

The New England Journal of Medicine

© Copyright, 1997, by the Massachusetts Medical Society

VOLUME 337

NOVEMBER 27, 1997

NUMBER 22



PROPHYLACTIC USE OF IMPLANTED CARDIAC DEFIBRILLATORS IN PATIENTS AT HIGH RISK FOR VENTRICULAR ARRHYTHMIAS AFTER CORONARY-ARTERY BYPASS GRAFT SURGERY

J. THOMAS BIGGER, JR., M.D., FOR THE CORONARY ARTERY BYPASS GRAFT (CABG) PATCH TRIAL INVESTIGATORS*

ABSTRACT

Background Patients with coronary heart disease, left ventricular dysfunction, and abnormalities on signal-averaged electrocardiograms have an increased risk of sudden death. We evaluated the effect on survival of the prophylactic implantation of cardioverter-defibrillators in such patients at the time of coronary-artery bypass surgery.

Methods Over the course of five years, 37 clinical centers screened all patients who were scheduled for elective coronary bypass surgery. Patients were eligible for the trial if they were less than 80 years old, had a left ventricular ejection fraction of less than 0.36, and had abnormalities on signal-averaged electrocardiograms. We identified 1422 eligible patients, enrolled 1055, and randomly assigned 900 to therapy with an implantable cardioverter-defibrillator (446 patients) or to the control group (454 patients). The primary end point of the study was overall mortality, and the two groups were compared in an intention-to-treat analysis.

Results The base-line characteristics of the two groups were similar. During an average (\pm SD) follow-up of 32 ± 16 months, there were 101 deaths in the defibrillator group (71 from cardiac causes) and 95 in the control group (72 from cardiac causes). The hazard ratio for death from any cause was 1.07 (95 percent confidence interval, 0.81 to 1.42; $P=0.64$). There was no statistically significant interaction between defibrillator therapy and any of 10 preselected base-line covariates.

Conclusions We found no evidence of improved survival among patients with coronary heart disease, a depressed left ventricular ejection fraction, and an abnormal signal-averaged electrocardiogram in whom a defibrillator was implanted prophylactically at the time of elective coronary bypass surgery. (N Engl J Med 1997;337:1569-75.)

©1997, Massachusetts Medical Society.

MANY cases of sudden death are caused by sustained ventricular tachyarrhythmias. Implantable cardioverter-defibrillators accurately detect and effectively terminate ventricular tachycardia or ventricular fibrillation in laboratory and clinical settings.^{1,2} Observational studies document low rates of sudden death among patients treated with implanted defibrillators,³ but only recently has a benefit in terms of overall mortality been demonstrated. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators report elsewhere in this issue of the *Journal*⁴ that patients with previous cardiac arrest or sustained ventricular tachycardia have lower mortality rates when treated with implanted cardioverter-defibrillators than when treated with either amiodarone or sotalol.

Patients who have out-of-hospital cardiac arrest have a very low probability of survival.^{5,6} Prevention or effective treatment of a first episode of cardiac arrest therefore remains an important goal. The prophylactic use of class I antiarrhythmic drugs in patients at high risk for sudden death after myocardial infarction increased mortality rates.⁷ The Multicenter Automatic Defibrillator Implantation Trial (MADIT) compared prophylaxis with an implanted defibrillator with conventional therapy (mostly amiodarone) in patients with coronary heart disease, left ventricular ejection fractions below 0.36, spontaneous unsustained ventricular tachycardia, and sustained ventricular tachycardia that could be induced during electrophysiologic study; overall mortality was strikingly reduced in the group randomly assigned to defibrillator therapy.⁸ Coronary bypass surgery also decreases the rate of sudden death and overall mor-

Address reprint requests to Dr. Bigger at the Data Coordinating Center, the CABG Patch Trial, PH 103-D, Columbia University, 630 W. 168th St., New York, NY 10032.

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

tality among patients with left ventricular dysfunction.^{9,10} In the Coronary Artery Bypass Graft (CABG) Patch Trial, we tested the hypothesis that the prophylactic implantation of a cardiac defibrillator at the time of bypass surgery would further improve long-term survival in patients at high risk for sudden death who were identified on the basis of a left ventricular ejection fraction below 0.36 and abnormalities on a signal-averaged electrocardiogram. We evaluated the effect on survival of the prophylactic implantation of a cardioverter-defibrillator in a group of patients among whom there were no significant differences in the frequency of therapy with antiarrhythmic drugs, beta-blocking drugs, thoracotomy, and cardiac revascularization.¹¹

METHODS

The trial was conducted at 37 clinical centers, 35 in the United States and 2 in Germany. The protocol was approved by the institutional review board at each clinical center.

Recruitment and Randomization

Enrollment in the trial began on August 14, 1990, with a pilot study.¹¹ In 1993, a full-scale study was launched in which the same inclusion and exclusion criteria were used. Patients of either sex who were scheduled for coronary bypass surgery were eligible if they were less than 80 years of age, had a left ventricular ejection fraction of less than 0.36, and had abnormalities on a signal-averaged electrocardiogram (duration of the filtered QRS complex, ≥ 114 msec; root-mean-square voltage in the terminal 40 msec of the QRS complex, $< 20 \mu\text{V}$; or duration of the terminal filtered QRS complex at $< 40 \mu\text{V}$, > 38 msec). A pilot study showed that patients with an abnormal signal-averaged electrocardiogram had a mortality rate in the two years after coronary bypass surgery that was twice as high as that among patients with a normal signal-averaged electrocardiogram.^{11,12} The signal-averaged electrocardiogram was the most feasible marker of arrhythmia for use in identifying patients for enrollment, given the short time between hospital admission and surgery.¹¹

Patients were excluded if they had a history of sustained ventricular tachycardia or fibrillation, diabetes mellitus with poor blood glucose control or recurrent infections, previous or concomitant aortic- or mitral-valve surgery, concomitant cerebrovascular surgery, a serum creatinine concentration greater than 3 mg per deciliter (265 mmol per liter), emergency coronary bypass surgery, a noncardiovascular condition with expected survival of less than two years, or an inability to attend follow-up visits.¹¹ Patients were enrolled in the trial after giving written informed consent.

Two independent randomization schedules were set up for each hospital, one for patients with left ventricular ejection fractions of 0.20 or less and another for patients with left ventricular ejection fractions from 0.21 to 0.35. Patients were randomly assigned to the defibrillator or control group within randomly permuted blocks. Randomization took place in the operating room after bypass grafting had been completed and patients were on partial cardiopulmonary bypass. The attending surgeon had the option not to have a patient randomly assigned to a treatment group if he or she thought that implanting and testing a defibrillator system in that patient was too risky.¹¹

Patients who were assigned to implanted-defibrillator therapy had an epicardial defibrillator system implanted and tested twice at 20 joules of energy. Guidant/CPI (St. Paul, Minn.) provided leads and pulse generators for the trial that were approved by the Food and Drug Administration. Most of the pulse generators implanted in the trial were committed devices (i.e., devices that deliver a shock even if the arrhythmia stops before the end of charging) that were not capable of storing electrograms.¹³ The trial

protocol prohibited the use of antiarrhythmic drugs for asymptomatic ventricular arrhythmia and specified that patients without contraindications should be treated with aspirin.

Follow-up

All variables listed on study forms were defined in a manual of operations. All qualifying signal-averaged electrocardiograms were interpreted a second time at the core study laboratory. Quality-control procedures for the measurement of the left ventricular ejection fraction have been described elsewhere.¹³ Patients were scheduled for follow-up visits every three months. Those who were eligible but not enrolled or enrolled but not randomly assigned to a study group were followed for 12 months to determine their vital status and rate of rehospitalization. For this report, we obtained each patient's vital status as of April 30, 1997.

Study Design and Statistical Analysis

The trial had a two-group parallel design with 900 patients randomly assigned with equal probability to prophylaxis with an implantable cardioverter-defibrillator or to no defibrillator therapy (the control group). The design ensured that the study had a power of more than 80 percent to detect a difference of 26 percent in mortality between the groups, a difference that corresponded to a 40 percent reduction in the hazard rate for death from all causes in the defibrillator group as compared with the control group, allowing for anticipated crossovers.¹¹ Details of the randomization scheme and adjustments that were made to sample size and follow-up have been published elsewhere.^{11,14} The nature of the intervention precluded the blinding of investigators or patients.

Accumulating data were reviewed by an independent Data and Safety Monitoring Board. Four interim analyses were scheduled and performed; they were based on sequential-monitoring procedures for the groups, with prospective stopping rules defined by a Lan-DeMets boundary with an O'Brien-Fleming spending function.^{15,16} Cumulative survival curves for each group were estimated by the Kaplan-Meier method.¹⁷ Cox proportional-hazards regression models were used to estimate hazard ratios (instantaneous relative risks).¹⁸ Log-rank tests, stratified according to ejection fraction and clinical center, were used to test hypotheses about differences between the groups. The secondary analyses reported here were also based on Cox models and examined survival after surgery and treatment interactions for prespecified subgroups. We selected 10 covariates prospectively and evaluated their interaction with the effect of implanted-defibrillator treatment on the risk of death: they were age, sex, presence or absence of heart failure, New York Heart Association (NYHA) functional class, left ventricular ejection fraction, presence or absence of diabetes mellitus, duration of the QRS complex (> 100 msec or ≤ 100 msec), use of angiotensin-converting-enzyme inhibitors, use of class I or class III antiarrhythmic drugs, and use of beta-adrenergic-blocking drugs. All analyses adhered to the intention-to-treat principle.

RESULTS

Study Sample and Comparison of the Treatment Groups

Five percent of the patients screened were excluded because they were 80 years of age or older and 74 percent because their left ventricular ejection fraction was 0.36 or greater.¹³ During screening, we identified 1422 eligible patients, of whom 1055 (74 percent) signed a consent form. Of the 1055 patients who were enrolled in the study, 900 were randomly assigned to the implanted-defibrillator group (446 patients) or to the control group (454 patients). The remaining 155 enrolled patients did not undergo randomization; 67 of them were found to meet one or more of the criteria for exclusion between enroll-

ment and the time of randomization; the remaining 88 were not randomly assigned to a group because intraoperative events made the implantation of a defibrillator too risky.¹³ The base-line characteristics of the two study groups were similar (Table 1).

Adherence to Protocol

During follow-up, there were 70 crossovers: 18 patients in the control group had a defibrillator implanted during the course of the trial; 12 patients assigned to implanted-defibrillator therapy never received a defibrillator because of death or hemodynamic instability in the operating room; and 40 patients in the defibrillator group had their implanted defibrillators removed, primarily because of infection (19 patients), because the implanted defibrillator reached the end of its service period and was not replaced (5), or because the patient requested removal (5). At 42 months, the cumulative rate of crossover to the control group was 10 percent, and the cumulative rate of crossover to the defibrillator group was less than 5 percent.

The use of cardiac drugs was similar in the two groups at the time of discharge after coronary bypass surgery, at three months, and one year after discharge from the hospital (Table 2). The rates of use of class I or III antiarrhythmic drugs and beta-blockers were similar in the two groups throughout the trial. Nearly all (93 percent) of 8854 scheduled follow-up visits occurred on schedule.

Decision to Report the Primary-End-Point Results

On April 2, 1997, the Data and Safety Monitoring Board took the last of four interim looks at the data on mortality, with 76 percent of the anticipated information on mortality available. The fourth interim analysis showed no difference between the defibrillator and control groups and a negligible chance that a difference would ever be found. Accordingly, the board recommended that data on the primary end point be reported as of April 30, 1997, while the trial continued to pursue its secondary objectives. On April 10, 1997, the director of the National Heart, Lung, and Blood Institute accepted the board's recommendation.

Effect of Implanted-Defibrillator Therapy on Mortality

There were 44 deaths in the first 30 days after randomization: 24 in the defibrillator group and 20 in the control group (P=0.60). The Kaplan–Meier cumulative-mortality curves for the two treatment groups show no long-term benefit of defibrillator therapy (Fig. 1). During an average (±SD) follow-up of 32±16 months, there were 101 deaths in the defibrillator group (71 from cardiac causes) and 95 in the control group (72 from cardiac causes). The hazard ratio from a Cox regression analysis that compared the risk of death per unit of time in the

TABLE 1. BASE-LINE CHARACTERISTICS OF 900 PATIENTS RANDOMLY ASSIGNED TO DEFIBRILLATOR THERAPY OR TO THE CONTROL GROUP.*

CHARACTERISTIC	DEFIBRILLATOR GROUP (N=446)	CONTROL GROUP (N=454)
Age (yr)	64±9	63±9
Sex (M/F)	386/60	373/81
Cardiovascular history (%)		
Cigarette smoking at any time	79	76
Angina pectoris	76	76
Myocardial infarction	83	82
≥2 Prior myocardial infarctions	30	33
Heart failure	51	49
Treatment for heart failure	49	47
NYHA functional class II or III	71	74
Treatment for hypertension	54	52
Diabetes mellitus	36	40
Diabetes treated with insulin	17	20
Treatment for ventricular arrhythmias	7	7
PTCA or atherectomy	11	11
CABG surgery	12	10
Electronic cardiac pacemaker	2	2
Heart rate (beats/min)	79±15	79±14
Systolic blood pressure (mm Hg)	126±19	123±19
Pulmonary rates (%)	20	25
S ₃ gallop (%)	14	11
Findings on 12-lead ECG (%)		
Duration of QRS complex >100 msec	71	74
Left bundle-branch block	10	12
Q-wave myocardial infarction	52	53
Left ventricular ejection fraction	0.27±0.06	0.27±0.06
Left ventricular end-diastolic pressure (mm Hg)	21±10	22±10
Findings on coronary angiography (%)		
One-vessel disease	8	9
Two-vessel disease	36	36
Three-vessel disease	55	55

*Plus-minus values are means ±SD. NYHA denotes New York Heart Association, PTCA percutaneous transluminal coronary angioplasty, CABG coronary-artery bypass graft, and ECG electrocardiogram. There was no significant difference between the two groups for any of the variables listed in this table.

defibrillator group with that in the control group was 1.07 (95 percent confidence interval, 0.81 to 1.42). A Cox regression model stratified according to clinical center and left ventricular ejection fraction yielded almost identical results (hazard ratio, 1.02; 95 percent confidence interval, 0.76 to 1.35). The hazard ratio (and 95 percent confidence interval) derived from a Cox model after adjustment for the 10 prespecified covariates was similar to the value obtained without adjustment, as was that for the period beginning 30 days after randomization (hazard ratio, 1.03; 95 percent confidence interval, 0.75 to 1.41).

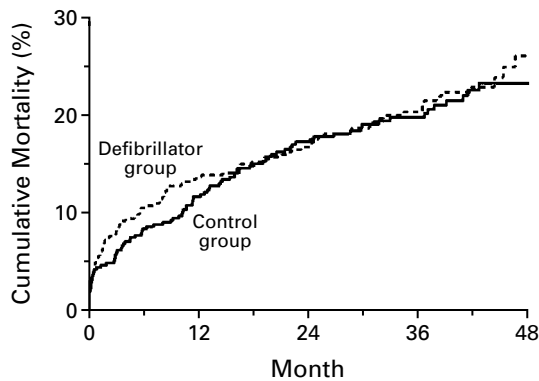
Secondary Analyses

Separate Cox regression analyses were performed for each of the 10 prespecified covariates, and no significant interaction with implanted-defibrillator therapy was found — that is, the hazard ratios for

TABLE 2. DRUG THERAPY AT HOSPITAL DISCHARGE, AT THREE MONTHS, AND ONE YEAR AFTER CORONARY-ARTERY BYPASS SURGERY.*

DRUG	At HOSPITAL DISCHARGE		At 3 Mo		At 1 Yr	
	DEFIBRILLATOR GROUP (N = 430)	CONTROL GROUP (N = 442)	DEFIBRILLATOR GROUP (N = 403)	CONTROL GROUP (N = 411)	DEFIBRILLATOR GROUP (N = 374)	CONTROL GROUP (N = 373)
	percentage of patients					
Oral antiarrhythmic drugs						
None	63.3	65.2	70.7	70.1	70.3	72.9
Class I drugs	16.7	12.0	8.2	5.8	7.5	4.8
Amiodarone	3.7	3.2	4.2	3.6	6.1	2.9
Sotalol	0.5	0.2	1.0	0.5	0.8	0.5
Beta-blockers (not sotalol)	17.9	24.0	16.4	21.7	16.0	19.8
Angiotensin-converting-enzyme inhibitors	54.7	53.8	60.3	63.7	64.2	67.8
Diuretics	57.2	47.1	61.3	57.2	64.7	55.2
Digitalis	68.6	64.5	70.7	62.5	70.6	60.1
Nitrates	8.1	8.1	10.9	12.2	15.8	16.9
Calcium-channel blockers	10.5	7.0	9.2	7.1	12.0	9.7
Antiplatelet drugs	82.8	85.1	78.2	83.7	79.1	82.6
Oral anticoagulants	15.3	14.7	20.6	16.8	20.1	16.6
Lipid-lowering drugs	9.5	8.4	12.9	13.4	23.0	23.3

*Data were not available for all patients.



Defibrillator group	446	384	313	213	61
Control group	454	399	308	199	57

Figure 1. Kaplan–Meier Analysis of the Probability of Death According to Study Group.

By April 30, 1997, 95 deaths had occurred in the control group and 101 in the defibrillator group. By four years of follow-up, the actuarial mortality was 24 percent in the control group and 27 percent in the group assigned to implanted-defibrillator therapy (P = 0.64). The numbers below the figure show the numbers of patients at risk.

the patients assigned to implanted-defibrillator therapy as compared with those in the control group were similar among subgroups defined according to the covariates.

Additional analyses were performed to examine the proportional-hazards assumption of the Cox model according to clinical center and left ventricular ejection fraction. The assumptions in the model remained valid in this stratified analysis.

The cumulative probability of a first implanted-defibrillator discharge in the group assigned to receive defibrillators is shown in Figure 2. Fifty-seven percent of the patients with an implanted defibrillator received a shock within the first two years after implantation.

Adverse Events

Significantly more postoperative infections were reported in the defibrillator group (Table 3), and significantly more myocardial infarctions were reported during long-term follow-up in the control group.

DISCUSSION

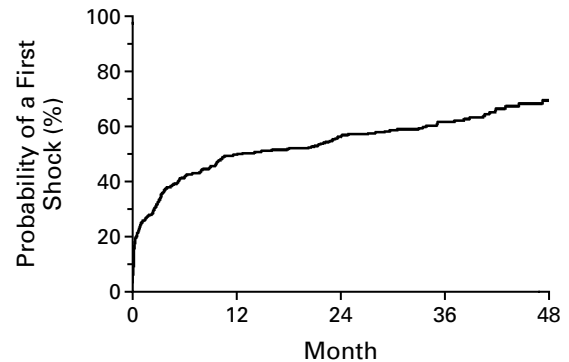
In this trial, we found that survival was not improved by the prophylactic implantation of a defibrillator at the time of elective coronary bypass surgery in patients at high risk for death from ventricular arrhythmia. We enrolled a high proportion of eligible patients sampled from a well-characterized population. The study had a simple design that compared implanted-defibrillator therapy with no preventive antiarrhythmic therapy after coronary bypass surgery. The study groups were well balanced with re-

spect to their base-line clinical characteristics, initial treatment of ischemia, and use of beta-adrenergic-blocking agents and antiarrhythmic drugs during follow-up. There was minimal crossover from one treatment group to the other.

Since ventricular tachyarrhythmias are the most common cause of sudden death,^{19,20} it was reasonable to postulate that the implanted defibrillator would improve survival among patients at high risk for sudden death. Previous studies have demonstrated that several factors predispose patients to sudden death, including a reduced left ventricular ejection fraction,²¹⁻²³ heart failure,²⁴⁻²⁷ and abnormalities on a signal-averaged electrocardiogram.²⁸⁻³⁰ Patients recruited into the trial constituted a high-risk sample with a 42-month mortality of 24 percent, about four times the mortality among all patients who undergo coronary bypass surgery. However, overall mortality was even higher in the AVID Trial and MADIT. The actuarial 24-month mortality was 32 percent in MADIT,⁸ 24 percent in the AVID Trial,⁴ and 18 percent in our trial.

It is unlikely that the almost identical mortality rates in the defibrillator and control groups in our trial represent a false negative result. The trial was designed with statistical power of more than 80 percent to detect a 26 percent treatment effect. The probability of observing a hazard-ratio point estimate of 1.0 or greater is about 3 percent if the risk of death was truly 26 percent lower in the defibrillator group than in the control group. At the mortality rates we observed, this trial had statistical power of more than 99 percent to detect an effect as large as that found in MADIT (a 54 percent reduction in the mortality rate).

The central questions raised by this trial, the AVID Trial, and MADIT are why mortality differed among the trials and why the group assigned to implanted-defibrillator therapy did not have lower mortality than the non-defibrillator group in our trial, as it did in the AVID Trial and MADIT. These differences must be due to differences in the patients at enrollment or differences in treatment during follow-up. The patients were similar in terms of age, sex, prevalence of heart failure, and average left ventricular ejection fraction in the three trials. One critical difference was the indicator of arrhythmia used to qualify patients for the study. The AVID Trial (a secondary-prevention trial) required spontaneous sustained ventricular tachyarrhythmias to enroll patients⁴; MADIT used inducible sustained ventricular tachyarrhythmias that were not suppressed by intravenous procainamide⁸; and we used abnormalities on a signal-averaged electrocardiogram (MADIT and our trial were primary-prevention trials). Comparison of the results of these trials suggests that the occurrence of sustained ventricular arrhythmias, either natural or induced, is a better marker than ab-



No. OF PATIENTS 428 195 142 78 26

Figure 2. Kaplan-Meier Analysis of the Probability of the Discharge of a First Shock from the Implanted Cardiac Defibrillator in the Defibrillator Group.

At one year, the actuarial incidence of first discharges was 50 percent; at two years, it was 57 percent.

TABLE 3. POSTOPERATIVE COMPLICATIONS AND ADVERSE EVENTS DURING LONG-TERM FOLLOW-UP.*

COMPLICATION OR ADVERSE EVENT	DEFIBRILLATOR GROUP (N = 446)	CONTROL GROUP (N = 454)
	percent	
Postoperative complications		
Myocardial infarction	4.0	3.5
Sustained ventricular tachycardia	5.8	6.8
Ventricular fibrillation	3.4	5.3
Bradycardia	2.9	4.4
Atrial fibrillation	22.9	20.7
Shock	9.2	7.5
New or more severe heart failure	15.7	12.6
Conduction defect	14.1	14.5
Residual central nervous system deficit	3.6	2.0
Bleeding treated with surgery	4.9	3.1
Postpericardiotomy syndrome	0.9	0.7
Deep sternal-wound infection	2.7	0.4†
Infection at wound or catheter site	12.3	5.9†
Pneumonia	8.5	4.0†
Other infection	6.3	3.3
Renal failure	6.7	4.8
Events during long-term follow-up		
Angina pectoris	27.0	27.5
Myocardial infarction	0.5	4.2†
New or worsening heart failure	42.5	42.5
Ventricular arrhythmias	19.4	14.3
Atrial fibrillation	14.7	10.1
Hospitalization	61.4	55.2
Repeat CABG surgery	0.0	0.7
PTCA or atherectomy	2.9	2.1
Permanent cardiac pacemaker	2.9	4.9

*CABG denotes coronary-artery bypass graft, and PTCA percutaneous transluminal coronary angioplasty.

†0.01 < P < 0.05, with no adjustment for multiple comparisons.

normalities on the signal-averaged electrocardiogram of a high risk of sudden death that might be prevented by the prophylactic implantation of a defibrillator. The failure of implanted-defibrillator therapy to improve survival in our trial, in contrast to the results in the AVID Trial and MADIT, implies that patients selected for the latter two trials had more episodes of arrhythmia in which death was preventable with implanted-defibrillator therapy.

Interestingly, the cumulative firing rate of the implanted defibrillators in this trial was similar to that in MADIT.⁸ Since most of the implanted defibrillators in both trials were committed, discharges could occur in response to atrial tachyarrhythmia or unsustained ventricular tachycardia, in addition to ventricular tachyarrhythmia. Because implanted defibrillators with stored electrograms were not marketed until late in the recruitment phase of our trial, only the last 40 defibrillators to be implanted were capable of storing electrograms. Data on the causes of implanted-defibrillator discharges in these 40 patients are being collected.

Differences in the treatment of ischemia may also have contributed to the differences in the response to implanted-defibrillator therapy among these trials. Patients in our trial underwent complete revascularization on the day of randomization. In the AVID Trial and MADIT, fewer patients underwent coronary bypass surgery or angioplasty, and revascularization was, on average, performed longer before recruitment for these trials. Some controlled data on patients with angina,^{9,10} along with uncontrolled experience in treating survivors of cardiac arrest³¹⁻³⁴ or recipients of implanted defibrillators,³⁵ suggest that coronary bypass surgery decreases the risk of sudden death. It is possible that ischemic triggering is important in the genesis of lethal ventricular tachyarrhythmias in coronary heart disease and that revascularization in our trial decreased the incidence of ischemically triggered arrhythmias far below the incidence in the other two trials. Also, it is possible that coronary bypass surgery beneficially altered the autonomic nervous input to the heart. The events committee of the Multicenter Post-Infarction Program estimated that 58 percent of deaths due to arrhythmia were preceded by acute myocardial ischemia,³⁶ and the Cardiac Arrhythmia Pilot Study estimated that proportion at 35 percent.³⁷ That mortality was lower in our trial than in MADIT and the AVID Trial, despite similar age, left ventricular ejection fraction, and rate of heart failure among the patients, is consistent with a significant benefit of cardiac revascularization in terms of survival.

Differences in drug therapy between the randomized groups could contribute in important ways to differences among the trials. Both the AVID Trial and MADIT compared implanted-defibrillator therapy with antiarrhythmic-drug therapy. It is possible

that implanted-defibrillator therapy actually had little benefit and that most of the apparent benefit was due to harmful effects of antiarrhythmic drugs. However, almost all patients in the antiarrhythmic-drug group in the AVID Trial and the majority (74 percent) in the conventional-therapy group in MADIT were treated with amiodarone, which other studies suggest has some benefit.³⁸ The rate of use of beta-blockers was substantially higher in the implanted-defibrillator groups in the AVID Trial and MADIT, a fact that may account for some of the reduced mortality in the implanted-defibrillator groups in these studies.³⁹ The rates of use of beta-blockers were not significantly different in the two groups in our trial.

The AVID Trial and MADIT have demonstrated the superiority of implanted-defibrillator therapy over antiarrhythmic-drug therapy in improving survival among patients at risk for sudden death due to ventricular tachyarrhythmias.^{4,8} The results of our trial tell us that not all patients who are at high risk for death from cardiac causes, as indicated by conventional base-line risk factors, will benefit from an implantable cardioverter-defibrillator.

Future research must be directed at the elucidation of the pathophysiology of sudden death from cardiac causes and at better identification of high-risk patients who will benefit from implantable defibrillators. In addition, the role of coronary bypass surgery in preventing sudden death needs to be clarified. For the present, electrophysiologic studies have a central role in identifying high-risk patients for whom the prophylactic implantation of a defibrillator is indicated.⁸ Both our results and the literature suggest that patients who present with sustained ventricular arrhythmias should be carefully evaluated and treated for myocardial ischemia.

Supported by grants (HL-48120 and HL-48159) from the National Heart, Lung, and Blood Institute, and by a grant from Guidant/CPI, St. Paul, Minn.

This article was based on data from version 1.0 of the CABG Patch Trial data base.

We are indebted to the patients who participated in this trial and to the attending physicians who referred their patients to this study.

APPENDIX

The following participated in the trial (asterisks indicate principal investigators): *Good Samaritan Hospital, Los Angeles* — D. Cannom,* G. Kay,* M. Jones, B. Firth, Y. Park; *Sequoia Hospital, Redwood City, Calif.* — R. Winkle,* V. Gaudiani,* P. Schmidt, J. Fujii; *University of Louisville, Louisville, Ky.* — I. Singer,* D. Slater,* A. Cicic, T. Martin; *University of Virginia, Charlottesville* — J. DiMarco,* I. Kron,* L. Shaw, S. Hennessy, S. Thompson; *Presbyterian-University of Pennsylvania Medical Center, Philadelphia* — L. Horowitz,* C. Gottlieb,* F. Marchlinski,* H. Kay,* D. Johnson,* R. Keeney, M.A. Roth, M. Deely; *Polyclinic Medical Center, Harrisburg, Pa.* — D. Scher,* C. Schaffer,* B. Tait; *Presbyterian Hospital in the City of New York, New York* — H. Spotnitz,* F. Livelli,* L. Pawlicky, N. Chalik, C. De Rosa; *Morristown Memorial Hospital, Morristown, N.J.* — G. Parr,* S. Winters,* L. Matriciano; *Sentara Norfolk General Hospital, Norfolk, Va.* — J. Herre,* L. Baker,* L. Klevan, K. Barackman; *University of Florida, Gainesville* — A. Curtis,* E. Staples,* C. Nelson, K. Worley; *Washington Hospital Center, Washington, D.C.* — E. Platin,* L. Mispireta,* S. Boyce,* J. Harrison, P. Bertheaud; *Cleveland Clinic Foundation, Cleveland* — J. Maloney,* G. Kidwell,* P. McCarthy,* S. Stein;

Kaiser Permanente Medical Center, Los Angeles — P. Mahrer,* T. Pfeffer,* N. Dullet, P. Jackinowicz, J. Child; *New England Medical Center Hospitals, Boston* — M. Estes III,* H. Rastegar,* D. Cliff; *Jewish Hospital at Washington University Medical Center, St. Louis* — J. Rottman,* R. Kleiger,* T. Wareing,* B. Daily,* C. Hoehn,* K. Anderson; *Hermann Hospital, University of Texas Medical School, Houston* — G. Naccarelli,* A. Dougherty,* M. Sweeney,* D. Wilson, C. Wainwright; *Medical College of Virginia, Richmond* — M. Wood,* R. Damiano,* L. Arnold, C. Dietrich; *Loyola Medical Center, Maywood, Ill.* — B. Olshansky,* D. Wilber,* B. Blakeman,* N. Perovic, R. Picchi Szocka, E. Galbraith, A. Florides; *East Carolina University School of Medicine, Greenville, N.C.* — H. DeAntonio,* J. Williams,* V. Alexander,* C. Grill, D. Brewer, M. Mann; *St. Joseph's Hospital, Atlanta* — H. Kopelman,* K. Thomas,* J. Shaftel, A. Thompson; *Westfälische Wilhelms-Universität Münster, Münster, Germany* — G. Breithardt,* H. Scheld,* M. Block,* D. Bocker, R. Gradua; *Ruprecht-Karls-Universität Heidelberg, Heidelberg, Germany* — J. Brachmann,* W. Saggau,* S. Hagl, K. Freigang; *LDS Hospital, Salt Lake City* — J. Anderson,* R. Millar,* M. Jacobsen, J. Jerman; *Florida Hospital, Orlando* — K. Schwartz,* C. Stowe,* B. Sickinger, D. Dukes, P. Carlson, N. Granger; *Northwest Cardiovascular Research Institute, Spokane, Wash.* — H. Goldberg,* W. Coleman,* M. Fisher, K. Brooks, L. Beamer; *Nebraska Heart Institute, Lincoln* — S. Krueger,* E. Raines,* B. Olander, C. Orosco; *Emory University System of Health Care, Atlanta* — P. Walter,* E. Jones,* J. Burnette; *Minneapolis Heart Institute, Minneapolis* — R. Hauser,* K. Arom,* P. Vatterott, C. Johnson, K. Hanson, T. Haas, S. Casey, P. Baldwin; *Bowman Gray School of Medicine, Winston-Salem, N.C.* — D. Fitzgerald,* J. Hammon, Jr.,* N. Sherrill; *University of Nebraska Medical Center, Omaha* — J. Windle,* T. Galbraith,* L. Smith, C. Reckling; *Brigham and Women's Hospital, Boston* — P. Friedman,* G. Couper,* J. Shea, M. Swat; *Baystate Medical Center, Springfield, Mass.* — R. Engelman,* J. Cook,* C. Gregory; *Buffalo General Hospital, Buffalo, N.Y.* — S. Raza,* S. Zador,* K. Hoelzl; *Hospital of Saint Raphael, New Haven, Conn.* — M. Schoenfeld,* M. Marieb,* V. Khachanc,* E. Matthews, P. Garofolo; *Loma Linda University Medical Center, Loma Linda, Calif.* — V. Torres,* S. Gundry,* M. Platt,* V. Bishop; *University of Chicago, Chicago* — D. Wilber,* R. Karp,* B. Sexton, M. Stasi; *Oregon Health Sciences University, Portland* — J. Kron,* A. Cobanoglu,* G. Ott,* G. Heywood; *Data Coordinating Center, Columbia University* — T. Bigger,* J. Fleiss,* S. Bigger, D. Bloomfield, R. Bornholdt, J. Campion, N. DiGiorgio, M. Gallagher, E. Koski, A. Kosok, B. Levin, G. McNeil, P. Meier, L. Morales, P. Namerow, M. Parides, L. Rolnitzky, L. Sosa, R. Steinman; *Signal-Averaged Electrocardiographic Reading Center, Philadelphia Heart Institute* — C. Gottlieb,* L. Cabrey; *Holter Core Laboratory, Columbia University* — T. Bigger,* D. Bloomfield, R. Bornholdt, G. Glembocki, P. Gonzalez, R. Steinman; *Data and Safety Monitoring Board* — D. Echt, C. Furberg (chair), G. Lan, J. Morganroth; *End-Point Review Committee* — L. Greene, M. Hodges, B. Pitt (chair); *National Heart, Lung, and Blood Institute* — Debra Egan, Michael Domanski.

REFERENCES

1. Mirowski M, Reid PR, Mower MM, et al. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *N Engl J Med* 1980;303:322-4.
2. Winkle RA, Mead RH, Ruder MA, et al. Long-term outcome with the automatic implantable cardioverter-defibrillator. *J Am Coll Cardiol* 1989; 13:1353-61.
3. Nisam S, Kaye SA, Mower MM, Hull M. AICD automatic cardioverter defibrillator clinical update: 14 years experience in over 34,000 patients. *Pacing Clin Electrophysiol* 1995;18:142-7.
4. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576-83.
5. Eisenberg MS, Pantridge JF, Cobb LA, Geddes LS. The revolution and evolution of prehospital cardiac care. *Arch Intern Med* 1996;156:1611-9.
6. Lombardi G, Gallagher J, Gennis P. Outcome of out-of-hospital cardiac arrest in New York City: the Pre-Hospital Arrest Survival Evaluation (PHASE) Study. *JAMA* 1994;271:678-83.
7. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. *JAMA* 1993;270:1589-95.
8. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary artery disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;335:1933-40.
9. Holmes DR Jr, Davis KB, Mock MB, et al. The effect of medical and surgical therapy on subsequent sudden cardiac death in patients with coronary artery disease: a report from the Coronary Artery Surgery Study. *Circulation* 1986;73:1254-63.
10. Varnauskas E, European Coronary Surgery Study Group. Survival, myocardial infarction, and employment status in a prospective randomized study of coronary bypass surgery. *Circulation* 1985;72:Suppl V-V-90-V-101.
11. The CABG Patch Trial Investigators and Coordinators. The Coronary Artery Bypass Graft (CABG) Patch Trial. *Prog Cardiovasc Dis* 1993;36:97-114.

12. Gottlieb CD, Bigger JT Jr, Steinman RC, Rolnitzky LM. Signal averaged ECG predicts death after CABG surgery. *Circulation* 1995;92:Suppl I:I-406. abstract.
13. Curtis AB, Cannom DS, Bigger JT Jr, et al. Baseline characteristics of patients in the Coronary Artery Bypass Graft (CABG) Patch Trial. *Am Heart J* (in press).
14. Bigger JT Jr, Parides MK, Meier P, Levin B, Rolnitzky LM. Changes in sample size and length of follow-up to maintain power in the CABG Patch Trial. *Control Clin Trials* (in press).
15. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70:659-63.
16. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. The early termination of clinical trials: causes, consequences, and control: with special reference to trials in the field of arrhythmias and sudden death. *Circulation* 1994;89:2892-907.
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
18. Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34: 187-220.
19. Baum RS, Alvarez H III, Cobb LA. Survival after resuscitations from out-of-hospital ventricular fibrillation. *Circulation* 1974;50:1231-5.
20. Bayes de Luna A, Coumel PH, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmias on the basis of data from 157 cases. *Am Heart J* 1989;117:151-9.
21. Bigger JT Jr, Fleiss JL, Kleiger RE, Miller JP, Rolnitzky LM. Multicenter Post-Infarction Research Group. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 1984;69:250-8.
22. Mukharji J, Rude RE, Poole WK, et al. Risk factors for sudden death after acute myocardial infarction: two-year follow-up. *Am J Cardiol* 1984; 54:31-6.
23. Ahnve S, Gilpin E, Henning H, Curtis G, Collins D, Ross J Jr. Limitations and advantages of the ejection fraction for defining high risk after acute myocardial infarction. *Am J Cardiol* 1986;58:872-8. [Erratum, *Am J Cardiol* 1987;59:A12.]
24. Packer M. Sudden unexpected death in patients with congestive heart failure: a second frontier. *Circulation* 1985;72:681-5.
25. Bigger JT Jr. Why patients with congestive heart failure die: arrhythmias and sudden cardiac death. *Circulation* 1987;75:Suppl IV:IV-28-IV-35.
26. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303-10.
27. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
28. Steinberg JS, Regan A, Sciacca RR, Bigger JT Jr, Fleiss JL. Predicting arrhythmic events after myocardial infarction using the signal-averaged electrocardiogram. *Am J Cardiol* 1992;69:13-21.
29. el-Sherif N, Denes P, Katz R, et al. Definition of the best prediction criteria of the time domain signal-averaged electrocardiogram for serious arrhythmic events in the postinfarction period: the Cardiac Arrhythmia Suppression Trial/Signal-Averaged Electrocardiogram (CAST/SAECG) Substudy Investigators. *J Am Coll Cardiol* 1995;25:908-14.
30. Signal-averaged electrocardiography. *J Am Coll Cardiol* 1996;27:238-49.
31. O'Rourke RA. Role of myocardial revascularization in sudden cardiac death. *Circulation* 1992;85:Suppl I:I-112-I-117.
32. Kelly P, Ruskin JN, Vlahakes GJ, Buckley MJ Jr, Freeman CS, Garan H. Surgical coronary revascularization in survivors of prehospital cardiac arrest: its effect on inducible ventricular arrhythmias and long-term survival. *J Am Coll Cardiol* 1990;15:267-73.
33. Kron IL, Lerman BB, Haines DE, Flanagan TL, DiMarco JP. Coronary artery bypass grafting in patients with ventricular fibrillation. *Ann Thorac Surg* 1989;48:85-9.
34. Every NR, Fahrenbruch CE, Hallstrom AP, Weaver WD, Cobb LA. Influence of coronary bypass surgery on subsequent outcome of patients resuscitated from out of hospital cardiac arrest. *J Am Coll Cardiol* 1992;19:1435-9.
35. Levine JH, Mellits ED, Baumgardner RA, et al. Predictors of first discharge and subsequent survival in patients with automatic implantable cardioverter-defibrillators. *Circulation* 1991;84:558-66.
36. Marcus FI, Cobb LA, Edwards JE, et al. Mechanism of death and prevalence of myocardial ischemic symptoms in the terminal event after acute myocardial infarction. *Am J Cardiol* 1988;61:8-15.
37. Greene HL, Richardson DW, Barker AH, et al. Classification of deaths after myocardial infarction as arrhythmic or nonarrhythmic (the Cardiac Arrhythmia Pilot Study). *Am J Cardiol* 1989;63:1-6.
38. Amiodarone Trials Meta-Analysis Investigators. The effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure. *Lancet* 1997;350:1417-24.
39. Pitt B. The role of β -adrenergic blocking agents in preventing sudden cardiac death. *Circulation* 1992;85:Suppl I:I-107-I-111.