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## AMIODARONE IN PATIENTS WITH CONGESTIVE HEART FAILURE AND ASYMPTOMATIC VENTRICULAR ARRHYTHMIA

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**Abstract Background.** Asymptomatic ventricular arrhythmias in patients with congestive heart failure are associated with increased rates of overall mortality and sudden death. Amiodarone is now used widely to prevent ventricular tachycardia and fibrillation. We conducted a trial to determine whether amiodarone can reduce overall mortality in patients with congestive heart failure and asymptomatic ventricular arrhythmias.

**Methods.** We used a double-blind, placebo-controlled protocol in which 674 patients with symptoms of congestive heart failure, cardiac enlargement, 10 or more premature ventricular contractions per hour, and a left ventricular ejection fraction of 40 percent or less were randomly assigned to receive amiodarone (336 patients) or placebo (338 patients). The primary end point was overall mortality, and the median follow-up was 45 months (range, 0 to 54).

**Results.** There was no significant difference in overall mortality between the two treatment groups ( $P=0.6$ ). The two-year actuarial survival rate was 69.4 percent (95 per-

cent confidence interval, 64.2 to 74.6) for the patients in the amiodarone group and 70.8 percent (95 percent confidence interval, 65.7 to 75.9) for those in the placebo group. At two years, the rate of sudden death was 15 percent in the amiodarone group and 19 percent in the placebo group ( $P=0.43$ ). There was a trend toward a reduction in overall mortality among the patients with nonischemic cardiomyopathy who received amiodarone ( $P=0.07$ ). Amiodarone was significantly more effective in suppressing ventricular arrhythmias and increased the left ventricular ejection fraction by 42 percent at two years.

**Conclusions.** Although amiodarone was effective in suppressing ventricular arrhythmias and improving ventricular function, it did not reduce the incidence of sudden death or prolong survival among patients with heart failure, except for a trend toward reduced mortality among those with nonischemic cardiomyopathy. (N Engl J Med 1995;333:77-82.)

**M**OST patients with heart failure are treated with a combination of drugs that usually includes cardiac glycosides, diuretics, and afterload-reducing agents.<sup>1,2</sup> Such regimens provide symptomatic relief,<sup>2</sup> but their effects on survival have been variable or uncertain. For example, the effects of diuretics or digoxin on overall mortality among patients with heart failure remain to be determined.<sup>3</sup> In a subgroup of patients, beta-blocking drugs may improve survival, although their use in these patients is still controversial and un-

clear.<sup>4</sup> On the other hand, afterload-reducing agents, such as hydralazine, nitrates, and especially angiotensin-converting-enzyme inhibitors,<sup>5</sup> have been found to prolong survival.

Patients with congestive heart failure and ventricular arrhythmias are at particularly high risk for fatal cardiovascular events.<sup>6-9</sup> Among patients with frequent and complex ventricular arrhythmias on Holter monitoring, the annual mortality rate is about 15 percent, and half the deaths are sudden, presumably caused by cardiac arrhythmias.<sup>6-9</sup> Attempts have been made to suppress ventricular arrhythmias with antiarrhythmic agents, in the expectation of prolonging survival.<sup>10-12</sup> The Cardiac Arrhythmia Suppression Trials showed that the suppression of arrhythmias with encainide or flecainide increased mortality among patients with myocardial infarction.<sup>13,14</sup>

The results of several small studies suggest that amiodarone may be beneficial in the treatment of patients with recent infarction.<sup>15,16</sup> Amiodarone is a powerful antiarrhythmic agent that markedly suppresses complex premature ventricular contractions and unsustained ventricular tachycardia, with little depressant effect on hemodynamic function.<sup>17</sup> The drug does not have impor-

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\*The institutions and investigators participating in the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure are listed in the Appendix.

tant proarrhythmic effects.<sup>18,19</sup> We therefore tested the hypothesis that amiodarone can prolong survival among patients with heart failure and asymptomatic but frequent and complex ventricular arrhythmias.

## METHODS

The design of the trial has been described elsewhere.<sup>19</sup> Patients were screened at 24 centers, listed in the Appendix. The protocol was approved by an institutional review board at each center, and all patients gave informed consent. The conduct of the study was monitored by an external data and safety monitoring board and by the Human Rights Committee of the Hines Veterans Affairs Cooperative Studies Program Coordinating Center.

Patients with a documented history of congestive heart failure, whether ischemic or nonischemic in origin, and at least 10 ventricular premature beats per hour, unaccompanied by symptoms, were eligible for the study. All patients had shortness of breath on exertion or paroxysmal nocturnal dyspnea, an echocardiogram showing a left ventricular internal diameter of at least 55 mm or a cardiothoracic ratio higher than 0.50, and a left ventricular ejection fraction of 40 percent or less. All patients received vasodilator therapy. Digoxin and diuretics were administered as deemed appropriate by the treating physicians.

Women of childbearing age were excluded from the study. Other criteria for exclusion were myocardial infarction within the three months before enrollment, symptomatic ventricular arrhythmia, a history of aborted sudden cardiac arrest or sustained ventricular tachycardia, uncontrolled thyroid disease, the need for antiarrhythmic therapy, electrocardiographic changes in the QRS interval ( $\geq 180$  msec) or QTc interval ( $\geq 500$  msec), a serious disease other than heart disease that was likely to be fatal within three years, and symptomatic hypotension or systolic blood pressure under 90 mm Hg.

Before randomization, the patients were stratified according to the cause of their heart disease (ischemic or nonischemic), the ejection fraction ( $< 30$  percent or 30 to 40 percent), and the participating hospital at which the patient was receiving care. Ischemic heart disease was documented on the basis of coronary angiographic studies, electrocardiographic changes indicative of myocardial infarction, and chest pain typical of angina with concomitant electrocardiographic changes or reversible defects on radioisotope perfusion scans. Each patient was randomly assigned to receive amiodarone (800 mg once a day for 14 days, then 400 mg once a day for 50 weeks, and then 300 mg once a day until the end of the study) or placebo throughout the trial. Clinic visits were made after 2 weeks and then monthly until the end of the study (maximal follow-up, 4.5 years). At each visit, a complete history was taken and a physical examination performed, with documentation of side effects and use of concomitant drugs.

A 24-hour continuous electrocardiogram was obtained at base line; at 2 weeks; at months 1, 3, 6, 9, and 12; and then every 6 months. Chest films (with the cardiothoracic ratio calculated), blood gas values, and pulmonary-function values were determined annually. The left ventricular ejection fraction was determined by radionuclide ventriculography at base line and at months 6, 12, and 24. Echocardiograms were obtained at base line and at months 12 and 24. Deaths and aborted cardiac arrests were reviewed in a blinded manner by a committee and classified as sudden or nonsudden deaths from cardiac causes or deaths from other causes. In patients with sustained ventricular tachycardia ( $\geq 30$  seconds), symptomatic unsustained ventricular tachycardia, or intolerable side effects, the study drug was withdrawn, but the patients were followed and included in the statistical analyses.

Patients were recruited for the study over a period of 3.5 years, and all patients were followed for 1 additional year after the enrollment period. Compliance was ensured by means of frequent clinic visits, telephone calls, and pill counts.

The study end points were overall mortality and sudden death from cardiac causes. Other factors examined included the effects of amiodarone on the left ventricular ejection fraction and on the suppression of ventricular arrhythmias.

## Statistical Analysis

All patients were followed until the completion of the study and were included in the statistical analysis according to the intention-

to-treat principle. Continuous and categorical data were compared at base line by the t-test and chi-square test, respectively. Differences in survival were analyzed with the Kaplan-Meier method. Data on surviving patients were censored at the date of the last follow-up visit. For the analysis of sudden deaths, data on deaths from other causes were censored on the date of the death. A two-sided alpha level less than or equal to 0.05 was considered to indicate statistical significance.

## RESULTS

### Characteristics of the Patients

During the 3.5-year period of enrollment, 1303 patients were screened, and 674 (52 percent) were randomly assigned to one of two treatment groups. A total of 336 patients were assigned to the amiodarone group, and 338 to the placebo group. The base-line characteristics of the randomized patients are shown in Table 1. The mean age of the entire group was 66 years. The median period of follow-up was 45 months (range, 0 to 54).

### Overall Mortality and Sudden Death

Amiodarone had no significant effect on survival. There were 274 deaths during the study: 131 (39 percent) in the amiodarone group and 143 (42 percent) in the placebo group. The overall actuarial survival at two years was 69.4 percent (95 percent confidence interval, 64.2 to 74.6 percent) in the amiodarone group and 70.8

Table 1. Base-Line Characteristics of 674 Patients with Congestive Heart Failure Who Were Randomly Assigned to Receive Amiodarone or Placebo.\*

CHARACTERISTIC	AMIODARONE GROUP (N = 336)	PLACEBO GROUP (N = 338)
Age — yr	65.0 $\pm$ 8.5	66.1 $\pm$ 8.1
Sex — no. (%)		
Men	333 (99.1)	334 (98.8)
Women	3 (0.9)	4 (1.2)
Cause of heart failure — no. (%)		
Ischemic	242 (72.0)	239 (70.7)
Nonischemic	94 (28.0)	99 (29.3)
Left ventricular ejection fraction — no. (%)		
<30%	226 (67.3)	222 (65.7)
30–40%	110 (32.7)	116 (34.3)
New York Heart Association class — no. (%)		
I	4 (1.3)	4 (1.2)
II	179 (56.3)	179 (54.7)
III or IV	135 (42.4)	144 (44.0)
Premature ventricular contractions/hr	254 $\pm$ 370	279 $\pm$ 387
Episodes of ventricular tachycardia/24 hr	77 $\pm$ 352	85 $\pm$ 281
Atrial fibrillation — no. (%)	51 (15.2)	52 (15.4)
Medication		
Beta-blocker — no. (%)	13 (3.9)	16 (4.7)
Digitalis — no. (%)	230 (68.5)	240 (71.0)
Vasodilator — no. (%)	306 (91.1)	320 (95.7)
Dose — mg (no. of patients)		
Enalapril	14.5 $\pm$ 9.9 (41)	22.6 $\pm$ 8.4 (37)
Captopril	75.7 $\pm$ 49.1 (217)	79.8 $\pm$ 79.7 (233)
Hydralazine	133.0 $\pm$ 67.0 (14)	139.0 $\pm$ 54.0 (13)
Furosemide	75.6 $\pm$ 61.2 (282)	80.5 $\pm$ 64.5 (279)
Systolic pressure — mm Hg	127 $\pm$ 18	127 $\pm$ 20
Heart rate — beats/min	80 $\pm$ 14	80 $\pm$ 12
Cardiothoracic ratio >0.50 — no. (%)	289 (86.0)	279 (82.5)
Left ventricular internal diameter $\geq$ 55 mm — no. (%)†	306 (91.1)	305 (90.2)

\*Plus-minus values are means  $\pm$ SD.

†The left ventricular internal diameter was determined by echocardiography.

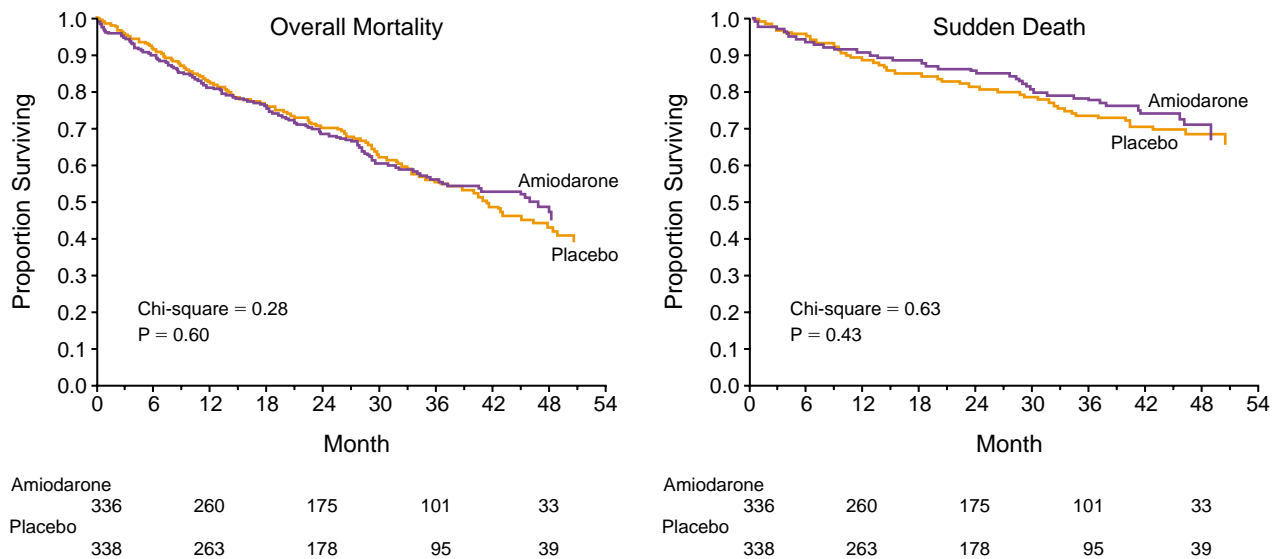


Figure 1. Kaplan–Meier Estimates of Overall Mortality and Sudden Death from Cardiac Causes.

Amiodarone had no significant effect, as compared with placebo, on either overall mortality or the incidence of sudden death. The numbers below the figures are the numbers of patients at risk.

percent (95 percent confidence interval, 65.7 to 75.9 percent) in the placebo group (P=0.6) (Fig. 1).

Sixty-four of the deaths in the amiodarone group (49 percent) and 75 of those in the placebo group (52 percent) were classified as sudden. The death was ascribed to pump failure in 34 patients in the amiodarone group (26 percent) and in 40 patients in the placebo group (28 percent); 22 patients in the amiodarone group (17 percent) and 23 in the placebo group (16 percent) died from noncardiac causes. The cause of death could not be ascertained in 11 patients in the amiodarone group and in 5 in the placebo group. As compared with pla-

cebo, amiodarone had no significant effect on sudden death; at two years, the rate of sudden death was 15 percent in the amiodarone group and 19 percent in the placebo group (P=0.43) (Fig. 1).

**Influence of Cause of Heart Failure on Outcome**

Coronary artery disease was diagnosed in 242 of the patients assigned to amiodarone (72 percent) and in 239 of those assigned to placebo (71 percent). Survival curves, according to the cause of heart disease, are shown in Figure 2. As compared with placebo, amiodarone had no significant effect on overall mortality

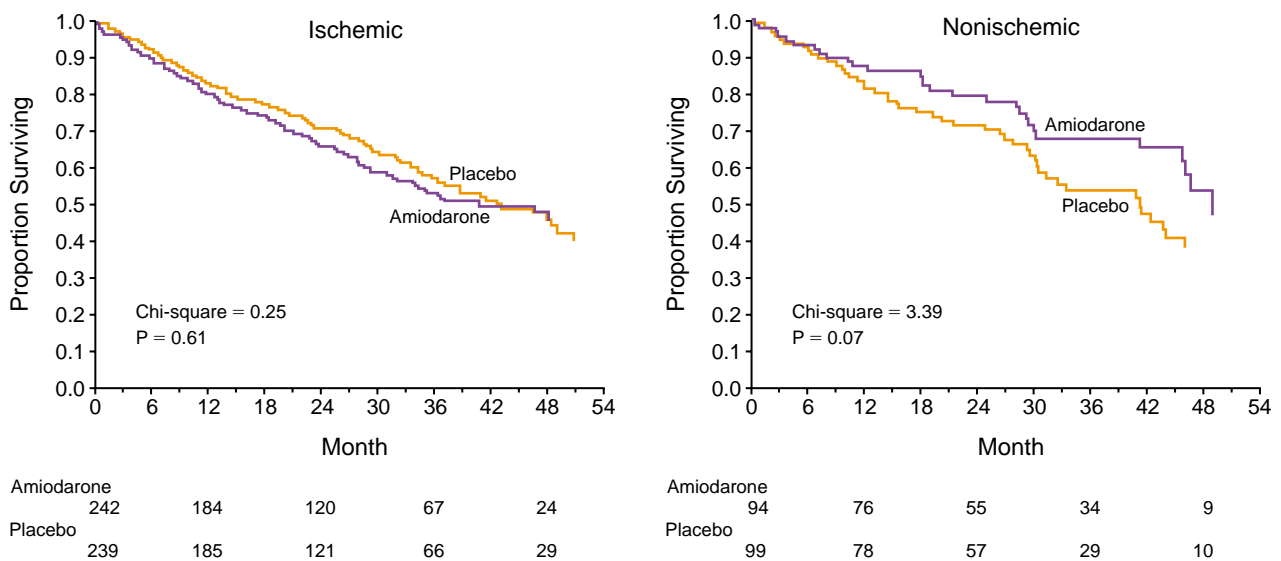


Figure 2. Kaplan–Meier Estimates of Overall Mortality, According to the Presence or Absence of Ischemic Cardiomyopathy.

Among the patients with ischemic cardiomyopathy, amiodarone had no significant effect on mortality, as compared with placebo; among those with heart failure of nonischemic origin, there was a trend toward a reduction in overall mortality induced by amiodarone. The numbers below the figures are the numbers of patients at risk.

among patients with ischemic heart disease (Fig. 2), but there was a trend in favor of amiodarone over placebo among those with nonischemic heart disease ( $P=0.07$ ) (Fig. 2).

### Suppression of Ventricular Arrhythmias

At base line the mean ( $\pm$ SD) heart rate was similar in the two treatment groups (Table 1). After two weeks of treatment, the heart rate was significantly lower in the group assigned to amiodarone ( $70\pm 12$  beats per minute, as compared with  $79\pm 13$  in the placebo group;  $P<0.001$ ). This difference persisted throughout the study.

At randomization, the mean frequency of premature ventricular contractions in the amiodarone group was  $254\pm 370$  per hour, with 77 percent of the patients having one or more episodes of ventricular tachycardia. In the placebo group, the mean frequency of premature ventricular contractions was  $279\pm 387$  per hour, with 85 percent of the patients having episodes of ventricular tachycardia. Two weeks after randomization, the average frequency of premature ventricular contractions was  $266\pm 412$  per hour in the placebo group, and it did not change significantly thereafter. In contrast, in the amiodarone group, the frequency of premature ventricular contractions fell to  $66\pm 156$  per hour ( $P<0.001$ ) at two weeks and to  $44\pm 145$  per hour ( $P<0.001$ ) at three months. In the placebo group, 76 percent of the patients continued to have episodes of ventricular tachycardia two weeks after randomization. In the amiodarone group, only 33 percent of the patients had episodes of ventricular tachycardia at two weeks, as compared with 77 percent at base line ( $P<0.001$ ), and the frequency of episodes of ventricular tachycardia remained lower in that group than in the placebo group throughout the study. Symptomatic ventricular tachycardia developed in 18 patients in the amiodarone group and in 20 in the placebo group ( $P$  not significant).

Survival did not differ significantly between the 159 patients in whom ventricular arrhythmias (premature ventricular contractions) were suppressed by 80 percent or more after two weeks of amiodarone therapy and the 71 patients in whom such suppression was not achieved ( $P=0.93$ ) (Fig. 3). Similarly, with respect to mortality, there was no significant difference between the group of 111 patients in whom episodes of ventricular tachycardia were eliminated by amiodarone at two weeks and the group of 65 patients in whom such episodes continued to occur ( $P=0.36$ ). Moreover, in the subgroup of patients with ventricular tachycardia at base line, amiodarone, as compared with placebo, had no effect on mortality.

### Effect of Amiodarone on Left Ventricular Ejection Fraction

At randomization, the mean ejection fraction was  $24.9\pm 8.3$  percent in the amiodarone group and  $25.7\pm 8.2$  percent in the placebo group. The patients in the amiodarone group had a significant improvement in the ejection fraction at six months ( $33.7\pm 11.0$  percent, as compared with  $29.2\pm 10.7$  in the placebo group;  $P<0.001$ ). At 12 and 24 months, the mean ejection

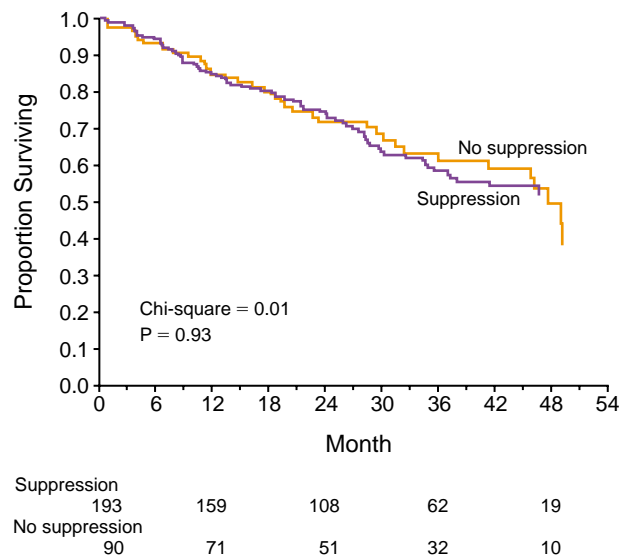


Figure 3. Kaplan–Meier Estimates of Overall Mortality, According to the Effect of Amiodarone on Premature Ventricular Contractions.

The comparison is between the patients in whom premature ventricular contractions were suppressed by 80 percent or more and the patients in whom this level of suppression was not achieved. For the purpose of the analysis, runs of ventricular tachycardia are included. There was no significant difference between the group with suppressed contractions and the group with unsuppressed contractions. A similar analysis revealed no significant difference in overall mortality between the group in which runs of ventricular tachycardia were present after two weeks of therapy and the group in which such runs were absent. The numbers below the figure are the numbers of patients at risk.

tion fractions in the amiodarone group were  $33.4\pm 11.9$  and  $35.4\pm 11.5$  percent, respectively. These values were significantly higher than those in the placebo group ( $29.7\pm 11.0$  and  $29.8\pm 12.2$  at 12 and 24 months, respectively;  $P<0.001$ ).

The overall mortality did not differ significantly between the two treatment groups according to the level of the left ventricular ejection fraction ( $<30$  percent or 30 to 40 percent). In both treatment groups, however, patients with a left ventricular ejection fraction under 30 percent had lower survival rates than those with a left ventricular ejection fraction of 30 to 40 percent ( $P<0.001$ ).

### Side Effects

The frequency of adverse effects during the study is shown in Table 2. Abnormalities in thyroid function were observed in four patients in the amiodarone group (1.2 percent) and in two patients in the placebo group (0.6 percent). Elevated hepatic-enzyme levels (at least twice the normal values) were seen in four patients in the amiodarone group (1.2 percent) and in two in the placebo group (0.6 percent). Severe pulmonary fibrosis occurred in four patients in the amiodarone group (1.2 percent) and in three patients in the placebo group (0.9 percent). There were no episodes of torsade de pointes in either group.

The study medication was discontinued in 90 pa-

Table 2. Severe Adverse Reactions.

REACTION	AMIODARONE	PLACEBO
	GROUP	GROUP
	<i>no. of patients</i>	
Pulmonary fibrosis	4	3
Pulmonary toxicity	6	1
Hypothyroidism	2	0
Hyperthyroidism	2	2
Atrioventricular block, third degree	6	5
Hepatitis	4	2
Gastrointestinal upset	20	16
Ataxia or gait disturbances	16	6
Skin discoloration	1	2

tients in the amiodarone group (27 percent) and in 78 patients in the placebo group (23 percent) because of intolerable side effects, as defined by the protocol or as decided by the physician or the patient; the difference between the two groups was not statistically significant ( $P=0.1$ ). An additional 46 patients in the amiodarone group and 32 in the placebo group withdrew from the study or were lost to follow-up.

### DISCUSSION

Our study shows that amiodarone, as compared with placebo, had no effect on overall mortality or sudden death, despite significant suppression of ventricular arrhythmias and a significant increase in the left ventricular ejection fraction. However, we observed a trend toward a lower mortality rate among patients with nonischemic cardiomyopathy who received amiodarone. There was no relation between the degree of impairment in the left ventricular ejection fraction (<30 percent or 30 to 40 percent) at base line and the effect of amiodarone on overall mortality.

Amiodarone is known to be effective in controlling life-threatening arrhythmias.<sup>20-22</sup> There is also evidence that the drug may be effective in reducing cardiac-related and overall mortality in survivors of myocardial infarction.<sup>15,16</sup> Our findings in patients with heart failure were therefore unexpected. In previous, smaller studies, the results have been variable. For example, in retrospective studies, Cleland et al.<sup>12</sup> and Chatterjee<sup>10</sup> reported improved survival in patients with heart failure treated with amiodarone, whereas a small, prospective, randomized trial reported by Nicklas et al.<sup>23</sup> found no benefit. A recent study<sup>24</sup> from Argentina (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina, or GESICA) reported a 28 percent reduction in overall mortality in the amiodarone group as compared with a control group ( $P=0.024$ ). The rates of sudden death and death due to progressive heart failure were reduced by 27 and 23 percent, respectively ( $P=0.16$ ). The fact that the GESICA trial was not blind probably does not explain the discrepancy between these results and ours. The most striking difference between the two studies is that the proportion of patients with coronary artery disease in the GESICA trial was smaller (39 percent) than in our study (70

percent). This difference is important, since in our study there was a trend toward a reduction in mortality among the patients with nonischemic cardiomyopathy ( $P=0.07$ ).

In our study, amiodarone increased the left ventricular ejection fraction by 42 percent at two years, confirming the results of previous studies.<sup>17</sup> These data are consistent with the observation that amiodarone may improve the capacity for exercise in patients with heart failure.<sup>25</sup> The observed improvement in systolic function may be related to the drug's property of lengthening the period of repolarization.<sup>26</sup> Increases in left ventricular ejection fraction induced by cardioactive drugs are often not positively correlated with a reduction in mortality.<sup>27,28</sup> Indeed, certain inotropic agents, such as beta-agonists and phosphodiesterase inhibitors, may even decrease survival,<sup>27</sup> although they increase ventricular function. In the second Vasodilator-Heart Failure Trial, a combination of hydralazine and isosorbide dinitrate resulted in a significantly greater improvement in the left ventricular ejection fraction but a higher mortality rate than treatment with enalapril.<sup>5</sup> Thus, there appears to be no systematic relation between changes in the left ventricular ejection fraction induced by amiodarone or other cardioactive drugs and their effect on survival.

Our data on amiodarone indicate a similar disparity between the suppression of arrhythmia and sudden death or overall mortality, a phenomenon that was evident in the Cardiac Arrhythmia Suppression Trials.<sup>13,14,21</sup> No difference in overall mortality was found between the group of patients in whom ventricular arrhythmias were suppressed (those with 80 percent or greater suppression of premature ventricular contractions) and those in whom arrhythmias were not suppressed.

Because our study was conducted at various Veterans Affairs medical centers, most of the patients were men. The effect of antiarrhythmic therapy on mortality among women with congestive heart failure and arrhythmia is unknown.

A number of conclusions can be drawn from this double-blind, placebo-controlled study of amiodarone in patients with mild-to-moderate heart failure. The drug was well tolerated and effective in suppressing arrhythmias and improving ventricular function, but it did not reduce the frequency of sudden death or prolong survival. Its effects were not significantly influenced by the level of the left ventricular ejection fraction or the degree of suppression of premature ventricular contractions on Holter monitoring. However, there was a trend toward reduced overall mortality among patients with nonischemic cardiomyopathy, which merits further study.

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### APPENDIX

The following Veterans Affairs medical centers and investigators participated in the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure: Bronx, N.Y. — P. Sweitzer and P. Patascil;

Chicago, West Side — J. Cumming and T. Redmond; Dallas — P. Grayburn and S. Dougherty; Fresno, Calif. — P.C. Deedwania and R. Kanefield; Jackson, Miss. — T.N. Srivastava and T. King; Kansas City, Mo. — D. Lewis and R. Corbett; Loma Linda, Calif. — D.R. Ferry and K. Okubo; Long Beach, Calif. — R. Wesley and S. Saniga; Louisville, Ky. — A. Joseph and N. Zettwoch; Madison, Wis. — P. Kosolcharoen and K. Cox; Miami — C.S. Chakko and J. Johnson; Newington, Conn. — M.J. Radford and D. Roth; North Chicago — R. Singh and A. Skillman; Oklahoma City — R. Lazzara and T. Deaton; Pittsburgh — M. Amidi and J. Pulman; Providence, R.I. — S. Sharma and E. Coccio; Richmond, Va. — K.A. Ellenbogen and E. Early; Salem, Va. — D. Russell and M. Judd; Salt Lake City — R. Klein and L. Morrison; San Francisco — B. Massie and E. Derr; Sepulveda, Calif. — V.N. Udhoji and P. Pekale; Syracuse, N.Y. — R. Warner and P. Lilja; Washington, D.C. — R. Hall and D. Lazzeri; West Haven, Conn. — I. Cohen and L. Canestri.

Cochairmen's office, Washington, D.C. — S.N. Singh and R.D. Fletcher; Cooperative Studies Program Central Research Pharmacy, Albuquerque, N.M. — M. Sather (chief) and C.L. Colling (study pharmacist); Central Holter Monitor Laboratory, Washington, D.C. — R.D. Fletcher; nurse coordinator, Washington, D.C. — D. Lazzeri; Hines Cooperative Studies Program Coordinating Center — W.G. Henderson (chief), S. Gross Fisher (biostatistician), L. Weber (study programmer), and D. Cavello and M. Biondic (study coordinators).

Data and Safety Monitoring Board — J.T. Bigger (chairman), J. Anderson, D. Echt, M. Packer, J. Morganroth, and G. Williams; Executive Committee — S. Singh, R. Fletcher, S. Gross Fisher, P. Deedwania, D. Lewis, B. Massie, B.N. Singh, and C. Colling; Mortality Committee — B.N. Singh (chairman), D. Lewis, S. Singh, and S. Gross Fisher; Department of Veterans Affairs Central Office — D. Deykin (chief of Cooperative Studies Program), J. Gold (administrative officer), and P. Huang (staff assistant).

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