the remodeled atrium: insights into the mechanisms of the superior efficacy of amiodarone. *Circulation* 2003;107:1440-6.
39. Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the Veterans Affairs Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT). *Circulation* 1998;98:2574-9.

Copyright © 2005 Massachusetts Medical Society.

CLINICAL TRIAL REGISTRATION

The *Journal* encourages investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors plan to consider clinical trials for publication only if they have been registered (see *N Engl J Med* 2004;351:1250-1). The National Library of Medicine's www.clinicaltrials.gov is a free registry, open to all investigators, that meets the committee's requirements.