

A COMPARISON OF ANTIARRHYTHMIC-DRUG THERAPY WITH IMPLANTABLE DEFIBRILLATORS IN PATIENTS RESUSCITATED FROM NEAR-FATAL VENTRICULAR ARRHYTHMIAS

THE ANTIARRHYTHMICS VERSUS IMPLANTABLE DEFIBRILLATORS (AVID) INVESTIGATORS\*

**ABSTRACT**

*Background* Patients who survive life-threatening ventricular arrhythmias are at risk for recurrent arrhythmias. They can be treated with either an implantable cardioverter-defibrillator or antiarrhythmic drugs, but the relative efficacy of these two treatment strategies is unknown.

*Methods* To address this issue, we conducted a randomized comparison of these two treatment strategies in patients who had been resuscitated from near-fatal ventricular fibrillation or who had undergone cardioversion from sustained ventricular tachycardia. Patients with ventricular tachycardia also had either syncope or other serious cardiac symptoms, along with a left ventricular ejection fraction of 0.40 or less. One group of patients was treated with implantation of a cardioverter-defibrillator; the other received class III antiarrhythmic drugs, primarily amiodarone at empirically determined doses. Fifty-six clinical centers screened all patients who presented with ventricular tachycardia or ventricular fibrillation during a period of nearly four years. Of 1016 patients (45 percent of whom had ventricular fibrillation, and 55 percent ventricular tachycardia), 507 were randomly assigned to treatment with implantable cardioverter-defibrillators and 509 to antiarrhythmic-drug therapy. The primary end point was overall mortality.

*Results* Follow-up was complete for 1013 patients (99.7 percent). Overall survival was greater with the implantable defibrillator, with unadjusted estimates of 89.3 percent, as compared with 82.3 percent in the antiarrhythmic-drug group at one year, 81.6 percent versus 74.7 percent at two years, and 75.4 percent versus 64.1 percent at three years ( $P < 0.02$ ). The corresponding reductions in mortality (with 95 percent confidence limits) with the implantable defibrillator were  $39 \pm 20$  percent,  $27 \pm 21$  percent, and  $31 \pm 21$  percent.

*Conclusions* Among survivors of ventricular fibrillation or sustained ventricular tachycardia causing severe symptoms, the implantable cardioverter-defibrillator is superior to antiarrhythmic drugs for increasing overall survival. (N Engl J Med 1997;337:1576-83.)

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**S**URVIVORS of ventricular fibrillation or symptomatic, sustained ventricular tachycardia have a high risk of recurrence of arrhythmia, which is often fatal.<sup>1,2</sup> Commonly prescribed treatments for the prevention of fatal recurrences are the implantable cardioverter-defibrillator and a variety of antiarrhythmic drugs. Whether the implantable cardioverter-defibrillator or antiarrhythmic-drug therapy is more effective in reducing mortality has not been shown.<sup>3-6</sup>

The results of the use of most antiarrhythmic drugs in the prevention of life-threatening ventricular tachyarrhythmias have been disappointing — even in the case of drugs that effectively reduce spontaneous ventricular arrhythmias.<sup>5-10</sup> The implantable defibrillator effectively terminates sustained ventricular tachyarrhythmias,<sup>11,12</sup> but its effectiveness as compared with antiarrhythmic drugs in prolonging survival has been demonstrated only in a small subgroup of patients at high risk for sudden death who had persistently inducible ventricular arrhythmias in the electrophysiology laboratory<sup>13</sup> — a feature not required of our patients.

Randomized clinical trials comparing defibrillators with antiarrhythmic drugs in patients resuscitated after near-fatal ventricular fibrillation or sustained ventricular tachycardia are being performed in the United States, Canada, and Europe,<sup>14-16</sup> and the study populations in these three trials are virtually identical. Our study, the Antiarrhythmics versus Implantable Defibrillators (AVID) Trial, examined the effect on overall survival of initial therapy with an implantable defibrillator as compared with initial therapy with amiodarone (Cordarone, Wyeth-Ayerst Laboratories, Philadelphia) or sotalol (Betapace, Berlex Laboratories, Wayne, N.J.) in patients resuscitated

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

from near-fatal ventricular fibrillation or those with symptomatic, sustained ventricular tachycardia with hemodynamic compromise.

## METHODS

### Study Design

The AVID Trial was a multicenter, randomized comparison of two treatment strategies for patients who were resuscitated from near-fatal ventricular fibrillation; sustained ventricular tachycardia with syncope; or sustained ventricular tachycardia with an ejection fraction of 0.40 or less and symptoms suggesting severe hemodynamic compromise due to the arrhythmia (near-syncope, congestive heart failure, and angina).<sup>14</sup> If patients underwent revascularization, the ejection fraction had to be  $\leq 0.40$  for them to be eligible for the study.

### Therapy

The therapies used in the two randomly assigned groups of patients were the best contemporary antiarrhythmic drugs and state-of-the-art implantable cardioverter-defibrillators. Patients had to be eligible for treatment with amiodarone to be enrolled. Consideration of the use of sotalol was left to the judgment of the physician, with common reasons for exclusion being a history of asthma, a low left ventricular ejection fraction, or a history of congestive heart failure. If patients randomly assigned to receive antiarrhythmic drugs were also eligible for treatment with sotalol, a second randomization procedure assigned them to either amiodarone at doses determined empirically or sotalol guided by electrophysiologic testing, Holter monitoring, or both.

Any advanced, state-of-the-art implantable cardioverter-defibrillator that met prespecified criteria<sup>14</sup> could be used. Almost all were transvenous systems that could be implanted without thoracotomy and provided tiered therapy, including antitachycardia pacing functions, bradycardia pacing, diagnostic memory, and in many, a capability for pectoral implantation. The defibrillators used were either approved for general use by the Food and Drug Administration or implanted under an Investigational Device Exemption to permit the use of the newest devices before market approval. The devices implanted in this study were manufactured by Guidant/CPI (St. Paul, Minn.), Sulzer Intermedics (Angleton, Tex.), Medtronic (Minneapolis), and Ventritex (Sunnyvale, Calif.).

A registry was maintained of all patients who qualified for the study but did not undergo randomization in order to compare the randomized and nonrandomized patients. In addition, the registry followed patients with ventricular fibrillation or ventricular tachycardia who were not eligible for randomization. Data on long-term mortality among the nonrandomized patients will be obtained from the National Death Index.

### Recruitment and Follow-up

The investigational review board of each institution approved the study. All patients gave written informed consent. Recruitment of patients began on June 1, 1993; patients were evaluated every three months and at the time of events. Randomization concluded on April 7, 1997. The primary end point was overall mortality. Secondary end points were cost and quality of life.

### Statistical Analysis

We tested the null hypothesis that there was no difference in overall mortality between therapy with an implantable defibrillator and antiarrhythmic-drug therapy.<sup>14</sup> Analysis was performed according to the intention-to-treat principle. Significance was based on a two-sided alpha level of 0.05 for comparisons of survival distributions. A sample size of 1200 patients was estimated to be sufficient, assuming an average follow-up of 2.6 years and an event rate of 40 percent in the control group (antiarrhythmic-drug group) at 4 years to detect a 30 percent decrease in mortality.<sup>14</sup>

At the end of the pilot phase, sequential data monitoring was performed every six months.<sup>17</sup> Criteria for termination of the study were based on an O'Brien-Fleming spending function, which requires a substantial difference between treatment groups to stop the study early.<sup>18</sup>

### Early Termination of the Study

The original goal was to enroll 1200 patients by March 1997. At its meeting on October 3, 1996, the Data and Safety Monitoring Board recommended that enrollment be extended to allow this goal to be reached. The board subsequently recommended stopping the AVID Trial on April 7, 1997, when analysis revealed that the difference in the primary outcome variable between the two groups had crossed the statistical boundary for early termination of the study. By that time, 1016 patients had been randomly assigned to treatment groups.

## RESULTS

### Base-Line Characteristics

Of 6035 patients screened, 4621 entered the registry; 1885 were found to be eligible for randomization. Of these, 1016 were randomly assigned to treatment with an implanted defibrillator or antiarrhythmic drugs. The base-line characteristics of these 1016 patients (Table 1) were similar in the two treatment groups, except for a history of atrial fibrillation or flutter and New York Heart Association class III heart failure. The mean age was 65 years; 79 percent of the patients were male, and 86 percent were white. A total of 455 patients had ventricular fibrillation, and 561 had ventricular tachycardia (216 with syncope, and 345 with other symptoms of serious hemodynamic compromise and with an ejection fraction  $\leq 0.40$ ).

The mean ( $\pm$ SD) left ventricular ejection fraction was  $0.32 \pm 0.13$  in the defibrillator group and  $0.31 \pm 0.13$  in the antiarrhythmic-drug group. The minor difference in ejection fraction was confined to the patients with ventricular fibrillation ( $0.36 \pm 0.15$  in the implanted-defibrillator group vs.  $0.33 \pm 0.15$  in the antiarrhythmic-drug group). The left ventricular ejection fraction was virtually identical ( $0.29 \pm 0.10$  vs.  $0.29 \pm 0.11$ ) among the patients with ventricular tachycardia in the two groups.

During hospitalization for the index arrhythmia, 10 percent of the patients in the defibrillator group and 12 percent in the antiarrhythmic-drug group underwent coronary revascularization.

### Therapy

The implantable cardioverter-defibrillator was the assigned therapy for 507 patients. A non-thoracotomy lead system was used in 93 percent; 5 percent received an epicardial system; and no device was implanted in 2 percent. Antiarrhythmic-drug treatment was the assigned therapy for 509 patients, of whom 356 immediately began empirical therapy with amiodarone, usually because they were not considered candidates for sotalol because of concern on the part of the investigators about heart failure,

**TABLE 1. HISTORY AND CHARACTERISTICS OF THE PATIENTS ASSIGNED TO RECEIVE IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS OR ANTIARRHYTHMIC DRUGS.\***

CHARACTERISTIC	DEFIBRILLATOR GROUP (N=507)	ANTIARRHYTHMIC-DRUG GROUP (N=509)
Age (yr)	65±11	65±10
Male sex (%)	78	81
White race (%)	87	86
Index arrhythmia (no.)		
Ventricular fibrillation	226	229
Sustained ventricular tachycardia	281	280
Clinical history before index arrhythmia (%)		
Atrial fibrillation or flutter	21	26
Ventricular fibrillation	5	5
Ventricular tachycardia	14	15
Unexplained syncope	11	15
Coronary artery disease	81	81
Myocardial infarction	67	67
Congestive heart failure	46	47
Hypertension	55	56
Diabetes	25	24
Angina	48	50
Peripheral vascular disease	16	15
Antiarrhythmic-drug therapy	16	15
Left ventricular ejection fraction	0.32±0.13	0.31±0.13
Median time from index event to measurement (days)	3	3
Angina at enrollment (%)		
No angina	64	65
CCS class I or II	34	33
CCS class III	2	2
Congestive heart failure at enrollment (%)†		
No congestive heart failure	45	40
NYHA class I or II	48	48
NYHA class III	7	12
Findings on base-line electrocardiogram‡		
Heart rate (beats/min)	77±18	78±17
PR interval (msec)	178±37	183±37
QRS complex (msec)	116±26	117±26
Corrected QT interval (msec)	441±40	445±39
Paced (% of patients)	3	4
Bundle-branch block (% of patients)	23	25

\*Plus-minus values are means ±SD. CCS denotes Canadian Cardiovascular Society, and NYHA New York Heart Association.

†Patients with class IV congestive heart failure were excluded from the study.

‡The base-line electrocardiogram was recorded when patients were taking no antiarrhythmic drugs and without cardiac pacing.

a low ejection fraction, or both. Antiarrhythmic-drug therapy was further randomly assigned in the remaining 153 drug patients: 79 to amiodarone and 74 to sotalol. In 53 of the 74 patients assigned to sotalol, electrophysiologic testing or ambulatory monitoring revealed sufficient arrhythmia to guide sotalol therapy. However, only 13 patients given sotalol (2.6 percent of those assigned to antiarrhythmic-drug therapy) had adequate suppression of arrhythmia and were receiving sotalol at discharge. The remaining patients assigned to be evaluated for sotalol therapy received amiodarone (58 patients) or another antiarrhythmic drug (1) or were treated with an implantable cardioverter-defibrillator (2).

The daily maintenance dose of amiodarone was progressively decreased throughout the course of follow-up (mean, 389±112 mg at three months; 331±99 mg at one year; 294±94 mg at two years; and 256±95 mg at three years). Most patients who were receiving amiodarone at discharge continued to take the drug (87 percent at one year and 85 percent at two years). The mean daily maintenance dose of sotalol during follow-up was stable over the course of the study (258±81 mg at three months, 248±88 mg at one year, 280±121 mg at two years, and 240±113 mg at three years).

Table 2 lists the concurrent therapies at hospital discharge and during follow-up. Investigators were encouraged to treat patients with aspirin, beta-blockers, and angiotensin-converting-enzyme inhibitors when clinically appropriate. More patients were taking beta-blockers ( $P<0.001$ ) and slightly more patients were taking digitalis ( $P=0.04$ ) in the defibrillator group than in the antiarrhythmic-drug group.

#### Outcome

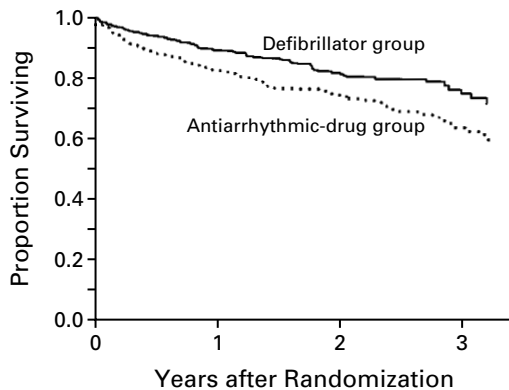
Fewer deaths occurred among the patients assigned to receive an implantable defibrillator (80 deaths) than in the antiarrhythmic-drug group (122). Over a mean follow-up of 18.2±12.2 months, the crude death rates (with 95 percent confidence limits) were 15.8±3.2 percent in the defibrillator group and 24.0±3.7 percent in the antiarrhythmic-drug group. Figure 1 shows survival (life-table) distributions (not adjusted for any base-line differences between the groups). Patients treated with defibrillators had better survival throughout the course of the study (Wilcoxon statistic, 3.32;  $P<0.02$ , adjusted for sequential monitoring). These survival figures represent a decrease in death rates (with 95 percent confidence limits) of 39±20 percent, 27±21 percent, and 31±21 percent, at one, two, and three years, respectively, though the accuracy of long-term data is limited because few patients had been followed beyond two years at the time the study ended. The average unadjusted length of additional life associated with cardioverter-defibrillator therapy was 2.7 months at 3 years.

Automatic pacing or shocks from the implantable cardioverter-defibrillator were more common among patients who entered the study with ventricular tachycardia than among those who had ventricular fibrillation as the index arrhythmia. The cumulative percentage of patients with any activation of the defibrillator, either antitachycardia pacing or shock, was as follows: for the patients with ventricular tachycardia, 36 percent at three months, 68 percent at one year, 81 percent at two years, and 85 percent at three years; for the patients with ventricular fibrillation, 15 percent, 39 percent, 53 percent, and 69 percent, respectively ( $P<0.001$  for patients with ventricular tachycardia vs. those with ventricular fibrillation).

TABLE 2. THERAPY AT DISCHARGE AND DURING FOLLOW-UP.\*

TREATMENT	At Discharge		At 12 Mo		At 24 Mo	
	DEFIBRILLATOR GROUP (N=497)	ANTIARRHYTHMIC-DRUG GROUP (N=496)	DEFIBRILLATOR GROUP (N=338)	ANTIARRHYTHMIC-DRUG GROUP (N=306)	DEFIBRILLATOR GROUP (N=171)	ANTIARRHYTHMIC-DRUG GROUP (N=162)
	percent					
Implantable cardioverter-defibrillator	98.6	1.4	97.9	9.5	95.7	9.8
Amiodarone	1.8	95.8	8.3	84.7	9.3	82.4
Sotalol	0.2	2.8	1.8	5.8	3.1	8.5
Beta-blocker	42.3	16.5	38.1	11.0	39.4	10.1
Calcium-channel blocker	18.4	12.1	22.9	16.6	19.4	14.1
Both beta-blocker and calcium-channel blocker	5.3	2.4	6.8	2.1	5.6	0.7
Digitalis	46.8	40.6	45.8	37.9	44.4	32.3
Diuretic agent	48.2	50.7	56.0	59.3	56.9	56.4
Other antiarrhythmic drug	4.2	1.2	7.1	3.8	10.0	4.0
Angiotensin-converting-enzyme inhibitor	68.8	68.2	68.4	65.5	68.1	63.1
Nitrate	36.4	37.0	29.1	27.9	28.1	29.5
Other antihypertensive agent	7.6	8.8	9.0	9.4	10.0	6.1
Lipid-lowering agent	13.2	11.5	19.5	17.2	23.1	19.5
Aspirin	60.7	59.2	55.4	55.4	62.5	56.4
Warfarin	21.9	34.8	24.8	35.4	22.5	30.2

\*Patients who died while in the hospital after the index event (n=19) are excluded, as are patients still in the hospital at the termination of the study (n=4).



Patients at risk	1016	644	333	104
Percent surviving				
Defibrillator group		89.3	81.6	75.4
Antiarrhythmic-drug group		82.3	74.7	64.1

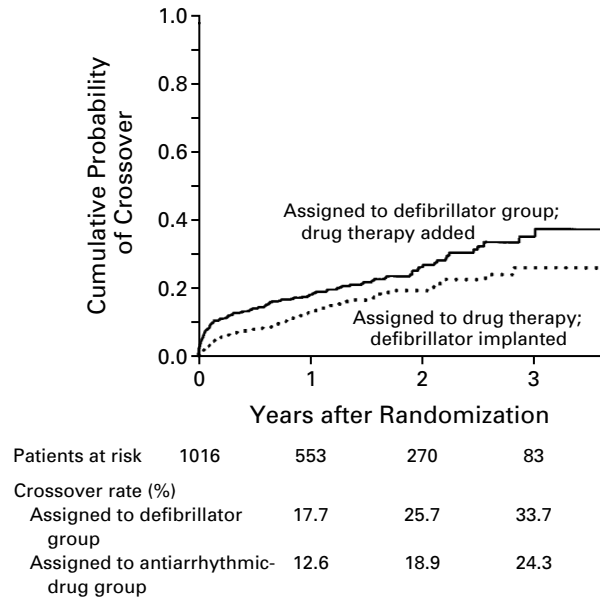
Figure 1. Overall Survival, Unadjusted for Base-Line Characteristics.

Survival was better among patients treated with the implantable cardioverter-defibrillator (P<0.02, adjusted for repeated analyses [n=6]).

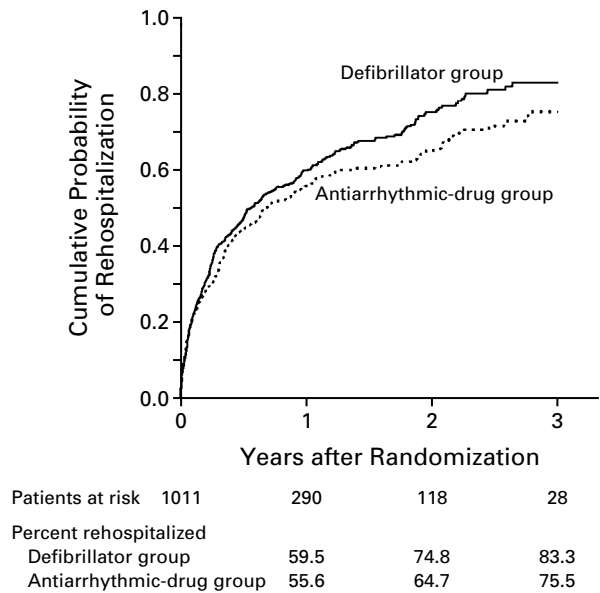
Figure 2 illustrates the length of time to crossover in the study groups. Overall, approximately 20 percent of patients had crossed over to or added the other therapy by 24 months. The crossover rate was higher among those initially assigned to therapy with a defibrillator (P<0.001).

Figure 3 shows the times to first rehospitalization in each group. Patients with an implanted defibrillator were rehospitalized somewhat sooner, on average, than patients treated with drugs, most often for evaluation of recurrent arrhythmias and defibrillator shocks. By one year, 60 percent of the patients in the defibrillator group had been rehospitalized, as had 56 percent in the antiarrhythmic-drug group (P=0.04).

Figure 4 shows the hazard ratios for death from any cause in subgroups defined according to variables prespecified in the study design: age, left ventricular ejection fraction, cardiac diagnosis, and qualifying arrhythmia. The hazard ratios were not significantly different for any of these subgroups, but the early termination of the study diminished its power to detect differences between the subgroups. Multivariate analysis showed that the beneficial effect of the implantation of a defibrillator persisted after adjustment for other factors, such as age, use of beta-blockers during follow-up, presence or absence of congestive heart failure, and ejection fraction at base line. Furthermore, revascularization after the index arrhythmia did



**Figure 2.** Time to Crossover in the Two Groups. Antiarrhythmic-drug therapy was added to defibrillator therapy more commonly than vice versa ( $P < 0.001$ ).



**Figure 3.** Time to First Rehospitalization. Data on patients who died were censored. Patients with implanted defibrillators were rehospitalized sooner than patients treated with antiarrhythmic drugs ( $P = 0.04$ ). The number of patients at risk at base line is 1011 because 5 patients were still hospitalized for the index arrhythmia at the time the study was stopped.

not alter survival. Estimates in which the Cox model was used to adjust for base-line differences in the presence or absence of heart failure, the ejection fraction, and history with respect to atrial fibrillation indicated that the reductions in mortality (with 95 percent confidence limits) that were attributable to the implantable defibrillator were  $37 \pm 22$  percent at one year,  $24 \pm 22$  percent at two years, and  $29 \pm 23$  percent at three years. Estimates adjusted for the use of beta-blockers were unchanged from the unadjusted values.

**Complications of Therapy**

Nonfatal torsade-de-pointes ventricular tachycardia was observed only once throughout the course of the study, in a patient given amiodarone. Pulmonary toxicity, though difficult to diagnose,<sup>19</sup> was suspected in 3 percent of the patients treated with amiodarone at one year and 5 percent at two years. One patient died from pulmonary toxicity. Thyroid-replacement medication was prescribed for 10 percent of the patients treated with amiodarone by one year and 16 percent by two years, as compared with 1 percent and 1 percent, respectively, for the patients treated with a defibrillator. No other serious complications of amiodarone were noted.

Serious complications of defibrillator therapy were infrequent. Twelve patients in the defibrillator group (2.4 percent) died within 30 days of the initiation of therapy (or by the time of hospital discharge, if discharge occurred later than 30 days after therapy began), as compared with 18 patients (3.5 percent) in the antiarrhythmic-drug group ( $P = 0.27$ ). Bleeding requiring reoperation or transfusion occurred in 6 patients in the defibrillator group, and serious hematomas in 13. Other complications included infection (in 10 patients), pneumothorax (8), and cardiac perforation (1). Early dislodgment or migration of leads occurred in three patients. The first attempt at implantation of the cardioverter-defibrillator without thoracotomy was unsuccessful in five patients — in four because of an excessively high defibrillation threshold and in one because of cardiac perforation. Three of these five patients subsequently underwent successful implantation procedures.

**DISCUSSION**

In patients who were resuscitated from ventricular fibrillation or who had sustained ventricular tachycardia causing symptoms and hemodynamic compromise, the implantable cardioverter-defibrillator improved survival in the AVID Trial as compared with antiarrhythmic-drug therapy.

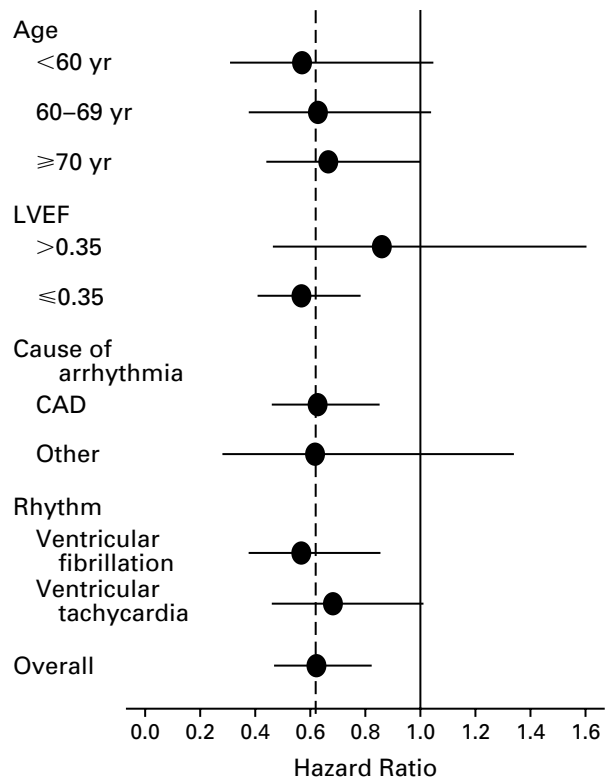
The effectiveness of defibrillator therapy in reducing overall mortality, as compared with the rates with other therapies, has been uncertain since its original clinical application in 1980.<sup>20,21</sup> Although contemporary models are quite successful in recognizing serious ventricular arrhythmias and initiating

cardioversion or defibrillation,<sup>11</sup> the effect of these devices on overall mortality, particularly in comparison with the best available antiarrhythmic-drug therapy, has remained unknown. Many studies of the defibrillator have emphasized only death due to arrhythmia.<sup>22,23</sup> However, assigning a cause of death can be difficult, particularly if a patient has congestive heart failure, and assignment may be biased when therapy has not been blinded.<sup>24,25</sup> Previous reports comparing treatment with the implantable cardioverter-defibrillator and antiarrhythmic-drug therapy have been complicated by the fact that the groups of patients given these two therapies have not been equivalent.<sup>26,27</sup> It is impossible to compare the defibrillator with antiarrhythmic drugs accurately with the use of historical controls, concurrent non-randomized controls, or matched case-control studies. Furthermore, any comparison of defibrillator with drug therapy reveals only the relative effect of these two therapies, not the difference between treatment and no treatment.

In the AVID Trial, the base-line clinical characteristics of the defibrillator and antiarrhythmic-drug groups were similar. The mean left ventricular ejection fraction was nonsignificantly lower in the antiarrhythmic-drug group; the entire difference occurred in those who had ventricular fibrillation as the index arrhythmia. In addition, the incidence of heart failure was slightly greater in the antiarrhythmic-drug group. However, stratified regression analysis suggests that these minor imbalances in base-line characteristics explained only about 8 percent of the observed difference in survival.

Beta-blockers were used less often in the antiarrhythmic-drug group than in the defibrillator group, as was also the case in the Multicenter Automatic Defibrillator Implantation Trial (MADIT).<sup>13</sup> Amiodarone has mild antiadrenergic properties, and sotalol is a more potent beta-blocker. Many physicians may have felt that the addition of a beta-blocker to amiodarone or sotalol was not necessary or might aggravate bradyarrhythmias. Furthermore, beta-blockers are often given to control the ventricular rate in atrial fibrillation, thus preventing inappropriate defibrillator shocks. Finally, beta-blockers may have been used less often in the antiarrhythmic-drug group because of an attempt by physicians to simplify drug regimens. Adjustment for this imbalance in the Cox regression analysis slightly reduced the estimated beneficial effect of defibrillator therapy on survival (unadjusted hazard ratio for the defibrillator group as compared with the antiarrhythmic-drug group, 0.62; adjusted hazard ratio, 0.67).

Amiodarone was administered empirically, whereas the dose of sotalol was based on the results of Holter monitoring or electrophysiologic testing for evidence of suppression of arrhythmias. Many patients did not have findings on these studies that



**Figure 4.** Hazard Ratios (and 95 Percent Confidence Limits) for Death from Any Cause in the Defibrillator Group as Compared with the Antiarrhythmic-Drug Group in Prespecified Subgroup Analyses in the Univariate Model.

No subgroup differed significantly from the entire population. The solid vertical line represents equal effectiveness of the two treatments; points to the left indicate better survival in the defibrillator group, and points to the right better survival in the antiarrhythmic-drug group. The dotted vertical line represents the results for the entire study (hazard ratio=0.62). LVEF denotes left ventricular ejection fraction, and CAD coronary artery disease.

allowed the guided use of sotalol, or they had contraindications to its use. The investigators decided at the beginning of the study that no comparison of mortality would be made between patients given amiodarone and those given sotalol, nor would the various models and manufacturers of the implantable cardioverter-defibrillator be compared.

Most patients randomly assigned to therapy with an implantable cardioverter-defibrillator received transvenous devices whose implantation did not require thoracotomy. The rate of nonfatal complications of implantation (5.7 percent) was lower than that previously reported for epicardial implantation.<sup>11,28</sup> Virtually all patients assigned to receive a defibrillator achieved an adequate defibrillation threshold; 30-day mortality in the defibrillator group was 2.4 percent, as compared with 3.5 percent in the antiarrhythmic-drug group.

Rates of crossover from the defibrillator group to drug therapy (25.7 percent) or from drug therapy to defibrillator therapy (18.9 percent) at two years were relatively low and did not compromise the power of the study. Most crossovers occurred because arrhythmia recurred, rather than because of intolerance of the drugs or devices. As expected, the addition of antiarrhythmic drugs to the treatment of patients who were initially assigned to defibrillator therapy was common because of the perceived need to reduce the frequency of shocks.

Data in the AVID registry demonstrate that the clinical characteristics of the patients who underwent randomization were similar to those of nonrandomized patients<sup>29</sup>; therefore, the population studied in this trial is representative of the general population of patients who are resuscitated from ventricular fibrillation or who have symptomatic, sustained ventricular tachycardia.

#### Limitations of the Study

The differences in base-line characteristics (notably the proportions with heart failure and atrial fibrillation) and concomitant drug therapy (with respect to beta-blockers) do not explain the differences in survival in our study group. Although many patients had to be screened to identify the 1016 survivors of ventricular fibrillation or sustained ventricular tachycardia who ultimately underwent randomization, the proportion of eligible patients randomly assigned to treatment groups (54 percent) was consistent with the rates in other, similar studies. Most patients who were not enrolled met prespecified criteria for exclusion, such as neurologic impairment, severe coexisting illness, or a decision by the patient or physician not to participate. However, data from the AVID registry confirm that the patients randomly assigned to groups were generally representative of the entire population at risk.<sup>29</sup>

The dose of amiodarone was determined empirically, not on the basis of electrophysiologic testing. The value of electrophysiologic testing in patients given amiodarone is controversial,<sup>30,31</sup> but the empirical use of amiodarone in survivors of ventricular fibrillation is more effective than guided therapy with conventional antiarrhythmic drugs.<sup>5</sup> The AVID Trial was purposely a comparison of defibrillator treatment with the antiarrhythmic-drug therapy that could be administered simply by most physicians to a large percentage of the target population.

No control group was included in the study design. We believed it would have been unethical to withhold all treatment from patients with the types of arrhythmias being studied. This study therefore addresses only the relative benefit of two treatments, rather than of a treatment and a control group.

Many different types of implantable cardioverter-defibrillator were used, and there was no standard pro-

gramming of devices for antitachycardia pacing. However, there is no evidence that one device is better than another in preventing death, and antitachycardia pacing protocols selected by physicians in the AVID Trial were similar among devices and institutions.

Although some might consider our use of overall mortality, rather than mortality due to arrhythmia, as the primary end point to be a limitation of the study, in fact it is a major strength. Particularly in an unblinded study, classification of death according to cause may be subject to bias.<sup>24,25,32</sup> Furthermore, we evaluated whether the prevention of death due to cardiac arrhythmia by the implantation of a cardioverter-defibrillator would translate into a benefit in terms of overall survival or would be offset by competing causes of death in this high-risk population.

#### Conclusions

Although the absolute magnitude of the benefit associated with the implantable-defibrillator therapy remains unknown, the greater efficacy of this device, relative to antiarrhythmic-drug therapy, is strongly supported by this study. The defibrillator was superior to antiarrhythmic-drug therapy in prolonging survival among patients resuscitated after symptomatic, sustained ventricular tachycardia or ventricular fibrillation causing hemodynamic compromise. It should be offered as first-line therapy to such patients.

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#### APPENDIX

The Investigators of the Antiarrhythmics versus Implantable Defibrillators (AVID) Trial (listed in order of number of patients randomized — highest number enrolled listed first):

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