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IMPROVED SURVIVAL WITH AN IMPLANTED DEFIBRILLATOR IN PATIENTS WITH CORONARY DISEASE AT HIGH RISK FOR VENTRICULAR ARRHYTHMIA

ARTHUR J. MOSS, M.D., W. JACKSON HALL, PH.D., DAVID S. CANNOM, M.D., JAMES P. DAUBERT, M.D., STEVEN L. HIGGINS, M.D., HELMUT KLEIN, M.D., JOSEPH H. LEVINE, M.D., SANJEEV SAKSENA, M.D., ALBERT L. WALDO, M.D., DAVID WILBER, M.D., MARY W. BROWN, M.S., AND MOONSEONG HEO, PH.D., FOR THE MULTICENTER AUTOMATIC DEFIBRILLATOR IMPLANTATION TRIAL INVESTIGATORS*

ABSTRACT

Background   Unsustained ventricular tachycardia in patients with previous myocardial infarction and left ventricular dysfunction is associated with a two-year mortality rate of about 30 percent. We studied whether prophylactic therapy with an implanted cardioverter–defibrillator, as compared with conventional medical therapy, would improve survival in this high-risk group of patients.

Methods   Over the course of five years, 196 patients in New York Heart Association functional class I, II, or III with prior myocardial infarction; a left ventricular ejection fraction ≤0.35; a documented episode of asymptomatic unsustained ventricular tachycardia; and inducible, nonsuppressible ventricular tachyarrhythmia on electrophysiologic study were randomly assigned to receive an implanted defibrillator (n=95) or conventional medical therapy (n=101). We used a two-sided sequential design with death from any cause as the end point.

Results   The base-line characteristics of the two treatment groups were similar. During an average follow-up of 27 months, there were 15 deaths in the defibrillator group (11 from cardiac causes) and 39 deaths in the conventional-therapy group (27 from cardiac causes) (hazard ratio for overall mortality, 0.46; 95 percent confidence interval, 0.26 to 0.82; P=0.009). There was no evidence that amiodarone, beta-blockers, or any other antiarrhythmic therapy had a significant influence on the observed hazard ratio.

Conclusions   In patients with a prior myocardial infarction who are at high risk for ventricular tachyarrhythmia, prophylactic therapy with an implanted defibrillator leads to improved survival as compared with conventional medical therapy. (N Engl J Med 1996;335:1933-40.)

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UNSUSTAINED ventricular tachycardia in patients who have had a previous myocardial infarction and have left ventricular dysfunction has been associated with a two-year mortality rate in the range of 30 percent.[1-3] Antiarrhythmic therapy has been widely used for unsustained ventricular tachycardia, but there has been no evidence of improved survival with this treatment.[4-6] In December 1990, we initiated a prophylactic trial in which high-risk patients with coronary heart disease and asymptomatic unsustained ventricular tachycardia were randomly assigned to receive an implantable cardioverter–defibrillator or conventional medical therapy. To ensure a population at high risk for malignant ventricular arrhythmias,[7,8] eligible patients had to have an inducible, sustained, nonsuppressible ventricular tachyarrhythmia on electrophysiologic testing. The end point of the trial was overall mortality during a five-year follow-up period.

METHODS

Organization of the Trial

The Multicenter Automatic Defibrillator Implantation Trial enrolled patients from 32 hospital centers (30 in the United States and 2 in Europe). The protocol was approved by the institutional

review boards of the participating centers. A data and safety monitoring committee independently reviewed the results at regular intervals throughout the trial. The study was totally supported by a research grant from CPI/Guidant. All investigators agreed in writing in advance of their participation in this study not to hold stock in CPI/Guidant or any other defibrillator-manufacturing company and to abide by the conflict-of-interest standards described by Healy et al.[9]

Recruitment of Patients

Enrollment in the trial began on December 27, 1990. Patients of either sex who were 25 to 80 years of age were eligible for the study if they had had a Q-wave or enzyme-positive myocardial infarction three weeks or more before entry; had had an episode of asymptomatic, unsustained ventricular tachycardia (a run of 3 to 30 ventricular ectopic beats at a rate >120 beats per minute) unrelated to an acute myocardial infarction that was documented by 12-lead, ambulatory, or exercise electrocardiography; had an ejection fraction ≤0.35, as assessed by angiography, radionuclide scanning, or echocardiography; were in New York Heart Association functional class I, II, or III; and had no indications for coronary-artery bypass grafting or coronary angioplasty on the basis of a cardiac evaluation within the past three months.

Patients were excluded from consideration for enrollment if one or more of the following conditions were present: previous cardiac arrest or ventricular tachycardia causing syncope that was not associated with an acute myocardial infarction; symptomatic hypotension while in a stable rhythm; and myocardial infarction within the past three weeks. Patients who had undergone coronary-artery bypass grafting within the past two months or coronary angioplasty within the past three months were excluded from the study, as were women of childbearing age who were not using medically prescribed contraceptives, patients with advanced cerebrovascular disease, patients with any condition other than cardiac disease that was associated with a reduced likelihood of survival for the duration of the trial, and patients who were participating in other clinical trials.

Eligible patients were referred for electrophysiologic study[10] at the discretion of the patients' attending physicians. Patients qualified for enrollment if sustained ventricular tachycardia or fibrillation was reproducibly induced and not suppressed after the intravenous administration of procainamide (or an equivalent intravenous antiarrhythmic agent if the patient had had a previous reaction to procainamide) according to a prespecified protocol, as previously described.[11] The enrolling centers did not keep consistent logs of the eligible patients who had no inducible ventricular tachyarrhythmia or in whom the inducible tachycardia was suppressed by procainamide. A total of 253 patients qualified in terms of clinical eligibility and electrophysiologic testing, and 196 of the qualified patients gave informed consent for enrollment. The clinical characteristics of the enrolled patients and the 57 eligible, qualified patients who did not consent to enrollment were similar.

Within 30 days after completing the qualifying electrophysiologic study, the patients were randomly assigned to receive either an implanted defibrillator or conventional medical therapy. The choice of conventional medical therapy, including the decision whether to use antiarrhythmic medications, was left to the patient's attending physician. Antiarrhythmic drugs approved and released by the Food and Drug Administration could be administered to patients in either group. The randomization scheme included stratification according to the interval between the most recent myocardial infarction and enrollment (<6 months or ≥6 months) and according to center.

Defibrillator Devices and Implantation

Only defibrillators and lead systems approved and released by the Food and Drug Administration were used in the trial. Investigational devices were specifically excluded. CPI/Guidant (St. Paul, Minn.) provided the pulse generators and lead systems. Monophasic (n=79) and biphasic (n=11) pulse generators were used.

When the trial began in December 1990, only transthoracic implants were approved for use. Nonthoracotomy transvenous leads were incorporated into the trial after full-market approval of the transvenous lead on August 27, 1993. Once transvenous devices were approved at a given center, a new stratum consisting of patients assigned to transvenous implantable cardioverter–defibrillators or conventional therapy was initiated. Standard techniques were used to implant the defibrillators. Defibrillation testing was carried out during the implantation procedure; every effort was made to achieve defibrillation with a 10-J safety margin.

Data Acquisition and Follow-up

Definitions for all variables were prespecified in a manual of operations. The qualifying episode of unsustained ventricular tachycardia required electrocardiographic documentation. Base-line electrocardiograms were coded according to the Manhattan criteria.[12]

Patients were seen in the follow-up clinic one month after randomization and every three months thereafter until the trial was stopped. At each follow-up visit, an appropriate clinical evaluation was carried out, medication use was recorded, and the defibrillator was tested. The patients underwent a final evaluation within one month after the completion of the study. The first patient enrolled was followed for 61 months, and the last patient enrolled was followed for less than 1 month. The average duration of follow-up for the 196 enrolled patients was 27 months, with an average of 37 months for the earlier transthoracic stratum (n=98 patients) and 16 months for the later transvenous stratum (n=98).

End Points

The primary end point was death from all causes. A two-member end-point subcommittee reviewed information on the causes and circumstances of deaths occurring on or before March 24, 1996. Each death was categorized as due to either a cardiac or a noncardiac cause, and the classification of Hinkle and Thaler[13] was used to evaluate the suspected mechanism of death from cardiac causes (arrhythmic or nonarrhythmic).

Statistical Analysis

When planned in 1990, the trial was designed to have an 85 percent power to detect a 46 percent reduction in the mortality rate among the defibrillator-treated patients as compared with a postulated two-year mortality rate of 30 percent among the patients randomly assigned to conventional therapy, with a two-sided significance level of 0.05. A triangular sequential design modified for two-sided alternatives[14] (Fig. 1) was used, with preset boundaries to permit termination of the trial if the efficacy or inefficacy of implantable cardioverter–defibrillators was established or if there was evidence that there was no difference in outcome between the two treatment groups. The data were analyzed weekly, beginning at the point at which 10 deaths had been reported. The trial was designed to be terminated when the path of the log-rank statistic, measuring imbalance between the survival curves for the two randomized groups, crossed one of the preset termination boundaries (efficacy, inefficacy, or no difference in outcome) of the sequential design.

The executive committee was unaware of the results of the study throughout the trial. During the course of the trial, the sequential design was revised by the executive committee on two occasions. On September 1, 1993, transvenous leads were introduced into the trial. Since this change could alter the type of patient referred for entry into the trial, the power requirement of the trial was increased from 85 to 90 percent so as not to compromise the credibility of the study. Because of the slow rate of enrollment and before the first patient enrolled had reached the fifth year of the study, it was decided on November 12, 1995, that data on patients would be censored for analytic purposes at five years, with subsequent follow-up information on such patients censored from the ongoing sequential analysis.

Analyses were stratified according to the type of device (trans-

thoracic or transvenous) and followed the intention-to-treat principle. All analyses and potential covariates were specified in advance of the trial's completion. After termination of the trial, sequential-analysis methods were used to calculate a P value and hazard ratio (median unbiased), along with a 95 percent confidence interval based on the P-value function.[14,15] Secondary analyses were performed with the Cox proportional-hazards regression model,[16] with adjustment for relevant covariates. Separate Cox regression analyses were carried out in the transthoracic and transvenous strata to determine whether the efficacy of defibrillators was similar in these two groups. Preselected base-line covariates and prescribed cardiac medications recorded at the one-month clinic visit were evaluated in the Cox model to determine their effect on the risk of death per unit of time in the defibrillator group as compared with that in the conventional-therapy group (the hazard ratio). Survival curves for patients assigned to defibrillator treatment and conventional treatment were determined according to the method of Kaplan and Meier.[17]

RESULTS

### Study Population and Similarity of Treatment Groups

Of the 196 patients enrolled, 98 were in the transthoracic stratum (45 in the defibrillator group and 53 in the conventional-therapy group) and 98 in the transvenous stratum (50 in the defibrillator group and 48 in the conventional-therapy group). The baseline characteristics of the defibrillator group (n=95) and the conventional-therapy group (n=101) are shown in Table 1. The two groups were clinically similar. The distribution of the qualifying Q-wave myocardial infarctions in terms of anterior, inferior, and posterior locations was similar in the two treatment groups. The prevalence of the use of cardiac medications one month after enrollment and at the last contact with the patient is shown in Table 2.

Sixteen crossovers occurred. Eleven patients in the conventional-therapy group received a defibrillator during the course of the trial because of an adverse drug reaction (n=2), unexplained syncope (n=2), episodes of ventricular tachyarrhythmia that were of concern to the investigator (n=6), and aborted cardiac arrest (ventricular fibrillation) (n=1). Five patients assigned to the defibrillator group never had a defibrillator implanted (one because of a high defibrillation threshold and four because of the patient's preference). Two patients had their defibrillators deactivated during the course of the trial.

The therapy-related adverse events in the two treatment groups are shown in Table 3. There were no operative deaths (death in the first 30 days). There were 1838 scheduled follow-up clinic visits during the course of the trial. The defibrillator-treated patients attended 92 percent of the scheduled visits, and the conventionally treated patients had an attendance record of 86 percent. Three patients were lost to follow-up, two in the conventional-therapy group and one in the defibrillator group.

Termination of the Trial

The efficacy boundary of the sequential design was crossed when 51 deaths were reported, and the
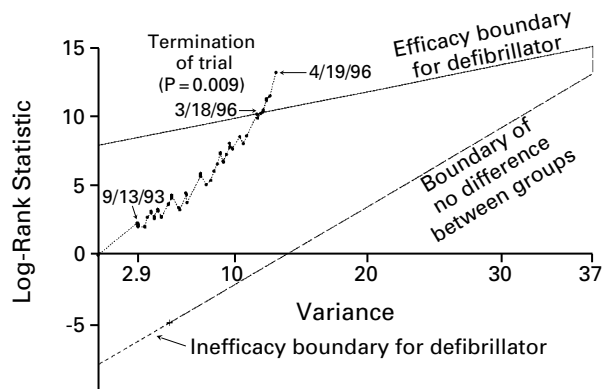
Figure 1. Sequential Monitoring in the Triangular Design.
The vertical axis is a measure of the accumulated differences in survival between the two treatments (log-rank statistic). The horizontal axis is the variance of the log-rank statistic and is closely related to the number of deaths. A positive value of the log-rank statistic indicates superiority of the defibrillator relative to conventional medical treatment, values close to zero indicate no difference between treatments, and negative values indicate inferiority of the defibrillator. The upper stopping boundary indicates defibrillator efficacy, whereas the lower boundary indicates defibrillator inefficacy or no difference between treatments. The solid circles reflect weekly analyses, which were initiated after 10 deaths had been recorded (September 13, 1993). The trial was stopped shortly after the path crossed the upper boundary (March 18, 1996), indicating the superiority of the defibrillator over conventional medical therapy in reducing mortality. The trajectory of the path provides evidence of the rejection of the null hypothesis at P=0.009 (two-sided), with a hazard ratio of 0.46 (95 percent confidence interval, 0.26 to 0.82) in favor of the defibrillator. The path continues upward after the termination of the trial as a result of a lag in reporting three additional deaths that occurred before the stopping date but were uncovered during the close-out procedure (April 19, 1996).

study was officially stopped at that time. The final sample path of the sequential trial, which included three additional deaths that occurred before the stopping date but were identified during the close-out procedure, is presented in Figure 1. The trajectory of the sample path indicates the superiority of the defibrillator over conventional medical treatment, with a P value of 0.009 (two-sided).

End-Point Analyses

The five-year overall mortality, the distribution of deaths from cardiac and noncardiac causes, and the cardiac causes of death are presented in Table 4. The hazard ratio comparing the risk of death per unit of time in the defibrillator group with that in the conventional-therapy group was 0.46 (95 percent confidence interval, 0.26 to 0.82). The Kaplan–Meier life-table cumulative-survival curves for the two treatment groups are shown in Figure 2. The two survival curves separate early and remain well separated throughout the five-year study.

The hazard ratio and confidence intervals derived

TABLE 1. BASE-LINE CHARACTERISTICS OF 196 RANDOMIZED PATIENTS.*

CHARACTERISTIC	CONVENTIONAL THERAPY (N=101)	DEFIBRILLATOR (N=95)
Age (yr)†	64±9	62±9
Sex (M/F)†	92/8	92/8
Cardiac history (%)		
≥2 prior myocardial infarctions†	29	34
Treatment for ventricular arrhythmias	35	42
NYHA class II or III†‡	67	63
Treatment for congestive heart failure†	51	52
Treatment for hypertension†	35	48
Insulin-dependent diabetes	5	7
Cigarette smoking (any time)	73	79
Coronary bypass surgery†	44	46
Coronary angioplasty	27	17
Implanted pacemaker	7	2
Interval of ≥6 mo between most recent myocardial infarction and enrollment (%)†	76	75
Cardiac findings at enrollment (%)		
Pulmonary congestion§	20	18
Blood urea nitrogen >25 mg/dl (8.92 mmol/liter)†	21	22
Cholesterol >200 mg/dl (5.17 mmol/liter)	49	41
Left bundle-branch block†	8	7
Ejection fraction†	0.25±0.07	0.27±0.07
Qualifying unsustained ventricular tachycardia (no. of consecutive beats)	9±10	10±9
Electrophysiologic study (%)		
Initial induction		
Monomorphic ventricular tachycardia	91	87
Polymorphic ventricular tachycardia	7	7
Ventricular fibrillation	2	6
Induction after antiarrhythmic challenge¶		
Monomorphic ventricular tachycardia	94	92
Polymorphic ventricular tachycardia	5	7
Ventricular fibrillation	1	1

*Plus–minus values are means ±SD.

†This variable was preselected for inclusion in the Cox regression analyses.

‡NYHA denotes New York Heart Association.

§Pulmonary congestion was defined radiographically as mild, moderate, or severe.

¶Rhythms were electrophysiologically induced after antiarrhythmic challenge with procainamide.

from the Cox model with adjustment for relevant covariates were similar to those obtained with the sequential-analysis design (Table 4). There was no evidence that the effects of the defibrillator differed between patients implanted with transthoracic leads and those who received transvenous leads (ratio of the hazard ratios, 0.86; P=0.78).

Additional Analyses

Separate Cox regression analyses revealed no evidence that antiarrhythmic medications, including amiodarone and beta-blockers, or other cardiac medications being given one month after enrollment (Table 2) or any of the 11 preselected base-line variables (Table 1) had a meaningful influence on the hazard ratio (P value >0.2 for all interactions). However, the power of the analysis for these interactions

is limited, especially in the case of amiodarone, since only two patients in the defibrillator group received the drug. In the conventional-therapy group, overall mortality was slightly higher among those who were receiving amiodarone at one month than among those who were not receiving the drug (36 percent vs. 26 percent).

The cumulative time to the first shock in the defibrillator group is presented in Figure 3. Sixty percent of the patients with an implanted defibrillator had a shock discharge within two years after enrollment. The overall appropriateness of the defibrillator discharges could not be assessed reliably, since only a small number of patients had pulse generators with electrogram storage and these units were implanted late in the clinical trial.

We evaluated the consistency of the beneficial

TABLE 2. CARDIAC MEDICATIONS ONE MONTH AFTER ENROLLMENT
AND AT THE LAST CONTACT, ACCORDING TO TREATMENT GROUP.

MEDICATION	ONE MONTH*		LAST CONTACT†	
	CONVENTIONAL THERAPY (N=93)	DEFIBRILLATOR (N=93)	CONVENTIONAL THERAPY (N=82)	DEFIBRILLATOR (N=86)
	percent			
Antiarrhythmic medication				
Amiodarone	74	2	45	7
Beta-blockers	8	26	5	27
Class I antiarrhythmic agents	10	12	11	11
Sotalol	7	1	9	4
Beta-blockers or sotalol	15	27	14	31
No antiarrhythmic medication	8	56	23	44
Other cardiac medication				
Angiotensin-converting–enzyme inhibitors	55	60	51	57
Digitalis	38	58	30	57
Diuretics	52	53	47	52

*Data were missing for eight patients in the conventional-therapy group and two patients in the defibrillator group.

†The last contact is the last recorded contact with the patient at the end of the trial, on the last clinic visit before he or she died, or on the last clinic visit before he or she was lost to follow-up.

TABLE 3. ADVERSE EVENTS RELATED TO
ANTIARRHYTHMIC THERAPY OR TO THE DEFIBRILLATOR.

ADVERSE EVENT	TREATMENT GROUP*	
	CONVENTIONAL THERAPY (N=101)	DEFIBRILLATOR (N=95)
	no. of events	
Hypotension	1	0
Syncope	5	1
Hypothyroidism	1	0
Sinus bradycardia	3	3
Pulmonary fibrosis	3	0
Pulmonary embolism	1	1
Atrial fibrillation	0	4
Pneumothorax	0	2
Bleeding	0	1
Venous thrombosis	0	1
Surgical infection	0	2
Problems with defibrillator lead	0	7
Malfunction of defibrillator generator	2	3
Total no. of patients with adverse events	12	19

*Some patients had more than one adverse event.

TABLE 4. FREQUENCY DISTRIBUTION OF DEATHS, ACCORDING TO
TREATMENT GROUP.

CAUSE OF DEATH	CONVENTIONAL THERAPY (N=101)	DEFIBRILLATOR (N=95)	HAZARD RATIO (95% CI)*	P VALUE†
	no. of patients			
Cardiac cause‡	27	11		
Primary arrhythmia	13	3		
Nonarrhythmia	13	7		
Uncertain	1	1		
Noncardiac cause	6	4		
Unknown cause	6	0		
Total	39	15	0.46 (0.26–0.82)	0.009

*The hazard ratio is the ratio of the risk of death per unit of time among patients randomly assigned to receive the defibrillator to that among patients randomly assigned to conventional medical therapy. A hazard ratio below 1.0 indicates a relative benefit for the defibrillator-treated patients. This hazard ratio is derived from the sequential design and takes into account the sequential stopping rule,[15] but it is not adjusted for covariates. CI denotes confidence interval.

†The P value is two-sided. See the text for details.

‡The classification of Hinkle and Thaler[13] was used to categorize the cause of death.

effect of defibrillator therapy in each of the two centers with the highest enrollments (42 and 21 patients) and compared the results in the high-enrollment centers with the results in the 30 centers with lower enrollment (a total of 133 patients). The reductions in mortality with the defibrillator were similar among these groups.

DISCUSSION

The implantable defibrillator was introduced into clinical medicine in 1980,[18] and several reports have substantiated the ability of this device to terminate ventricular fibrillation automatically.[19-24] In this trial we found a significant reduction in overall mortality associated with the implantation of a defibrillator in
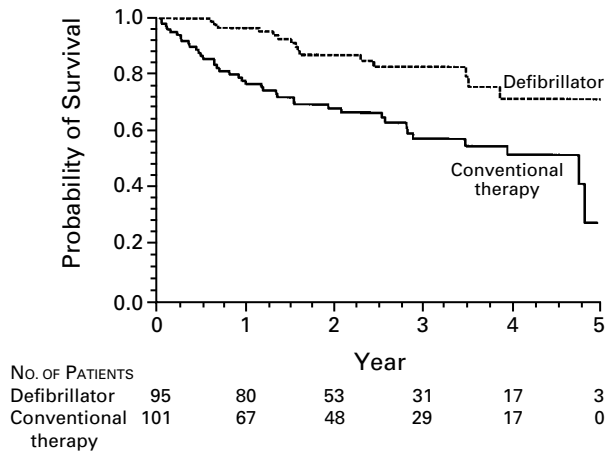
Figure 2. Kaplan–Meier Analysis of the Probability of Survival, According to Assigned Treatment.

The difference in survival between the two treatment groups was significant (P = 0.009).

No. of Patients

Defibrillator	95	80	53	31	17	3
Conventional therapy	101	67	48	29	17	0
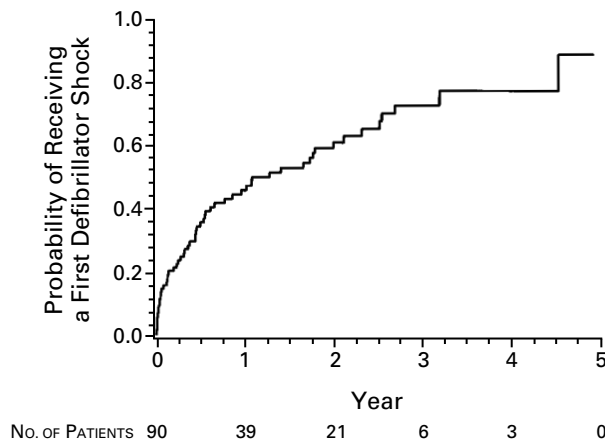
Figure 3. Kaplan–Meier Analysis of the Probability of the Discharge of a First Shock with the Implanted Cardioverter–Defibrillator.

No. of Patients 90   39   21   6   3   0

high-risk patients with coronary disease and left ventricular dysfunction, asymptomatic unsustained ventricular tachycardia, and inducible sustained ventricular tachycardia. Prescribed medications, including beta-blockers, had no discernible effect on the survival benefit derived from the defibrillator in this population. Patients randomly assigned to receive the defibrillator had a much lower rate of death from primary arrhythmia than patients assigned to conventional therapy (Table 4). It is noteworthy that there were more deaths from nonarrhythmic causes in the conventional-therapy group than in the defibrillator group, possibly reflecting inaccuracy in classifying

the cause of death or conceivably related to the higher rate of use of amiodarone in the conventional-therapy group.

When we designed the study, we did not include a comparison group that received no treatment because we thought that such a stipulation would make enrollment extremely difficult in this high-risk, arrhythmia-prone population. We did not prespecify an antiarrhythmic-drug protocol since we anticipated that the safety and efficacy of antiarrhythmic drugs would change over the course of the study. The attending physicians were allowed to prescribe antiarrhythmic medications for patients in either treatment group. We anticipated that more amiodarone therapy would be prescribed for patients in the conventional-therapy group than in the defibrillator group, and this was indeed the case. Amiodarone therapy was ultimately discontinued in 46 percent of conventionally treated patients, a rate similar to that observed by others when amiodarone is used prophylactically in high-risk patients.[25] The specific reasons for this high rate of discontinuation are unclear but are probably related to physicians' knowledge of the potential of amiodarone to cause adverse effects during long-term administration. Only a small number of patients received sotalol and class I antiarrhythmic agents. Beta-blockers were used more frequently in the defibrillator group, but less than 30 percent of the patients in this group received beta-blockers during the course of the study.

The question is whether these imbalances in antiarrhythmic-medication use between the two groups contributed to the observed results. No evidence was found by Cox regression analyses that an imbalance in antiarrhythmic-medication use in the two treatment groups had a meaningful influence on the observed hazard ratio; in other words, there were no significant interactions between any of the antiarrhythmic medications, including amiodarone and beta-blockers, and the assigned treatment. In a recent double-blind, placebo-controlled study of patients with congestive heart failure, amiodarone did not reduce the incidence of sudden death or prolong survival in patients with chronic coronary heart disease, asymptomatic ventricular arrhythmias, and impaired ventricular function.[25]

We believe that the use of electrophysiologic testing enhanced the process of stratification for arrhythmia and helped select a population at particularly high risk that benefited from the defibrillator. The mortality rate in the conventional-therapy group was high (32 percent at two years), but it was consistent with that previously reported for a similar group of patients with inducible or nonsuppressible ventricular tachycardia.[8] Similarly, the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure reported a two-year mortality rate of 30 percent in both the amiodarone group and the placebo

group; these patients had ischemic cardiomyopathy, ejection fractions of 0.40 or less, mild-to-moderate heart failure, and ventricular ectopy.[25]

A limitation of this study is that we do not know how many patients attending physicians screened to identify patients who were eligible. In addition, the enrolling centers did not keep consistent logs of eligible patients who did not qualify on the basis of the electrophysiologic study. Thus, we do not know the true denominator from which the study population was drawn or the magnitude of selection bias that may have occurred during enrollment.

The triangular, fully sequential design used in this trial is highly effective for conducting a focused trial that minimizes the number of both deaths and patients required for a statistically significant conclusion.[14] In clinical trials using fixed-sample or group-sequential design,[26] safety and efficacy monitoring is carried out infrequently or when prespecified numbers or anticipated percentages of end points are accumulated. In contrast, the sequential design permits termination of the trial on early evidence of benefit, of the absence of a difference between groups, or of harm, and the stopping boundaries take into account the multiple data analyses. A limitation associated with the sequential design is that early termination minimizes the amount of information collected, thereby reducing the power for exploratory subgroup analyses.

In the present study, the implanted defibrillator provided effective protection against death in high-risk patients with coronary heart disease and left ventricular dysfunction, spontaneous asymptomatic unsustained ventricular tachycardia, and inducible and nonsuppressible ventricular tachyarrhythmia on electrophysiologic testing. Prophylactic defibrillator therapy may reduce mortality among other high-risk patients with cardiac disease who are selected on the basis of different or less restrictive criteria. However, until the results of other randomized trials of defibrillators become available,[27,28] the findings from this investigation should be applied only to the narrowly defined population of patients described in this study.

We are indebted to the patients who participated in this trial; to the attending physicians who referred their patients to this study; and to CPI/Guidant Corporation for its support and sustained commitment, for supplying the defibrillators, and for the independence it provided to the investigators to conduct the study.

APPENDIX

The following investigators also participated in the Multicenter Automatic Defibrillator Implantation Trial: **S. Sridhar,** Affiliated Cardiologists, Phoenix, Ariz.; **T. Mattioni,** Arizona Heart Institute and Foundation, Phoenix; **J. Maloney** and **B. Wilkoff,** Cleveland Clinic Hospital, Cleveland; **R. Krol,** Eastern Heart Institute, Passaic, N.J.; **A. Leon,** Emory Clinic, Atlanta; **R. Cierpka** and **H.-J. Trappe,** Hanover Medical School, Hanover, Germany; **S. Kutalek,** Hahnemann University Hospital, Philadelphia; **J. Rottman,** Jewish Hospital of St. Louis, St. Louis; **T. Guanieri** and **G. Tomaselli,** Johns Hopkins University Hospital, Baltimore; **B. Olshansky,** Loyola University Medical Center, Maywood, Ill.; **J. Salerno,** Matteo Hospital, Pavia, Italy; **B. Crevey,** Methodist Hospital, Indianapolis; **C. Pratt** and **D. Zhu,** Methodist Hospital, Houston; **M. Pritzker,** Minneapolis Heart Institute, Minneapolis; **S. Winters,** Morristown Memorial Hospital, Morristown, N.J.; **A. Kadish,** Northwestern Memorial Hospital, Chicago; **F. Abi-Samra,** Ochsner Clinic, New Orleans; **B. Halperin, J. Kron,** and **J. McAnulty,** Oregon Health Sciences University, Portland; **J. Steinberg,** Roosevelt–St. Luke's Medical Center, New York; **S. Greenberg** and **D. Hoch,** Saint Francis Hospital–Heart Center, Roslyn, N.Y.; **J. Gallagher,** Sanger Clinic–Carolina Heart Institute, Charlotte, N.C.; **J. Ilvento,** Santa Barbara Cottage Hospital, Santa Barbara, Calif.; **R. Winkle,** Sequoia Hospital, Palo Alto, Calif.; **M. Lehmann,** Sinai Hospital, Detroit; **M. Scheinman,** University of California Medical Center, San Francisco; **R. Myerburg,** University of Miami Medical Center, Miami; **T. Akiyama, A. Mushlin,** and **W. Zareba,** University of Rochester Medical Center, Rochester, N.Y.; **R. Ruffy,** University of Utah School of Medicine, Salt Lake City; and **E. Platia,** Washington Hospital Center, Washington, D.C.; Data and Safety Monitoring Committee — **D. Goldblatt, W. Hood, Jr.** (chair), **D. Oakes,** and **M. Tanner;** End-Point Review Committee — **L. Cobb** and **R. Goldstein** (chair); Rochester Coordination and Data Center — **M. Andrews, E. Garcia, N. Kellogg, B. MacKecknie, D. Ramsell,** and **P. Severski;** and statistical support — **J. Whitehead** and **S. Chen.**

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