

AMIODARONE TO PREVENT RECURRENCE OF ATRIAL FIBRILLATION

DENIS ROY, M.D., MARIO TALAJIC, M.D., PAUL DORIAN, M.D., STUART CONNOLLY, M.D.,
 MARK J. EISENBERG, M.D., M.P.H., MARTIN GREEN, M.D., TERESA KUS, M.D., JEAN LAMBERT, PH.D.,
 MARC DUBUC, M.D., PIERRE GAGNÉ, M.D., STANLEY NATTEL, M.D., AND BERNARD THIBAUT, M.D.,
 FOR THE CANADIAN TRIAL OF ATRIAL FIBRILLATION INVESTIGATORS*

ABSTRACT

Background The restoration and maintenance of sinus rhythm is a desirable goal in patients with atrial fibrillation, because the prevention of recurrences can improve cardiac function and relieve symptoms. Uncontrolled studies have suggested that amiodarone in low doses may be more effective and safer than other agents in preventing recurrence, but this agent has not been tested in a large, randomized trial.

Methods We undertook a prospective, multicenter trial to test the hypothesis that low doses of amiodarone would be more efficacious in preventing recurrent atrial fibrillation than therapy with sotalol or propafenone. We randomly assigned patients who had had at least one episode of atrial fibrillation within the previous six months to amiodarone or to sotalol or propafenone, given in an open-label fashion. The patients in the group assigned to sotalol or propafenone underwent a second randomization to determine whether they would receive sotalol or propafenone first; if the first drug was unsuccessful the second agent was prescribed. Loading doses of the drugs were administered and electrical cardioversion was performed (if necessary) within 21 days after randomization for all patients in both groups. The follow-up period began 21 days after randomization. The primary end point was the length of time to a first recurrence of atrial fibrillation.

Results Of the 403 patients in the study, 201 were assigned to amiodarone and 202 to either sotalol (101 patients) or propafenone (101 patients). After a mean of 16 months of follow-up, 71 of the patients who were assigned to amiodarone (35 percent) and 127 of those who were assigned to sotalol or propafenone (63 percent) had a recurrence of atrial fibrillation ($P < 0.001$). Adverse events requiring the discontinuation of drug therapy occurred in 18 percent of the patients receiving amiodarone, as compared with 11 percent of those treated with sotalol or propafenone ($P = 0.06$).

Conclusions Amiodarone is more effective than sotalol or propafenone for the prevention of recurrences of atrial fibrillation. (N Engl J Med 2000;342:913-20.)

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ATRIAL fibrillation is the most common arrhythmia requiring treatment and affects 5 percent of people older than 65 years.^{1,2} The number of hospital admissions for atrial fibrillation in the United States more than doubled from 1984 to 1994, from 111,000 to 270,000.³ These numbers are probably underestimates, because many episodes of atrial fibrillation are treated on an

outpatient basis or in emergency rooms, and admissions for complications such as stroke and heart failure are not necessarily attributed to atrial fibrillation.

There are multiple clinical consequences of atrial fibrillation. Patients often have disabling palpitations. In addition, the loss of effective atrial contraction may result in impaired cardiac performance, even after control of the ventricular response rate is achieved; such impairment can lead to reduced exercise tolerance and, in some patients, to congestive heart failure.⁴⁻⁷ Atrial fibrillation is associated with a quintupling of the risk of stroke in patients who are not receiving anticoagulant therapy and a doubling of the rate of death in all patients.^{1,8-10}

To control symptoms, improve functional capacity, and reduce the risk of embolism, it is common practice to restore sinus rhythm; however, atrial fibrillation recurs within three to six months in at least one half of treated patients.^{8,11-22} The long-term use of quinidine and other class I agents for the treatment of atrial fibrillation has recently been questioned, because retrospective analyses have suggested that such agents may increase mortality.^{11,23} Concern about proarrhythmic effects is particularly pertinent for patients with atrial fibrillation since, by itself, atrial fibrillation is rarely fatal.

Data from several nonrandomized trials and two small, randomized trials have suggested that low-dose amiodarone may be more effective than other antiarrhythmic agents in treating atrial fibrillation^{22,24-29}; however, the limited available results are not conclusive. We conducted a large, prospective, nonblinded, randomized trial to test the hypothesis that low-dose amiodarone is more efficacious in preventing recurrences of atrial fibrillation than antiarrhythmic therapy with sotalol or propafenone.

METHODS**Study Design**

The details of the protocol have been published previously.³⁰ The Canadian Trial of Atrial Fibrillation was conducted in 19 car-

From the Montreal Heart Institute, Montreal (D.R., M.T., M.J.E., J.L., M.D., P.G., S.N., B.T.); St. Michael's Hospital, Toronto (P.D.); Hamilton General Hospital and McMaster University, Hamilton, Ont. (S.C.); the University of Ottawa Heart Institute, Ottawa, Ont. (M.G.); and Hôpital du Sacré-Cœur de Montréal, Montreal (T.K.) — all in Canada. Address reprint requests to Dr. Roy at the Montreal Heart Institute, 5000 Belanger St. E., Montreal, QC H1T 1C8, Canada, or at roy@icm.umontreal.ca.

*The institutions and investigators participating in the trial are listed in the Appendix.

diology centers throughout Canada. The investigational review board of each institution approved the study, and all patients gave written informed consent. Recruitment began in November 1996, randomization was concluded in February 1998, and follow-up was terminated in February 1999.

Inclusion Criteria

To be eligible, patients had to have had an episode of symptomatic atrial fibrillation within the preceding six months for which long-term antiarrhythmic drug therapy was planned. At least one episode of atrial fibrillation had to have lasted more than 10 minutes (determined by history taking), and electrocardiographic confirmation was required. This criterion was chosen arbitrarily in an attempt to prevent the enrollment of patients with clinically inconsequential atrial tachyarrhythmias.

Exclusion Criteria

The exclusion criteria were as follows: atrial fibrillation known to have been present continuously for more than 6 months, myocardial infarction during the previous 6 months, cardiac surgery during the previous 30 days, moderate or severe cardiac disability (New York Heart Association functional class III or IV), atrial fibrillation associated with an acute reversible condition, a serum creatinine concentration of more than 2.8 mg per deciliter (250 μmol per liter), a serum alanine aminotransferase concentration more than 2.5 times the upper limit of normal, chronic lung disease requiring bronchodilator therapy, the Wolff-Parkinson-White syndrome, previous long-term therapy (lasting 4 weeks or more) or intolerance of study drugs, untreated hypothyroidism, a corrected QT interval of more than 480 msec or an uncorrected QT interval of more than 500 msec in the absence of bundle-branch block, bradycardia (defined as a heart rate of less than 50 beats per minute for a period of more than one minute while the patient was awake), second-degree or third-degree atrioventricular block or a sinus pause of more than two seconds without a permanent pacemaker, an age of less than 18 years, a need for antiarrhythmic therapy for arrhythmias other than atrial fibrillation, and any medical condition that would make survival for 1 year unlikely. In addition, premenopausal women who had not undergone tubal ligation or hysterectomy were excluded.

Randomization, Therapy, and Follow-up

Patients with atrial fibrillation lasting more than 48 hours had to undergo treatment with an anticoagulant agent at a dosage adjusted to achieve an international normalized ratio of 2 or more for a minimum of three weeks before randomization.³¹ After written informed consent was obtained, patients were randomly assigned to receive amiodarone or to receive sotalol or propafenone, in an open-label fashion. The patients assigned to sotalol or propafenone underwent a second randomization to determine whether they would receive sotalol or propafenone first. Loading doses of the drugs were administered and electrical cardioversion, if necessary, was performed within 21 days after randomization for the patients in both groups. Cardioversion was recommended if atrial fibrillation persisted after 14 days of loading doses of amiodarone and after 4 days of treatment with either sotalol or propafenone. If the first drug administered to a patient assigned to sotalol or propafenone was unsuccessful, the second agent was prescribed and cardioversion was reattempted. An electrocardiogram was transmitted by telephone on days 7 and 14, and patients were reevaluated in the clinic 21 days after randomization.

Amiodarone was given at a dose of 10 mg per kilogram of body weight each day for 14 days, followed by 300 mg per day for 4 weeks, after which a daily maintenance dose of 200 mg was given. Sotalol was administered as follows: 160 mg every 12 hours to men 70 years of age or younger who had a creatinine concentration of 1.5 mg per deciliter (130 μmol per liter) or less and who weighed at least 70 kg; 80 mg every 8 hours to men who were older than 70, men who had a creatinine concentration of more than 1.5 mg per deciliter, men who weighed less than 70 kg, and

to women 70 or younger who had a creatinine concentration of 1.2 mg per deciliter (110 μmol per liter) or less; and 80 mg every 12 hours to women who were older than 70 or who had a creatinine concentration of more than 1.2 mg per deciliter. Propafenone was given at a dose of 300 mg every 12 hours or 150 mg every 6 hours to patients who were 70 years of age or younger and who weighed at least 70 kg; a dose of 150 mg every 8 hours was given to patients older than 70 or those who weighed less than 70 kg.

Patients were assessed by a nurse coordinator and a physician at three months and every six months thereafter. The minimal duration of follow-up was one year. Twelve-lead electrocardiograms were obtained at each visit. Chest x-ray films were obtained at 6, 12, and 24 months, and measurements of thyrotropin and alanine aminotransferase were obtained every 6 months for the patients receiving amiodarone. Patients were provided with electrocardiographic monitors capable of transmitting data over the telephone and were instructed to transmit an electrocardiogram if cardiac symptoms occurred.

The primary end point was the length of time to a first electrocardiographically confirmed recurrence of atrial fibrillation. Only episodes lasting longer than 10 minutes (as indicated by the history) were considered to be clinically significant. For the purpose of the primary end point, day 21 after randomization was considered to be the beginning of follow-up (day 0). Patients in whom sinus rhythm was not achieved within 21 days after randomization were classified as having had a recurrence on day 1. Secondary end points were adverse effects related to the study medication, thromboembolic events, and death. The system of Hinkle and Thaler was used to classify deaths.³² All primary outcome events and major clinical events were reviewed by a committee whose members had no other affiliation with the study and were unaware of the treatment assignments.

Statistical Analysis

Summary data are expressed as means \pm SD or numbers and percentages of patients. Analyses were performed according to the intention-to-treat principle. Data were censored if the patient died, reached the end of the follow-up period (February 1999), or was lost to follow-up without an occurrence of the primary end point. The cumulative risk of recurrence of atrial fibrillation was estimated by the product-limit method of Kaplan and Meier, and the difference between treatment groups was assessed with the log-rank test.³³ The Cox proportional-hazards model was used to calculate relative risk and to investigate potential differences in the effects of the study drugs among subgroups.³⁴ We estimated that the enrollment of 400 patients with symptomatic atrial fibrillation would be necessary in order for the study to achieve a power of more than 0.80 to detect a reduction of 30 percentage points in the rate of recurrence of atrial fibrillation in the amiodarone group with a two-sided alpha level of 0.05, assuming a recurrence rate of 50 percent at one year in the group assigned to sotalol or propafenone and a 15 percent loss to follow-up.

RESULTS

A total of 403 patients were enrolled: 201 in the group assigned to amiodarone and 202 in the group assigned to sotalol or propafenone (with 101 assigned to each drug). Ten patients (2.5 percent) were lost to follow-up. Thirteen patients who were first randomly assigned to propafenone and 11 patients who were first randomly assigned to sotalol received the other drug during the 21-day period after randomization. Forty-four patients assigned to treatment with amiodarone underwent a total of 48 electrical cardioversions during the 21-day period after randomization, as compared with 63 patients assigned to treatment

with sotalol or propafenone, who underwent a total of 84 cardioversions. Among the patients in whom electrical cardioversion was attempted, the procedure was ultimately successful in 77 percent of those assigned to amiodarone and 81 percent of those assigned to sotalol or propafenone.

Base-Line Characteristics

The clinical, electrocardiographic, and echocardiographic characteristics of the patients at the time of enrollment are shown in Table 1. With the exception of the percentage of patients with left ventricular hypertrophy, there were no significant differences in base-line characteristics between the treatment groups.

Therapy

Table 2 lists the mean daily doses of the study drugs the patients received. Table 3 lists the percentages of patients taking various concomitant medications at base line and during follow-up.

Recurrence of Atrial Fibrillation

Over the course of a mean follow-up period of 468±150 days, 71 patients assigned to amiodarone (35 percent) had first recurrences of atrial fibrillation, as did 127 of the patients assigned to sotalol or propafenone (63 percent, P<0.001). The median length of time to a recurrence was 98 days for the patients assigned to sotalol or propafenone. No median time could be calculated for the amiodarone group, because more than 50 percent of the patients in this group remained in sinus rhythm without recurrence of atrial fibrillation at the end of follow-up (therefore the median time was more than 468 days).

Figure 1A shows the actuarial probability of remaining in sinus rhythm without a recurrence of atrial fibrillation for both treatment groups. Ninety-three percent of the patients assigned to amiodarone and 81 percent of the patients assigned to sotalol or propafenone were in sinus rhythm at the beginning of follow-up, 21 days after randomization. The probability of remaining in sinus rhythm for one year without a recurrence of atrial fibrillation was higher among the patients assigned to amiodarone (69 percent) than among those assigned to sotalol or propafenone (39 percent, P<0.001). For the patients in the amiodarone group, the hazard ratio for a recurrence was 0.43, reflecting a 57 percent reduction in the risk of recurrence of atrial fibrillation. Similarly, when the analysis included only the 350 patients who were in sinus rhythm 21 days after randomization, the actuarial probability of remaining free of a recurrence of atrial fibrillation was significantly higher among the patients assigned to amiodarone than among those assigned to sotalol or propafenone (Fig. 1B). As Figure 1C shows, the rate of recurrence of atrial fibrillation was virtually the same for the patients assigned to sotalol and those assigned to propafenone.

TABLE 1. BASE-LINE CLINICAL, ELECTROCARDIOGRAPHIC, AND ECHOCARDIOGRAPHIC CHARACTERISTICS OF THE PATIENTS.*

| CHARACTERISTIC | AMIODARONE (N=201) | SOTALOL OR PROPAFENONE (N=202) | P VALUE |
|--|--------------------|--------------------------------|---------|
| Male sex (%) | 55 | 56 | 0.81 |
| Age (yr) | 65±11 | 65±11 | 0.68 |
| Medical history (% of patients) | | | |
| Coronary disease | 19 | 18 | 0.68 |
| Valvular disease | 14 | 13 | 0.76 |
| Hypertension | 44 | 48 | 0.45 |
| No cardiovascular disease | 36 | 34 | 0.65 |
| Diabetes | 10 | 10 | 0.75 |
| History of atrial fibrillation (%) | | | 0.25 |
| Paroxysmal | 49 | 43 | |
| Persistent† | 51 | 57 | |
| Electrocardiographic findings‡ | | | |
| Sinus rhythm (%) | 64 | 61 | 0.64 |
| Atrial fibrillation (%) | 35 | 38 | 0.56 |
| Other rhythm (%) | 3 | 2 | 0.72 |
| Heart rate (beats/min) | 75±24 | 79±26 | 0.14 |
| Echocardiography | | | |
| Left atrial dimension (mm) | 41±7 | 41±7 | 0.66 |
| Left ventricular ejection fraction <50 percent (%) | 12 | 12 | 0.85 |
| Left ventricular hypertrophy (%) | 13 | 21 | 0.04 |
| Clinically significant mitral-valve or aortic-valve abnormality (%)§ | 22 | 21 | 0.75 |

*Plus-minus values are means ±SD. Percentages are of patients in each treatment group.

†Atrial fibrillation was defined as persistent if, in the opinion of the investigator, more than 50 percent of episodes had required intravenous drug therapy or electrical cardioversion.

‡Some patients had more than one type of rhythm.

§Clinically significant mitral-valve or aortic-valve abnormality was defined as the presence of any degree of valvular stenosis or the presence of moderate-to-severe regurgitation.

TABLE 2. MEAN DAILY DOSES OF STUDY DRUGS.*

| STUDY DRUG | DAY 21 | 3 MONTHS | 6 MONTHS | 12 MONTHS |
|-------------|--------------------|----------|----------|-----------|
| | milligrams per day | | | |
| Amiodarone | 327±134 | 205±44 | 196±39 | 186±48 |
| Propafenone | 547±139 | 527±111 | 520±122 | 471±121 |
| Sotalol | 230±80 | 231±81 | 219±85 | 224±83 |

*All values are means ±SD. Doses are reported only for the patients taking the study drug at the time in question.

Subgroups

Figure 2 shows the hazard ratios for the recurrence of atrial fibrillation according to a variety of dichotomous base-line, clinical, and echocardiographic characteristics. The hazard ratios did not differ significantly according to any of these variables; more-

TABLE 3. PATIENTS RECEIVING CONCOMITANT MEDICATION.

| MEDICATION | BASE LINE | | 3 MONTHS | | 6 MONTHS | | 12 MONTHS | |
|--------------------------------|------------------------|---------------------------|------------|---------------------------|------------|---------------------------|------------|---------------------------|
| | AMIODARONE | SOTALOL OR PROPAPENONE | AMIODARONE | SOTALOL OR PROPAPENONE | AMIODARONE | SOTALOL OR PROPAPENONE | AMIODARONE | SOTALOL OR PROPAPENONE |
| | percentage of patients | | | | | | | |
| Digoxin | 34 | 33 | 16 | 28 | 16 | 24 | 16 | 25 |
| Beta-blockers | 29 | 28 | 18 | 15 | 16 | 12 | 18 | 18 |
| Calcium-channel blockers | 9 | 12 | 10 | 12 | 12 | 14 | 13 | 14 |
| Aspirin | 23 | 27 | 24 | 24 | 27 | 27 | 30 | 29 |
| Anticoagulant drugs | 58 | 57 | 53 | 61 | 52 | 57 | 51 | 56 |
| Thyroid-replacement medication | 10 | 7 | 11 | 7 | 11 | 8 | 16 | 12 |

over, all 95 percent confidence intervals included the overall hazard ratio and did not include 1.0.

Major Clinical Events

During the course of the study, nine patients assigned to amiodarone died, as compared with eight assigned to sotalol or propafenone. Four deaths were presumed to be due to arrhythmia; three of these four occurred in patients assigned to amiodarone (two of these had discontinued the drug for more than one year before death). One patient in each group died of acute myocardial infarction. One patient assigned to sotalol or propafenone died of congestive heart failure. Death was due to a vascular cause in one patient assigned to amiodarone (mesenteric infarction) and in one assigned to sotalol or propafenone (stroke). The cause of death was noncardiovascular for four patients in each group (five died of cancer, and three of other causes).

Thirty-six patients assigned to amiodarone (18 percent) were treated for a total of 45 nonfatal major clinical events, and 35 patients assigned to sotalol or propafenone (17 percent) were treated for 42 such events. Among these events, not all of which are described here, one patient receiving propafenone was resuscitated from cardiac arrest due to torsade de pointes. Congestive heart failure requiring intravenous therapy occurred in 11 patients assigned to amiodarone and 9 assigned to sotalol or propafenone. Strokes and intracranial hemorrhages were less common among the patients assigned to amiodarone than among those assigned to sotalol or propafenone (one patient vs. nine patients, $P=0.01$). Eight of these patients (one patient assigned to amiodarone and seven assigned to sotalol or propafenone) were receiving warfarin at the time of the event. Two patients in each group had a major hemorrhage in a location other than the nervous system. There were 7 cancers (3 among patients assigned to amiodarone and 4 among patients

assigned to sotalol or propafenone) and 13 other nonfatal events (8 and 5, respectively).

Discontinuation of Study Drug

Overall, 68 of the patients assigned to amiodarone (34 percent) and 93 of those assigned to sotalol or propafenone (46 percent) stopped taking the study medication ($P=0.01$). Seventeen patients assigned to amiodarone (8 percent) discontinued taking the study drug because of a lack of efficacy (defined as frequent recurrences of atrial fibrillation or the need for repeated cardioversion), as compared with 56 assigned to sotalol or propafenone (28 percent, $P<0.001$). Fifteen patients assigned to amiodarone (7 percent) and 14 assigned to sotalol or propafenone (7 percent) were noncompliant with the study protocol or discontinued taking the medication for other reasons. Thirty-six patients assigned to amiodarone (18 percent) discontinued taking the study drug because of adverse events, as compared with 23 assigned to sotalol or propafenone (11 percent, $P=0.06$).

The incidence of cardiac events requiring permanent discontinuation of the study medication was similar in the two groups: ventricular tachycardia, none in the amiodarone group and one in the group assigned to sotalol or propafenone; prolongation of the QT interval, one and none, respectively; heart failure, two and three; and serious bradyarrhythmias, six and seven. The most common noncardiac adverse events responsible for discontinuation of the study medication were gastrointestinal events (eight patients in the amiodarone group and three in the group assigned to sotalol or propafenone), central nervous system events (two and one, respectively), insomnia or fatigue (six and four), and visual or dermatologic events (two and one).

Treatment with amiodarone was discontinued in four patients (2 percent) because of pulmonary abnormalities. Although amiodarone-induced pulmonary

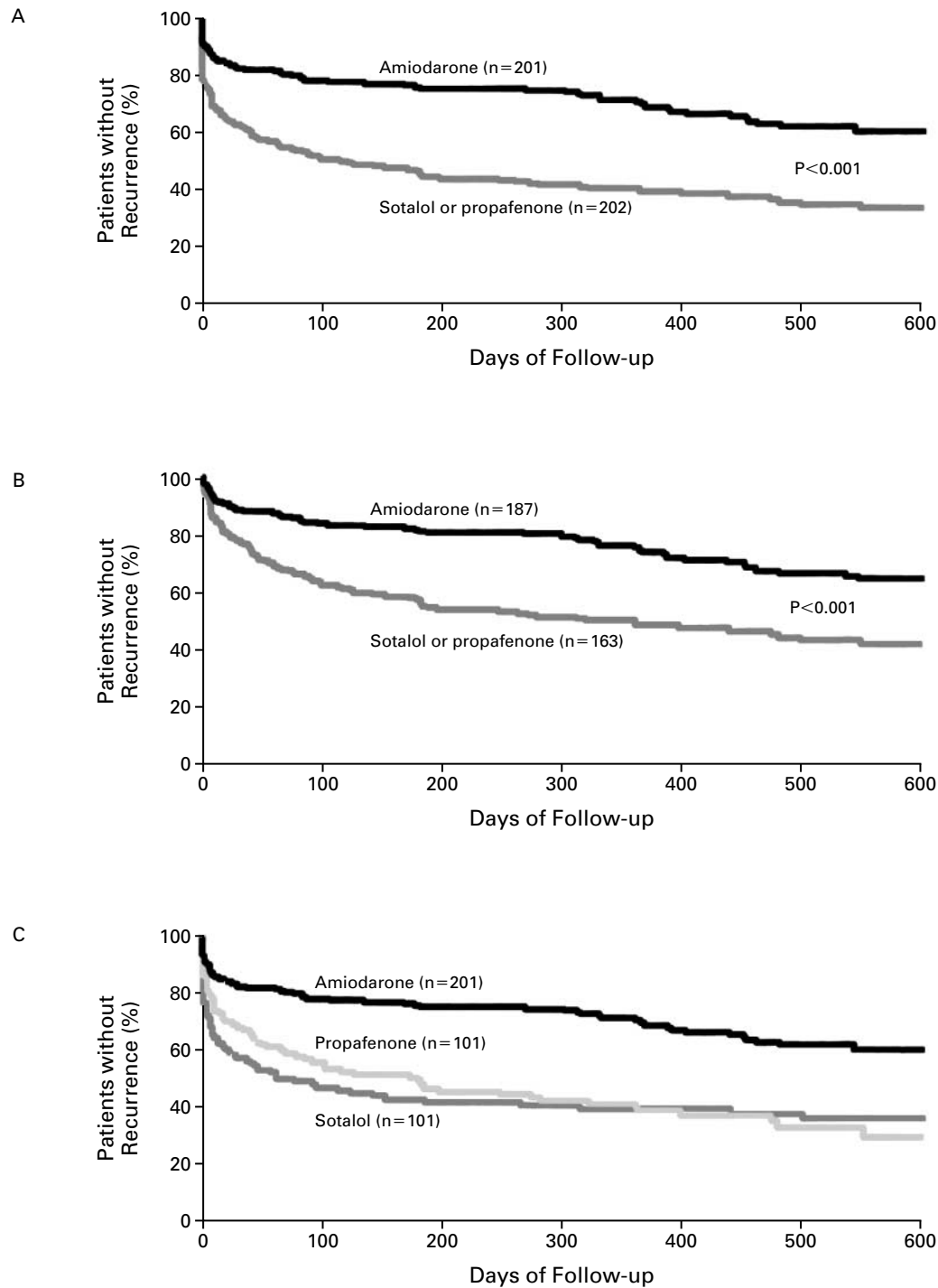


Figure 1. Kaplan–Meier Estimates of the Percentage of Patients Remaining Free of Recurrence of Atrial Fibrillation.

Panel A shows the estimates of the proportion of patients with no recurrence of atrial fibrillation in the two groups (hazard ratio for recurrence among patients in the amiodarone group, 0.43 [95 percent confidence interval, 0.32 to 0.57]); Panel B shows the estimates for the 350 patients (187 in the amiodarone group and 163 in the group assigned to sotalol or propafenone) who were in sinus rhythm 21 days after randomization (hazard ratio, 0.45 [95 percent confidence interval, 0.32 to 0.63]); and Panel C shows the estimates for the patients who received amiodarone, those who received sotalol, and those who received propafenone. Follow-up began 21 days after randomization (designated day 0).

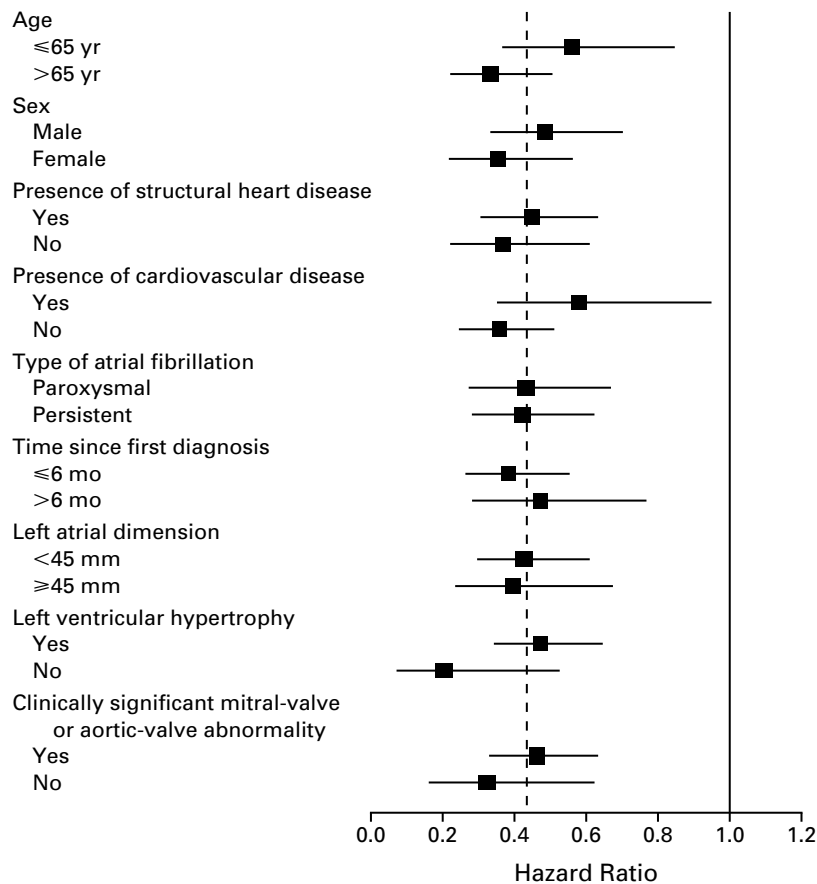


Figure 2. Hazard Ratios and 95 Percent Confidence Intervals for the Recurrence of Atrial Fibrillation in the Amiodarone Group as Compared with the Group Assigned to Sotalol or Propafenone. The solid vertical line represents equal effectiveness of the two treatments. Points to the left indicate better results in the amiodarone group. The dotted vertical line represents the results for the entire study population.

toxicity is difficult to prove, the diagnosis was felt to be definite in one patient and possible in three. Pulmonary toxicity was suspected in one other patient in whom pulmonary abnormalities developed two months after the discontinuation of amiodarone due to a lack of efficacy. No patient died as a result of pulmonary toxicity. Treatment with amiodarone was discontinued in two patients because of hypothyroidism and in one because of hyperthyroidism. Five patients (two assigned to amiodarone and three assigned to sotalol or propafenone) discontinued treatment because of other reasons.

DISCUSSION

The results of this large, randomized trial show that amiodarone is more effective than sotalol or propafenone in the maintenance of sinus rhythm in patients with atrial fibrillation.

The difference in efficacy we observed is striking;

amiodarone was about twice as effective as two commonly used antiarrhythmic agents in preventing recurrences of atrial fibrillation. Our findings indicate that amiodarone warrants consideration as first- or second-line therapy in patients in whom maintenance of sinus rhythm is desired. No difference was found in the occurrence of atrial fibrillation between the patients who received sotalol and those who received propafenone, a finding that is compatible with previous observations.¹⁸ Furthermore, the rates of recurrence in the patients treated with these agents in our study were very similar to those reported for patients treated with other class I drugs, such as quinidine and flecainide.^{14,21,22}

Amiodarone was generally well tolerated, and serious adverse events were uncommon. No proarrhythmic effect was observed among the patients assigned to amiodarone, and clinically relevant thyroid and pulmonary abnormalities occurred in a small proportion

of patients. The proportion of patients in our study who discontinued taking amiodarone because of adverse events (18 percent) was lower than that previously reported in other large trials.^{35,36} At one year, more patients in the amiodarone group were still receiving the drug to which they had been assigned (72 percent) than was the case in the group receiving sotalol or propafenone (58 percent). The adverse effects associated with amiodarone have usually been related to the dose and duration of therapy, and much of the concern about its use has arisen from experience with high daily doses in patients treated for ventricular tachyarrhythmias.^{35,37-39} This trial provides additional information regarding the safety of low doses of amiodarone (200 mg per day or less) for the treatment of atrial fibrillation.

Whether maintaining sinus rhythm in patients with atrial fibrillation will translate into improved survival or a reduction in the risk of thromboembolic events will require further study. Mortality was not the primary outcome measured in this trial, for several reasons. First, the absolute mortality among patients with atrial fibrillation is relatively low, and death is due primarily to associated cardiovascular diseases, making the sample needed for a study of mortality extremely large. Second, the ongoing Atrial Fibrillation Follow-up Investigation of Rhythm Management of the National Heart, Lung, and Blood Institute is comparing the mortality associated with various approaches to treating atrial fibrillation in older patients who have one or more risk factors for stroke. Finally, our study was designed to identify the most effective agent for maintaining sinus rhythm in a heterogeneous group of patients for whom the clinical decision to try to suppress atrial fibrillation had already been made. This information may help in designing subsequent trials with mortality as an end point.

Since this was a relatively short study, it did not address the potential for serious long-term adverse effects associated with low-dose amiodarone. Since the goal of this trial was to compare the relative efficacy of two treatments in patients believed by their physicians to require drug therapy for the maintenance of sinus rhythm, the use of a placebo group was deemed inappropriate. An open-label design was selected, because it would have been technically difficult to maintain blinding in a two-treatment study in which three drugs with different pharmacokinetics, pharmacodynamics, dosing regimens, and safety profiles were used. To minimize the potential effects of bias, the primary end point (recurrence of atrial fibrillation) had to be objectively confirmed by electrocardiography. In addition, all primary end points and fatal and non-fatal major events were reviewed by an independent committee, the members of which were unaware of the treatment assignments.

Overall, we found that amiodarone was more effective in preventing recurrences of atrial fibrillation

than two widely used antiarrhythmic drugs. Even recognizing the limitations of the study, we believe that our results challenge the notion that amiodarone should be used only in patients whose conditions are resistant to other drugs. Since other antiarrhythmic agents are less effective and are associated with higher risks,^{11,22,40} and the safety of amiodarone with regard to cardiovascular complications is well recognized,³⁶ amiodarone should be a drug of choice for patients with recurrent atrial fibrillation and structural heart disease, particularly those with left ventricular dysfunction. Amiodarone should also be considered for patients with refractory conditions who do not have heart disease, before therapies with irreversible effects, such as atrioventricular-nodal ablation, are attempted. Finally, new class III antiarrhythmic agents are currently being evaluated as treatments for atrial fibrillation in placebo-controlled trials. Comparative safety and efficacy data from well-controlled studies of other accepted therapies should complement the findings of these trials. Amiodarone seems an obvious choice for such comparisons.

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APPENDIX

The study sites and investigators of the Canadian Trial of Atrial Fibrillation are listed below in descending order according to the number of patients randomized. For each site, the first person listed was the principal investigator: St. Michael's Hospital and Satellite Centers (Northwestern General Hospital, Scarborough General Hospital, Scarborough Centenary Hospital, Peel Memorial Hospital, York Finch Hospital, Scarborough Grace Hospital, Etobicoke General Hospital, Humber Memorial Hospital, North York General Hospital, Toronto East General Hospital, Oshawa General Hospital, York County Hospital), Toronto: P. Dorian, D. Newman, and J. Mitchell; Institut de Cardiologie de Montréal, Montreal: D. Roy, M. Talajic, M. Dubuc, B. Thibault, P. Gagné, and D. Beaudoin; Centre Hospitalier Régional de Lanaudière, Joliette, Que.: S. Kouz, G.S. Kiwan, J.-P. Deschamps, H. Ouimet, M. Laforest, M. Roy, and C. Rémillard; Hôpital Santa Cabrini, Montreal: O. Ruscito and S. Vinci; Centre Hospitalier Le Gardeur, Repentigny, Que.: G. Gosselin, M. David, and C. Côté; University of Alberta Hospital, Edmonton, Alta.: K. Kavanagh and R. Tabler; Réseau Santé Richelieu-Yamaska, Saint-Hyacinthe, Que.: D. Grandmont, C. Van Kieu, and B. Lecours; Sunnybrook Health Sciences Center, North York, Ont.: Z. Wulffhart, C. Joyner, and M. Aprile; Hôpital Notre-Dame, Montreal: B. Coutu, C. Guimond, and J. Frenette; Centre Hospitalier Pierre-Boucher, Longueuil, Que.: A. Ouellet and L. Leroux; Hôpital Jean-Talon, Montreal: R. Castan, B. Descoings, and A. Beaudoin; Institut de Cardiologie de Québec, Sainte-Foy, Que.: G. O'Hara and L. Charbonneau; Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Que.: R. Harvey and A. Maltais; Hôpital du Sacré-Coeur de Montréal, Montreal: T. Kus, F. Molin, and G. Gaudette; Toronto General Hospital, Toronto: E. Downar and C. Hale; Hamilton General Hospital, McMaster University, Hamilton, Ont.: S. Connolly, C. Le Feuvre, S. Kahn, and S. Morgan; Cité de la Santé de Laval, Laval, Que.: R. Gendreau and R. Couturier; Hôpital Maisonneuve-Rosemont, Montreal: D. Gossard and C. Roy; University of Ottawa Heart Institute, Ottawa, Ont.: M. Green, A. Tang, and M. Luce. **Steering Committee:** D. Roy (chair), M. Talajic (co-chair), P. Dorian, S. Connolly, M. Green, T. Kus, M.J. Eisenberg, A. Ciampi, and M. Morello; **External Safety and Efficacy Monitoring Committee:** G. Dagenais (chair), R. Nadeau, R. Roberts, and M. Tech; **Validation and Events Committee:** I. Dyrda (chair), J. Diodati, J. Nasmi, and N. Racine; Co-

ordinating and Methods Center: Montreal Heart Institute, Faculty of Medicine, University of Montreal, Montreal — D. Roy and M. Talajic (principal investigators); B. Thibault, M. Dubuc, M. Morello, C. Dupont, A. Couturier, J. Lambert, M.J. Eisenberg, and S. Nattel.

REFERENCES

- Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham Study. *N Engl J Med* 1982;306:1018-22.
- Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications. *Arch Intern Med* 1995;155:469-73.
- Braunwald E. Shattuck Lecture — cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med* 1997;337:1360-9.
- Morris JJ Jr, Entman M, North WC, Kong Y, McIntosh H. The changes in cardiac output with reversion of atrial fibrillation to sinus rhythm. *Circulation* 1965;31:670-8.
- Shapiro W, Klein G. Alterations in cardiac function immediately following electrical conversion of atrial fibrillation to normal sinus rhythm. *Circulation* 1968;38:1074-84.
- Lewis RV, Irvine N, McDevitt DG. Relationships between heart rate, exercise tolerance and cardiac output in atrial fibrillation: the effects of treatment with digoxin, verapamil and diltiazem. *Eur Heart J* 1988;9:777-81.
- Gosselink ATM, Crijns HJGM, van den Berg MP. Functional capacity before and after cardioversion of atrial fibrillation: a controlled study. *Br Heart J* 1994;72:161-6.
- Pritchett ELC. Management of atrial fibrillation. *N Engl J Med* 1992;326:1264-71.
- Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983-8.
- Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449-57. [Erratum, *Arch Intern Med* 1994;154:2254.]
- Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion: a meta-analysis of randomized control trials. *Circulation* 1990;82:1106-16. [Erratum, *Circulation* 1991;83:714.]
- Dethy M, Chassat C, Roy D, Mercier L-A. Doppler echocardiographic predictors of recurrence of atrial fibrillation after cardioversion. *Am J Cardiol* 1988;62:723-6.
- Van Gelder IC, Crijns HJ, Van Gilst WH, Verwer R, Lie KI. Prediction of uneventful cardioversion and maintenance of sinus rhythm from direct-current electrical cardioversion of chronic atrial fibrillation and flutter. *Am J Cardiol* 1991;68:41-6.
- Juul-Moller S, Edvardsson N, Rehnqvist-Ahlberg N. Sotalol versus quinidine for the maintenance of sinus rhythm after direct current conversion of atrial fibrillation. *Circulation* 1990;82:1932-9.
- Connolly SJ, Hoeffert DL. Usefulness of propafenone for recurrent paroxysmal atrial fibrillation. *Am J Cardiol* 1989;63:817-9.
- Pritchett ELC, McCarthy EA, Wilkinson WE. Propafenone treatment of symptomatic paroxysmal supraventricular arrhythmias: a randomized, placebo-controlled, crossover trial in patients tolerating oral therapy. *Ann Intern Med* 1991;114:539-44.
- Antman EM, Beamer AD, Cantillon C, McGowan N, Goldman L, Friedman PL. Long-term oral propafenone therapy for suppression of refractory symptomatic atrial fibrillation and atrial flutter. *J Am Coll Cardiol* 1988;12:1005-11. [Erratum, *J Am Coll Cardiol* 1989;13:264.]
- Reimold SC, Cantillon CO, Friedman PL, Antman EM. Propafenone versus sotalol for suppression of recurrent symptomatic atrial fibrillation. *Am J Cardiol* 1993;71:558-63.
- Van Gelder IC, Crijns HJGM, Van Gilst WH, Van Wijk LM, Hamer HPM, Lie KI. Efficacy and safety of flecainide acetate in the maintenance of sinus rhythm after electrical cardioversion of chronic atrial fibrillation or atrial flutter. *Am J Cardiol* 1989;64:1317-21.
- Anderson JL, Gilbert EM, Alpert BL, et al. Prevention of symptomatic recurrences of paroxysmal atrial fibrillation in patients initially tolerating antiarrhythmic therapy: a multicenter, double-blind, crossover study of flecainide and placebo with transtelephonic monitoring. *Circulation* 1989;80:1557-70.
- Naccarelli GV, Dorian P, Hohnloser SH, Coumel P. Prospective comparison of flecainide versus quinidine for the treatment of paroxysmal atrial fibrillation/flutter. *Am J Cardiol* 1996;77:A53-A59.
- Nattel S, Hadjis T, Talajic M. The treatment of atrial fibrillation: an evaluation of drug therapy, electrical modalities and therapeutic considerations. *Drugs* 1994;48:345-71.
- Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halperin JL, Hart RG. Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. *J Am Coll Cardiol* 1992;20:527-32.
- Middlekauff HR, Wiener I, Stevenson WG. Low-dose amiodarone for atrial fibrillation. *Am J Cardiol* 1993;72:75F-81F.
- Vitolo E, Tronci M, Larovere MT, Rumolo R, Morabito A. Amiodarone versus quinidine in the prophylaxis of atrial fibrillation. *Acta Cardiol* 1981;36:431-44.
- Gosselink AT, Crijns HJ, Van Gelder IC, Hillige H, Wiesfeld ACP, Lie KI. Low-dose amiodarone for maintenance of sinus rhythm after cardioversion of atrial fibrillation or flutter. *JAMA* 1992;267:3289-93.
- Chun SH, Sager PT, Stevenson WG, Nademanec 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.
- Zaremski DG, Nolan PE Jr, Slack MK, Caruso AC. Treatment of resistant atrial fibrillation: a meta-analysis comparing amiodarone and flecainide. *Arch Intern Med* 1995;155:1885-91.
- 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.
- Roy D, Talajic M, Thibault B, et al. Pilot study and protocol of the Canadian Trial of Atrial Fibrillation (CTAF). *Am J Cardiol* 1997;80:464-8.
- Talajic M, MacDonald RG, Nattel S. Restoration of sinus rhythm in patients with atrial fibrillation. *Can J Cardiol* 1996;12:Suppl A:29A-35A.
- Hinkle LE Jr, Thaler HT. Clinical classification of cardiac deaths. *Circulation* 1982;65:457-64.
- Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163-70.
- Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Vorperian VR, Havighurst TC, Miller S, January CT. Adverse effects of low dose amiodarone: a meta-analysis. *J Am Coll Cardiol* 1997;30:791-8.
- 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.
- Mason JW. Amiodarone. *N Engl J Med* 1987;316:455-66.
- Collaborative Group for Amiodarone Evaluation. Multicenter controlled observation of a low-dose regimen of amiodarone for treatment of severe ventricular arrhythmias. *Am J Cardiol* 1984;53:1564-9.
- Raeder EA, Podrid PJ, Lown B. Side effects and complications of amiodarone therapy. *Am Heart J* 1985;109:975-83.
- Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction: an overview of results from randomized controlled trials. *JAMA* 1993;270:1589-95.