

The New England Journal of Medicine

Copyright © 2002 by the Massachusetts Medical Society

VOLUME 346

MARCH 21, 2002

NUMBER 12



PROPHYLACTIC IMPLANTATION OF A DEFIBRILLATOR IN PATIENTS WITH MYOCARDIAL INFARCTION AND REDUCED EJECTION FRACTION

ARTHUR J. MOSS, M.D., WOJCIECH ZAREBA, M.D., PH.D., W. JACKSON HALL, PH.D., HELMUT KLEIN, M.D.,
DAVID J. WILBER, M.D., DAVID S. CANNOM, M.D., JAMES P. DAUBERT, M.D., STEVEN L. HIGGINS, M.D.,
MARY W. BROWN, M.S., AND MARK L. ANDREWS, B.B.S.,
FOR THE MULTICENTER AUTOMATIC DEFIBRILLATOR IMPLANTATION TRIAL II INVESTIGATORS*

ABSTRACT

Background Patients with reduced left ventricular function after myocardial infarction are at risk for life-threatening ventricular arrhythmias. This randomized trial was designed to evaluate the effect of an implantable defibrillator on survival in such patients.

Methods Over the course of four years, we enrolled 1232 patients with a prior myocardial infarction and a left ventricular ejection fraction of 0.30 or less. Patients were randomly assigned in a 3:2 ratio to receive an implantable defibrillator (742 patients) or conventional medical therapy (490 patients). Invasive electrophysiological testing for risk stratification was not required. Death from any cause was the end point.

Results The clinical characteristics at base line and the prevalence of medication use at the time of the last follow-up visit were similar in the two treatment groups. During an average follow-up of 20 months, the mortality rates were 19.8 percent in the conventional-therapy group and 14.2 percent in the defibrillator group. The hazard ratio for the risk of death from any cause in the defibrillator group as compared with the conventional-therapy group was 0.69 (95 percent confidence interval, 0.51 to 0.93; $P=0.016$). The effect of defibrillator therapy on survival was similar in subgroup analyses stratified according to age, sex, ejection fraction, New York Heart Association class, and the QRS interval.

Conclusions In patients with a prior myocardial infarction and advanced left ventricular dysfunction, prophylactic implantation of a defibrillator improves survival and should be considered as a recommended therapy. (N Engl J Med 2002;346:877-83.)

Copyright © 2002 Massachusetts Medical Society.

PATIENTS with myocardial infarction and reduced left ventricular function are at risk for congestive heart failure and arrhythmia-related sudden death. In 1996, the implantation of a defibrillator was reported to improve survival in patients with coronary heart disease, reduced ventricular function, unsustained ventricular tachycardia, and inducible ventricular tachycardia,¹ and this finding was confirmed in 1999.² In both studies, patients underwent invasive electrophysiological testing to determine their risk of arrhythmia. The prognostic value of electrophysiological testing for the identification of patients with coronary heart disease who are at risk for ventricular arrhythmias is uncertain.³ We reasoned that in patients with a prior myocardial infarction and advanced left ventricular dysfunction, the scarred myocardium would serve as a trigger for malignant ventricular arrhythmias. The Multicenter Automatic Defibrillator Implantation Trial II was designed to evaluate the potential survival benefit of a prophylactically implanted defibrillator (in the absence of electrophysiological testing to induce arrhythmias) in patients with a prior myocardial infarction and a left ventricular ejection fraction of 0.30 or less.

From the Cardiology Unit of the Department of Medicine (A.J.M., W.Z., J.P.D., M.W.B., M.L.A.) and the Department of Biostatistics (W.J.H.), University of Rochester Medical Center, Rochester, N.Y.; the Division of Cardiology, University Hospital, Magdeburg, Germany (H.K.); the Cardiology Unit, Loyola University Medical Center, Maywood, Ill. (D.J.W.); Cardiology Associates, Good Samaritan Hospital, Los Angeles (D.S.C.); and the Department of Cardiology, Scripps Memorial Hospital, La Jolla, Calif. (S.L.H.). Address reprint requests to Dr. Moss at the Heart Research Follow-up Program, Box 653, University of Rochester Medical Center, Rochester, NY 14642, or at heartajm@heart.rochester.edu.

*The investigators who participated in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) are listed in the Appendix.

METHODS

Organization of the Trial

The trial began on July 11, 1997, and enrolled patients from 76 hospital centers (71 in the United States and 5 in Europe). The protocol was approved by the institutional review boards of the participating hospitals. A data and safety monitoring board independently reviewed the results at regular intervals throughout the trial. All investigators agreed to abide by the conflict-of-interest guidelines described by Healy et al.⁴ A description of the design and study protocol has been published previously.⁵

Recruitment and Follow-up

Patients of either sex who were more than 21 years of age (there was no upper age limit) were eligible for the study if they had had a myocardial infarction one month or more before entry, as documented by the finding of an abnormal Q wave on electrocardiography, elevated cardiac-enzyme levels on laboratory testing during hospitalization for suspected myocardial infarction, a fixed defect on thallium scanning, or localized akinesis on ventriculography with evidence of obstructive coronary disease on angiography, and an ejection fraction of 0.30 or less within three months before entry, as assessed by angiography, radionuclide scanning, or echocardiography. Potentially eligible patients were referred by local cardiologists, internists, and primary care physicians. Patients were not

required to undergo electrophysiological screening for inducible ventricular arrhythmias.

Patients were excluded from enrollment if they had an indication approved by the Food and Drug Administration (FDA) for an implantable defibrillator; were in New York Heart Association functional class IV at enrollment; had undergone coronary revascularization within the preceding three months; had had a myocardial infarction within the past month, as evidenced by measurement of cardiac-enzyme levels; had advanced cerebrovascular disease; were of childbearing age and were not using medically prescribed contraceptive measures; had any condition other than cardiac disease that was associated with a high likelihood of death during the trial; or were unwilling to sign the consent form for participation.

When the trial began in July 1997, eligible patients had to have frequent or repetitive ventricular ectopic beats during 24-hour Holter monitoring. On January 1, 1998, after the enrollment of 23 patients, the executive committee eliminated this requirement because almost all eligible patients had such arrhythmias. On May 4, 2001, the executive committee increased the enrollment goal from 1200 to 1500 patients, so that enrollment would be ongoing while data on outcomes were still accruing.

Randomization

After patients had provided written informed consent, a base-line clinical history and 12-lead electrocardiogram were obtained and a physical examination was conducted. The patients were randomly

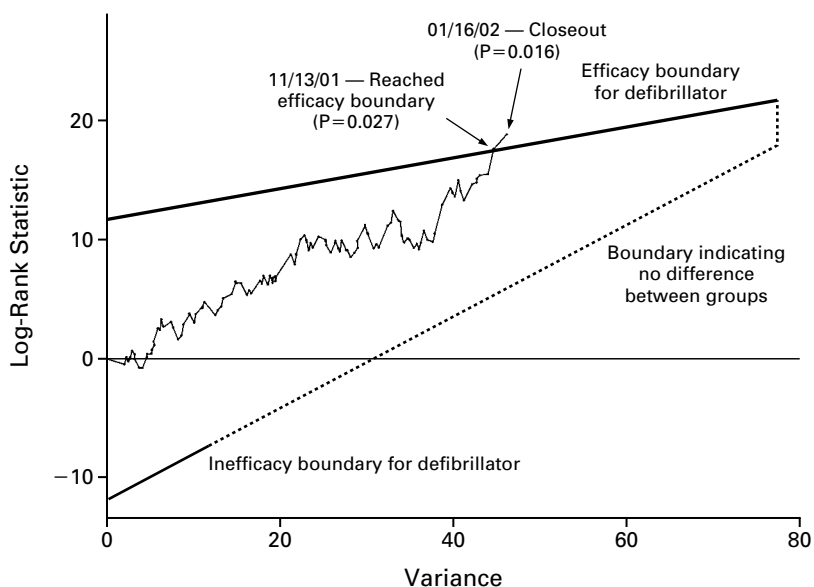


Figure 1. Sequential Monitoring in the Triangular Design.

The log-rank statistic is a measure of the cumulative differences in survival between the two treatments. A positive value for the log-rank statistic indicates that treatment with the defibrillator was superior to conventional medical therapy. The variance of the log-rank statistic is closely related to the number of deaths. Three boundaries are shown: one indicating the inefficacy of the implantation of a defibrillator as compared with conventional medical therapy, one indicating no difference between the groups, and one indicating the superiority of treatment with a defibrillator. The trial was stopped on November 20, 2001, shortly after the upper boundary, indicating superiority of the defibrillator, was reached ($P=0.027$). The values of the log-rank statistic continue to increase after the termination of the trial ($P=0.016$) as a result of a lag in reporting additional survival data and five additional deaths that occurred before the stopping date but were uncovered during the closeout procedure (on January 16, 2002).

assigned in a 3:2 ratio to receive either an implantable defibrillator or conventional medical therapy. Patients who were assigned to the defibrillator group were not responsible for the costs of the defibrillator, implantation, or the hospitalization for the procedure.

Therapy

Transvenous defibrillator systems (Guidant, St. Paul, Minn.) that had been approved by the FDA were used in the trial. Standard techniques were used to implant the defibrillators. The defibrillators were tested during the implantation procedure, and every effort was made to achieve defibrillation within a 10-J safety margin. Programming the defibrillator and prescribing medications were left to the discretion of the patients' physicians. The appropriate use of beta-blockers, angiotensin-converting-enzyme inhibitors, and lipid-lowering drugs was strongly encouraged in both study groups.

Statistical Analysis

The primary end point was death from any cause. Analysis was performed according to the intention-to-treat principle. The trial was designed to have 95 percent power to detect a 38 percent reduction in the two-year mortality rate among the patients in the defibrillator group, given a postulated two-year mortality rate of 19 percent among patients assigned to conventional therapy, with a two-sided significance level of 0.05. For proportional-hazards modeling, power was maintained for a true hazard ratio of 0.63, after allowance for crossovers. We used a triangular sequential design, which was modified for two-sided alternatives⁶ and corrected for the lag in obtaining data accrued but not reported before the termination of the trial, for weekly monitoring, with preset boundaries to permit termination of the trial if the defibrillator therapy was found to be superior to, inferior to, or equal to conventional medical therapy. Secondary analyses were performed with use of the Cox proportional-hazards regression model.⁷ We determined survival curves according to the method of Kaplan and Meier,⁸ with comparisons of cumulative mortality based on logarithmic transformations. P values were termed nominal when they were not adjusted for sequential monitoring. All P values were two-tailed.

At the recommendation of the data and safety monitoring board the trial was stopped on November 20, 2001, shortly after an analysis revealed that the difference in mortality between the two groups had reached the prespecified efficacy boundary (P=0.027) (Fig. 1). Analyses used version 2.0 of the data base, which was released on January 16, 2002. The investigators had full access to the data and performed the data analysis with no limitations imposed by the sponsor.

RESULTS

Study Population

The clinical characteristics of the 1232 randomized patients are provided in Table 1. Follow-up averaged 20 months (range, 6 days to 53 months). The base-line characteristics and the prevalence of the use of various cardiac medications at the time of the last follow-up visit were similar in the two groups. Fifty-four crossovers occurred. Twenty-two patients in the conventional-therapy group (4.5 percent) received a defibrillator during the trial, 21 for documented or suspected malignant ventricular arrhythmias and 1 at the physician's discretion. Twenty-one patients assigned to the defibrillator group (2.8 percent) did not have a defibrillator implanted, and 11 had their defibrillator removed during the trial (1.5 percent),

TABLE 1. CLINICAL CHARACTERISTICS OF THE 1232 PATIENTS.*

CHARACTERISTIC	DEFIBRILLATOR GROUP (N=742)	CONVENTIONAL-THERAPY GROUP (N=490)
Age (yr)	64±10	65±10
Male sex (%)	84	85
NYHA functional class (%)†		
I	35	39
II	35	34
III	25	23
IV	5	4
Treatment for hypertension (%)	53	53
Diabetes (%)	33	38
Current or former cigarette smoker (%)	80	82
Coronary bypass surgery (%)	58	56
Coronary angioplasty (%)	45	42
Interval of >6 mo between most recent myocardial infarction and enrollment (%)	88	87
Cardiac findings at enrollment (%)		
Blood urea nitrogen >25 mg/dl (8.92 mmol/liter)	29	32
Atrial fibrillation	9	8
QRS interval ≥0.12 sec	50	51
Nonspecific conduction defect	22	26
Right bundle-branch block	9	7
Left bundle-branch block	19	18
Left ventricular ejection fraction	23±5	23±6
Medications at last contact (%)‡		
Amiodarone	13	10
Angiotensin-converting-enzyme inhibitors	68	72
Beta-blockers	70	70
Calcium-channel blockers	9	9
Class I antiarrhythmic agents	3	2
Digitalis	57	57
Diuretics	72	81
Lipid-lowering statin drugs	67	64

*Plus-minus values are means ±SD. Patients were randomly assigned in a 3:2 ratio to receive an implanted defibrillator (60.2 percent) or conventional medical therapy (39.8 percent).

†Values reflect the highest New York Heart Association (NYHA) functional class recorded in the three-month period before enrollment. Eligibility was limited to patients who were in NYHA class I, II, or III at the time of enrollment.

‡The mean interval from enrollment to the time of the last follow-up visit in which medication use was recorded was 17 months in the conventional-therapy group and 18 months in the defibrillator group.

including 9 who underwent heart transplantation. Twelve patients had their defibrillator deactivated during the trial, usually as a result of terminal illness.

There were 8749 scheduled follow-up visits during the trial, with a 94 percent rate of attendance in the conventional-therapy group and a 97 percent rate in the defibrillator group. The status of three patients was not known at the termination of the trial (one patient in the conventional-therapy group and two in the defibrillator group). All three patients were known to be alive within six months before the trial ended.

Outcome

The sample path of the sequential trial is presented in Figure 1. The trajectory of the path indicates the superiority of defibrillator therapy over nondefibrillator therapy, with $P=0.016$ (two-sided, adjusted for the stopping rule).

The numbers of deaths in each group and the hazard ratio for death per unit of time are presented in Table 2. The hazard ratio of 0.69 indicates a 31 percent reduction in the risk of death at any interval among patients in the defibrillator group as compared with patients in the conventional-therapy group.

TABLE 2. HAZARD RATIO FOR DEATH.

VARIABLE	DEFIBRILLATOR GROUP (N=742)	CONVENTIONAL-THERAPY GROUP (N=490)	HAZARD RATIO (95% CI)*	P VALUE†
No. of deaths (%)	105 (14.2)	97 (19.8)	0.69 (0.51–0.93)	0.016

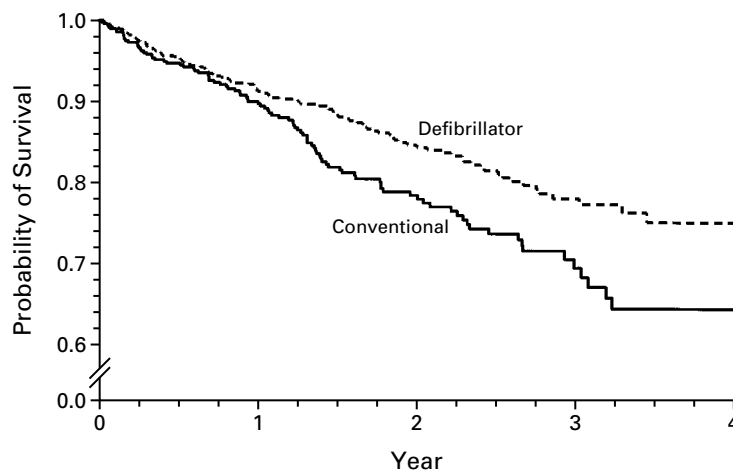
*The value is the risk of death per unit of time among patients who were randomly assigned to the defibrillator group as compared with that among patients who were randomly assigned to the conventional-therapy group. The hazard ratio, 95 percent confidence interval (CI), and P value were derived from the sequential design with use of a proportional-hazards assumption and took into account the sequential stopping rule.

†The P value is two-sided.

Kaplan-Meier estimates of survival in the two groups are shown in Figure 2. The two survival curves began to diverge at approximately nine months and continued their separate paths thereafter (nominal $P=0.007$). These survival curves represent reductions in the rates of death after defibrillator therapy of 12 percent at one year (nominal 95 percent confidence interval, -27 to 40 percent), 28 percent at two years (nominal 95 percent confidence interval, 4 to 46 percent), and 28 percent at three years (nominal 95 percent confidence interval, 5 to 46 percent). There were no significant differences in the effect of defibrillator therapy on survival in subgroup analyses stratified according to age, sex, ejection fraction, New York Heart Association class, or the QRS interval (Fig. 3). There were also no significant differences in the effect of defibrillator therapy on survival in subgroup analyses classified according to the presence or absence of hypertension, diabetes, left bundle-branch block, or atrial fibrillation; the interval since the most recent myocardial infarction (six months or less vs. more than six months); the type of defibrillator implanted (single chamber vs. dual chamber); or the blood urea nitrogen level (25 mg per deciliter or less vs. more than 25 mg per deciliter).

Adverse Effects

Serious complications related to defibrillator therapy were infrequent. No deaths occurred during im-



NO. AT RISK					
Defibrillator	742	503 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

Figure 2. Kaplan-Meier Estimates of the Probability of Survival in the Group Assigned to Receive an Implantable Defibrillator and the Group Assigned to Receive Conventional Medical Therapy. The difference in survival between the two groups was significant (nominal $P=0.007$, by the log-rank test).

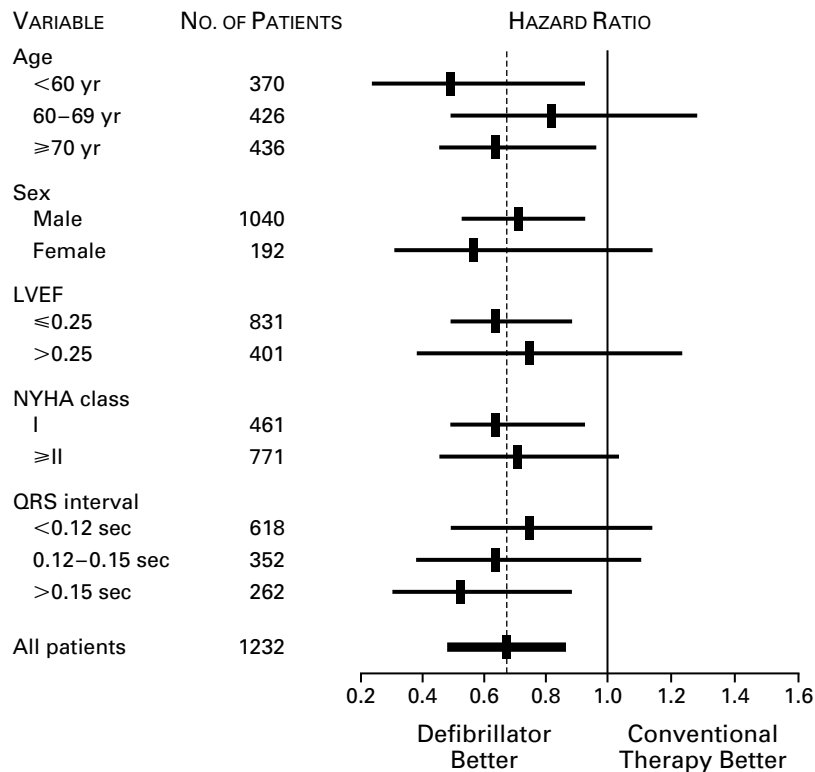


Figure 3. Hazard Ratios and 95 Percent Confidence Intervals for Death from Any Cause in the Defibrillator Group as Compared with the Group Assigned to Receive Conventional Medical Therapy, According to Selected Clinical Characteristics.

The hazard ratios in the various subgroups were similar, with no statistically significant interactions. The dotted vertical line represents the results for the entire study (nominal hazard ratio, 0.66, without adjustment for the stopping rule). The horizontal lines indicate nominal 95 percent confidence intervals. LVEF denotes left ventricular ejection fraction, and NYHA New York Heart Association.

plantation. Thirteen lead problems (1.8 percent) and five nonfatal infections (0.7 percent) required surgical intervention in the defibrillator group. The incidence of new or worsened heart failure was slightly higher in the defibrillator group than in the conventional-therapy group. Specifically, 73 patients (14.9 percent) in the conventional-therapy group and 148 in the defibrillator group (19.9 percent) were hospitalized with heart failure, representing 9.4 and 11.3 patients so hospitalized per 1000 months of active follow-up, respectively (nominal $P=0.09$).

DISCUSSION

Our findings indicate that the implantation of a defibrillator improves survival among patients with a prior myocardial infarction and a left ventricular ejection fraction of 0.30 or less. As compared with conventional medical therapy, defibrillator therapy was associated with a 31 percent reduction in the risk of

death. Electrophysiologic testing or inducible ventricular arrhythmias were not eligibility criteria. The two groups were balanced and received appropriate therapy with standard cardiac agents; high percentages of patients in both groups received angiotensin-converting-enzyme inhibitors, beta-blockers, diuretics, and lipid-lowering statin drugs.

In contrast with the earlier Multicenter Automatic Defibrillator Implantation Trial, in which the survival rate improved within the first few months after the implantation of the device,¹ in the current study the survival benefit began approximately nine months after the device was implanted. The difference may reflect a somewhat lower mortality rate in the conventional-therapy group in the current study, the absence of risk stratification for arrhythmia as an entry criterion, the use of a lower cutoff value for the ejection fraction as a criterion for eligibility, and the use of more vigorous medical treatment. These same pop-

ulation differences may also explain the relatively higher hazard ratio in our study than in the earlier study (0.69 vs. 0.46).¹

We are concerned by the finding that new or worsened heart failure requiring hospitalization was slightly more frequent in the defibrillator group than in the conventional-therapy group. Patients saved from malignant ventricular arrhythmias by the implantation of a defibrillator live longer than conventionally treated patients and would thus have more time for heart failure to develop. Defibrillator shocks might contribute to rehospitalization⁹ and myocardial injury.¹⁰ Backup ventricular pacing may impair ventricular function.¹¹ Patients with a reduced ejection fraction who receive an implantable defibrillator should be carefully monitored for the development or exacerbation of heart failure.

An estimated 3 million to 4 million patients have coronary heart disease and advanced left ventricular dysfunction in the United States, and there are approximately 400,000 new cases annually.^{12,13} If a meaningful number of these patients receive an implantable defibrillator prophylactically, the cost to the health care system would be substantial. We hope that market forces will drive down the cost of this therapy.

Our findings show that the implantation of a defibrillator improves survival in patients with a prior myocardial infarction and advanced left ventricular dysfunction. Thus, prophylactic implantation of a defibrillator is recommended in these patients.

Supported by a research grant from Guidant, St. Paul, Minn., to the University of Rochester School of Medicine and Dentistry.

Drs. Cannom, Daubert, and Higgins have given lectures sponsored by Guidant.

We are indebted to the patients who participated in this trial, to the study coordinators at each of the enrolling centers, and to Guidant Corporation for its support, sustained commitment, and the independence it provided to the investigators in the conduct of this study.

APPENDIX

The following investigators also participated in the MADIT-II (listed in descending order of the number of randomly assigned patients): **Investigators** — L. Berenbom, Mid-America Research Organization and University of Kansas Medical Center Research Institute, Kansas City; D. Glascock, Toledo Hospital, Toledo, Ohio; H. Klein, University Hospital Magdeburg, Magdeburg, Germany; H. Pitschner, Kerkhoff Clinic, Bad Nauheim, Germany; J. Butler, Florida Heart Association, Fort Myers; A. Leon, Crawford Long Hospital, Atlanta; J. Steinberg, St. Luke's–Roosevelt Hospital Center, New York, and Valley Hospital, Ridgewood, N.J.; S. Wittenberg, Baystate Medical Center, Springfield, Mass.; D. Switzer, Buffalo Medical Group, Buffalo, N.Y.; R. Corbisiero, Deborah Heart & Lung Center, Brown Mills, N.J.; D.J. Wilber, University of Chicago, Chicago; Northwest Community Hospital, Chicago; Loyola University Medical Center, Maywood, Ill.; W. Brodine, Kansas City Cardiology Associates, Kansas City, Kans.; D. Weiss, Florida Arrhythmia Consultants, Fort Lauderdale; A. Waldo, University Hospitals of Cleveland, Cleveland; J. Jentzer, Northeast Cardiology Associates, Bangor, Me.; M. Akhtar, Heart Care Associates, Milwaukee; K. Tucker, Orange County Heart Institute, Orange, Calif.; J. Baker, Heart Group, Nashville; D. Cannom, Good Samaritan Heart Institute, Los Angeles; C. Schuger, Henry Ford Hospital, Detroit; D. Hoch, St.

Francis Hospital–Heart Center, Roslyn, N.Y.; J. Daubert, University of Rochester Medical Center, Rochester, N.Y.; M. Rashtian, Foothill Cardiology, Pasadena, Calif.; S. Higgins, Scripps Memorial Hospital, La Jolla, Calif.; G. Ziady, University of Pittsburgh Medical Center, Pittsburgh; B. Crevey, Clarian Health Methodist Hospital, Indianapolis; J. Herre, Sentara Norfolk General Hospital, Norfolk, Va.; S. Klein, Le Bauer Cardiovascular Research Foundation, Greensboro, N.C.; J. Merrill, Valley Heart Associates, Modesto, Calif.; C. Sueta, University of North Carolina, Chapel Hill; C. Kim, Rochester General Hospital, Rochester, N.Y.; S. Compton, Alaska Heart Institute, Anchorage; I. Singer, University of Louisville, Louisville, Ky.; K. Adams, Jacksonville Heart Center, Jacksonville, Fla.; J. Patterson, St. Vincent's Medical Center, Jacksonville, Fla.; M. Estes, New England Medical Center, Boston; D. Zhu, Minnesota Heart Clinic, Edina; S. Sakena, Eastern Heart Institute, Passaic, N.J.; J. Ruskin, Massachusetts General Hospital, Boston; G. Sosa-Suarez, St. Peter's Hospital, Albany, N.Y.; D. Wilkinson, Swedish Medical Center–Providence Campus, Seattle; D. Fitzgerald, Wake Forest University, Winston-Salem, N.C.; Y. Greenberg, Maimonides Medical Center, Brooklyn, N.Y.; T. Talbert, Park Ridge Medical Center, Chattanooga, Tenn.; R. Jadonath, North Shore University Hospital, Manhasset, N.Y.; J. Windle, University of Nebraska Medical Center, Omaha; L. Siddoway, York Hospital, York, Pa.; D. Borowski, Consultants in Cardiology, Inc., Erie, Pa.; E. Nsah, Peninsula Cardiology Associates, Salisbury, Md.; S. Geraci, University of Florida, Jacksonville; S. Brownstein, St. Vincent Mercy Medical Center, Toledo, Ohio; M. Schali, Leiden University Hospital, Leiden, the Netherlands; A. Medina, Bikur Cholim Hospital, Jerusalem, Israel; E. Platia, Washington Hospital Center, Washington, D.C.; P. Friedman, Cardiovascular Specialists, Hyannis, Mass.; J. Zebede, Mount Sinai Medical Center, Miami; F. Leonelli, Cardiology Associates of Mobile, Mobile, Ala.; E.W. Grogan, Wisconsin Heart, Madison; W. Crawford, Montgomery Cardiovascular Associates, Montgomery, Ala.; D. Watton, Heart Center of Nevada, Las Vegas; J. Souza, Asheville Cardiology Associates, Asheville, N.C.; C. Fuenzalida, Western Cardiology Associates, Aurora, Colo.; S. Lanza, Florida Heart Group, Orlando; B. Belhassen, Tel Aviv Medical Center, Tel Aviv, Israel; R. Winkle, Sequoia Hospital, Palo Alto, Calif.; M. Illovsky, National Naval Medical Center, Bethesda, Md.; A. Dougherty, University of Texas, Houston; O. Fujimura, State University of New York Upstate Medical University, Syracuse; H. Lee, University of Iowa Health Care, Iowa City; C. Rizo-Patron, Cardiology Associates of Lubbock, Lubbock, Tex.; D. Pederson, Austin Heart, Austin, Tex.; F. Gilliam, Virginia Cardiovascular Specialists, Richmond; **Data and Safety Monitoring Committee** — D. Oakes (chair), T. Pearson, R. Pomerantz; **End-Point Review Committee** — H. Greenberg (chair), R. Case; **Noninvasive Electrocardiology** — W. Zareba (head), J. Palma, D. Passantino; **Rochester Coordination and Data Center** — M. Brown (head), M. Andrews, D. Johnsen, D. Ramsell, B. MacKecknie, A. Sorce, P. Severski, E. Carroll; **Biostatisticians** — W. Hall (head), V. Dragalin, P. Huang, K. Ding, C. Feng, J. Whitehead (consultant); **Executive Committee** — A. Moss (chair), M. Brown, D. Cannom, J. Daubert, W. Hall, S. Higgins, H. Klein, D. Wilber, W. Zareba.

REFERENCES

1. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;335:1933-40.
2. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341:1882-90. [Erratum, *N Engl J Med* 2000;342:1300.]
3. Buxton AE, Lee KL, DiCarlo L, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. *N Engl J Med* 2000;342:1937-45.
4. Healy B, Campeau L, Gray R, et al. Conflict-of-interest guidelines for a multicenter clinical trial of treatment after coronary-artery bypass-graft surgery. *N Engl J Med* 1989;320:949-51.
5. Moss AJ, Daubert JP, Hall WJ, et al. Multicenter Automatic Defibrillator Implantation Trial II (MADIT II): design and clinical protocol. *Ann Noninvasive Electrocardiol* 1999;4:83-91.
6. Whitehead J. The design and analysis of sequential clinical trials. Rev. 2nd ed. Chichester, England: John Wiley, 1997.
7. Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
8. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
9. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable de-

fibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576-83.

10. Hurst TM, Hinrichs M, Breidenbach C, Katz N, Waldecker B. Detection of myocardial injury during transvenous implantation of automatic cardioverter-defibrillators. *J Am Coll Cardiol* 1999;34:402-8.

11. Ellenbogen KA, Thames MD, Mohanty PK. New insights into pacemaker syndrome gained from hemodynamic, humoral and vascular responses during ventriculo-atrial pacing. *Am J Cardiol* 1990;65:53-9.

12. Cohn JN, Bristow MR, Chien KR, et al. Report of the National Heart, Lung, and Blood Institute Special Emphasis Panel on Heart Failure Research. *Circulation* 1997;95:766-70.

13. Myerburg RJ. Sudden cardiac death: exploring the limits of our knowledge. *J Cardiovasc Electrophysiol* 2001;12:369-81.

Copyright © 2002 Massachusetts Medical Society.