

A RANDOMIZED STUDY OF THE PREVENTION OF SUDDEN DEATH IN PATIENTS WITH CORONARY ARTERY DISEASE

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ABSTRACT

Background Empirical antiarrhythmic therapy has not reduced mortality among patients with coronary artery disease and asymptomatic ventricular arrhythmias. Previous studies have suggested that antiarrhythmic therapy guided by electrophysiologic testing might reduce the risk of sudden death.

Methods We conducted a randomized, controlled trial to test the hypothesis that electrophysiologically guided antiarrhythmic therapy would reduce the risk of sudden death among patients with coronary artery disease, a left ventricular ejection fraction of 40 percent or less, and asymptomatic, unsustained ventricular tachycardia. Patients in whom sustained ventricular tachycardia were induced by programmed stimulation were randomly assigned to receive either antiarrhythmic therapy, including drugs and implantable defibrillators, as indicated by the results of electrophysiologic testing, or no antiarrhythmic therapy. Angiotensin-converting-enzyme inhibitors and beta-adrenergic-blocking agents were administered if the patients could tolerate them.

Results A total of 704 patients with inducible, sustained ventricular tachycardia were randomly assigned to treatment groups. Five-year Kaplan-Meier estimates of the incidence of the primary end point of cardiac arrest or death from arrhythmia were 25 percent among those receiving electrophysiologically guided therapy and 32 percent among the patients assigned to no antiarrhythmic therapy (relative risk, 0.73; 95 percent confidence interval, 0.53 to 0.99), representing a reduction in risk of 27 percent. The five-year estimates of overall mortality were 42 percent and 48 percent, respectively (relative risk, 0.80; 95 percent confidence interval, 0.64 to 1.01). The risk of cardiac arrest or death from arrhythmia among the patients who received treatment with defibrillators was significantly lower than that among the patients discharged without receiving defibrillator treatment (relative risk, 0.24; 95 percent confidence interval, 0.13 to 0.45; $P < 0.001$). Neither the rate of cardiac arrest or death from arrhythmia nor the overall mortality rate was lower among the patients assigned to electrophysiologically guided therapy and treated with antiarrhythmic drugs than among the patients assigned to no antiarrhythmic therapy.

Conclusions Electrophysiologically guided antiarrhythmic therapy with implantable defibrillators, but not with antiarrhythmic drugs, reduces the risk of sudden death in high-risk patients with coronary disease. (N Engl J Med 1999;341:1882-90.)

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DESPITE recent decreases in the rates of death from cardiovascular disease, mortality after discharge from the hospital remains high among survivors of acute myocardial infarction who have substantial left ventricular dysfunction. Among such persons, the 6-to-12-month mortality is 10 percent or higher and the 4-to-5-year mortality is 20 percent or higher.¹⁻⁴ Sudden death accounts for approximately one third of the late mortality.^{2,5} The appropriate treatment for survivors of out-of-hospital cardiac arrest has been clarified by recent study results.⁶ However, only 2 to 30 percent of persons who have cardiac arrest survive.^{5,7-9} Thus, primary prevention of cardiac arrest is imperative.

The Multicenter Unsustained Tachycardia Trial was initiated in 1989 to test the hypothesis that antiarrhythmic therapy guided by electrophysiologic testing can reduce the risks of sudden death and cardiac arrest among patients with coronary artery disease, left ventricular dysfunction, and spontaneous unsustained ventricular tachycardia.

METHODS

Patients

Patients at 85 study sites in the United States and Canada were identified as having coronary artery disease, a left ventricular ejection fraction of 40 percent or less, and asymptomatic unsustained ventricular tachycardia (lasting for three or more beats). The qualifying unsustained tachycardia had to occur six months or less before enrollment, and four or more days after the most recent myocardial infarction or revascularization procedure. Written informed consent was obtained from all the patients before randomization. The institutional review board at each study site approved the protocol.

Either cardiac catheterization or exercise testing within six months before enrollment was required. If exercise-induced ischemia was detected, appropriate treatment was required before enrollment. Patients with a history of syncope or sustained ventricular tachycardia or fibrillation more than 48 hours after the onset of myocardial infarction were excluded, as were patients whose unsustained ventricular tachycardia occurred only in the setting of acute ischemia, metabolic disorders, or drug toxicity.

Protocol

A detailed description of the study protocol has been published previously.¹⁰ An electrophysiologic study that included the deliv-

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*Other participants in the trial are listed in the Appendix.

ery of one to three extrastimuli and burst pacing at two right ventricular sites during two paced cycle lengths was performed in the absence of antiarrhythmic drugs. Stimulation was stopped after sustained ventricular tachyarrhythmia had been reproducibly induced.

Patients with sustained, monomorphic ventricular tachycardia induced by any method of stimulation and those with sustained polymorphic ventricular tachycardia (including ventricular flutter and fibrillation) induced by one or two extrastimuli were randomly assigned in equal numbers to receive either antiarrhythmic therapy guided by the results of electrophysiologic testing or no antiarrhythmic therapy. Patients who refused to undergo randomization were also followed. Patients in whom no sustained tachyarrhythmia was induced at the base-line study were followed without antiarrhythmic therapy in a registry. Treatment with beta-adrenergic-blocking agents and angiotensin-converting-enzyme inhibitors was strongly recommended.

Patients assigned to electrophysiologically guided therapy underwent serial drug testing with antiarrhythmic drugs approved by the Food and Drug Administration.¹⁰ Drugs were assigned randomly, with the exception of amiodarone. Amiodarone could be tested at the discretion of the investigator in patients in whom at least two tests had failed. After four to five half-lives (approximately two to three days; amiodarone was tested after at least one week of loading), programmed stimulation was repeated. If fewer than 15 complexes were induced, long-term therapy with that regimen was permissible. If no drug regimen could be found that rendered the tachyarrhythmia noninducible, the investigator could discharge the patient with a drug regimen that was associated with hemodynamic stability during induced tachycardia.¹⁰ No empirical antiarrhythmic-drug therapy was used.

Implantation of a defibrillator could be recommended after at least one unsuccessful drug test. This aspect of the protocol was changed during the course of the trial in order to reflect changes in practice. The protocol initially required that three or more drug tests had to fail in patients assigned to receive electrophysiologically guided antiarrhythmic therapy before a defibrillator could be implanted. After 358 patients with inducible tachyarrhythmia had been enrolled, the protocol was changed, allowing implantation of a defibrillator after one or more unsuccessful drug trials. Patients who declined to undergo implantation of a defibrillator were discharged receiving no antiarrhythmic drugs. Patients were evaluated one month after discharge and every three months thereafter.

End Points

The primary end point was cardiac arrest or death from arrhythmia. Secondary end points included death from all causes, death from cardiac causes, and spontaneous, sustained ventricular tachycardia. A modified Hinkle-Thaler system was used to classify deaths.¹¹ Deaths from arrhythmia included unwitnessed deaths, witnessed instantaneous deaths, nonsudden deaths due to incessant tachycardia, deaths considered to be sequelae of cardiac arrest, deaths caused by the toxic effects of antiarrhythmic drugs, and deaths resulting from complications of implanted defibrillators. The deaths of patients with end-stage heart failure or cardiogenic shock were not classified as deaths from arrhythmia. Cardiac arrest was defined as sudden loss of consciousness requiring direct-current countershock to restore consciousness or a stable blood pressure and rhythm. Narrative descriptions of events and hospital records were edited by the data-coordinating center to ensure that the outcomes were classified without knowledge of treatment assignment or whether tachycardia could be induced in any of the patients.

Statistical Analysis

On the basis of previous reports, we anticipated a two-year rate of arrhythmic events of 15 to 20 percent in the group assigned to no antiarrhythmic therapy and a reduction of at least 33 percent in the rate of events in the group assigned to electrophysiologically guided therapy. Using these rates and an alpha level of 0.05, we determined that a total of 900 patients with inducible, sustained tachyarrhythmia would provide the study with more than 80 percent power to detect an event rate of 15 percent and more

than 90 percent power to detect a rate of 20 percent. We encountered considerable difficulty in meeting the targeted sample size, and the enrollment of patients was stopped in October 1996, after 704 patients with inducible, sustained ventricular tachyarrhythmia had undergone randomization. The patients were to be followed for at least two years.

Treatment groups were compared in an intention-to-treat analysis, and all statistical tests were two-tailed. Cumulative event rates were calculated by the Kaplan-Meier method, with the time to the first event as the outcome variable.¹² The significance of the difference between treatment groups was assessed with the log-rank test.¹³ Relative risk was expressed as a hazard ratio derived from the Cox proportional-hazards model.¹⁴ Interim analyses of the data were performed at regular intervals according to standard practices of the National Institutes of Health and were reviewed by an independent data and safety monitoring board. Comparisons of major outcomes in the interim analyses were monitored with two-sided, symmetric O'Brien-Fleming boundaries generated with the Lan-DeMets spending-function approach to group-sequential testing.^{15,16}

To compare the outcomes of the patients assigned to electrophysiologically guided therapy who received defibrillators with the outcomes of those who did not, we performed observational comparisons. The outcomes of the patients who received defibrillators within 90 days after enrollment and before the occurrence of any arrhythmic event were compared with the outcomes of patients who were not given defibrillators before that time.

In addition, covariate-adjusted assessments of the effect of defibrillator therapy on major outcomes were performed with the Cox proportional-hazards regression model, in which receipt of a defibrillator was treated as a time-dependent covariate. Covariates examined in these analyses included age; sex; race; the date of enrollment (relative to the start of the trial); whether or not the patient had a prior myocardial infarction, prior bypass surgery, prior angioplasty, palpitations, or angina; ejection fraction; and the use or nonuse of digitalis, beta-blockers, and angiotensin-converting-enzyme inhibitors at base line.

RESULTS

A total of 2202 patients were enrolled from November 1, 1990, to October 31, 1996. This total included 767 patients with inducible, sustained ventricular tachyarrhythmia, of whom 704 agreed to undergo randomization and 63 refused but were followed in the registry, and 1435 patients without inducible tachyarrhythmia (as defined by the protocol). Of the 704 patients who underwent randomization, 351 were assigned to receive electrophysiologically guided therapy and 353 were assigned to receive no antiarrhythmic therapy. Among the patients assigned to no antiarrhythmic therapy, 96 percent received no therapy. Complications of the base-line electrophysiologic study occurred in five of the patients with inducible, sustained ventricular tachyarrhythmia (0.7 percent); none were fatal. The base-line characteristics of the patients in the two groups were similar (Table 1). The median ejection fraction was 29 percent in the group assigned to no antiarrhythmic therapy and 30 percent in the group assigned to electrophysiologically guided therapy.

Nonantiarrhythmic Medical Therapy

After enrollment, 40 percent of all 704 patients were discharged from the hospital receiving beta-adrenergic-blocking agents. Use of beta-blockers was

TABLE 1. CLINICAL CHARACTERISTICS OF THE PATIENTS AT BASE LINE.*

VARIABLE	ELECTRO-PHYSIOLOGICALLY GUIDED THERAPY (N=351)	No ANTIARRHYTHMIC THERAPY (N=353)
Median age (yr)	67 (60–72)	66 (58–72)
Male sex (%)	90	90
White race (%)	90	86
Median ejection fraction (%)	30 (20–35)	29 (22–35)
History of myocardial infarction (%)	96	93
Time between most recent myocardial infarction and enrollment (%)		
≤1 mo	16	18
≤1 yr	40	38
>3 yr	49	52
Prior coronary-bypass grafting (%)	56	56
Uniform, sustained ventricular tachycardia induced at base line (%)	88	92
Median cycle length of uniform ventricular tachycardia induced at base line (msec)	245 (227–265)	250 (230–272)
NYHA class (%)†		
I	37	36
II	39	38
III	24	25
IV	0	0
Medications at hospital discharge (%)		
Beta-blockers	29‡	51
Angiotensin-converting-enzyme inhibitors	72	77
Aspirin	64	63
Digitalis	52	53
Diuretic agent	58	58

*Values in parentheses are 25th and 75th percentiles; categorical variables are presented as percentages.

†Data were available for 59 percent of the patients in each treatment group. Because of rounding, not all percentages total 100. NYHA denotes New York Heart Association.

‡P=0.001 for the comparison with the patients assigned to no antiarrhythmic therapy.

more frequent among the patients assigned to no antiarrhythmic therapy (Table 1). The use of antiarrhythmic agents with beta-blocking properties accounted for much of the disparity in the use of beta-blockers. In addition to the 29 percent of patients who were taking “pure” beta-blockers in the group assigned to electrophysiologically guided therapy, 23 percent were taking antiarrhythmic agents with beta-blocking properties. During follow-up, an additional 11 percent of the patients assigned to electrophysiologically guided therapy and 2 percent of those assigned to no antiarrhythmic therapy were being treated with beta-blockers. The rate of use of other cardiac medications was similar in the two groups.

Antiarrhythmic Therapy

Among the 351 patients assigned to electrophysiologically guided therapy, 158 (45 percent) were discharged with antiarrhythmic drugs (class I agents, 26

percent; amiodarone, 10 percent; and sotalol, 9 percent) and 161 (46 percent) were given defibrillators. Six patients (2 percent) died while they were in the hospital. Seven percent of the patients in this group refused antiarrhythmic therapy at various points during the study. After discharge, 17 percent of the patients assigned to electrophysiologically guided therapy had a change in the type of drug therapy they were receiving and 12 percent switched from antiarrhythmic drugs to a defibrillator. One patient treated with a defibrillator died as a direct result of an infection complicating the revision of the lead system 18 months after the initial implantation.

Follow-up

Most of the patients adhered to the therapy to which they had been assigned. At the last follow-up, 305 patients (87 percent) assigned to electrophysiologically guided therapy were receiving treatment. One hundred three patients (29 percent) were receiving antiarrhythmic drugs, and 202 patients (58 percent) received defibrillators. Among the patients assigned to no antiarrhythmic therapy, 3 percent had received a defibrillator by the last follow-up and 10 percent had been given antiarrhythmic drugs without having had cardiac arrest, sustained ventricular tachycardia, or syncope. Atrial fibrillation was the indication for antiarrhythmic drugs in 57 percent of these cases.

The median duration of follow-up was 39 months. All but four patients were followed for two years or more, and all but two events could be classified on the basis of the information that was available. Among the patients assigned to no antiarrhythmic therapy, the two-year rate of cardiac arrest or death from arrhythmia was 18 percent and the five-year rate was 32 percent. The corresponding rates for the patients assigned to electrophysiologically guided therapy were 12 percent and 25 percent ($P=0.04$ for the five-year rates; relative risk, 0.73; 95 percent confidence interval, 0.53 to 0.99) (Fig. 1). The overall mortality rates after two years and after five years were 28 percent and 48 percent, respectively, for the patients assigned to no antiarrhythmic therapy, as compared with 22 percent and 42 percent for those assigned to electrophysiologically guided therapy ($P=0.06$ for the five-year rates; relative risk, 0.80; 95 percent confidence interval, 0.64 to 1.01) (Fig. 2). At five years, the rate of death from cardiac causes was significantly higher among the patients assigned to no antiarrhythmic therapy than among those assigned to electrophysiologically guided therapy (40 percent vs. 34 percent, $P=0.05$). There was no significant difference in the incidence of spontaneous, sustained ventricular tachycardia between the two groups (21 percent among the patients assigned to no antiarrhythmic therapy and 20 percent among those assigned to electrophysiologically guided therapy, $P=0.90$).

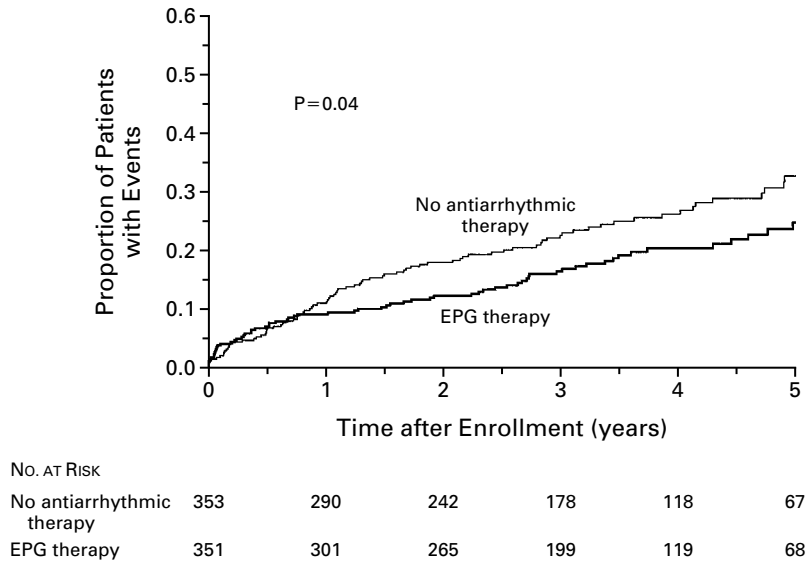


Figure 1. Kaplan–Meier Estimates of the Rates of Cardiac Arrest or Death from Arrhythmia. EPG denotes electrophysiologically guided.

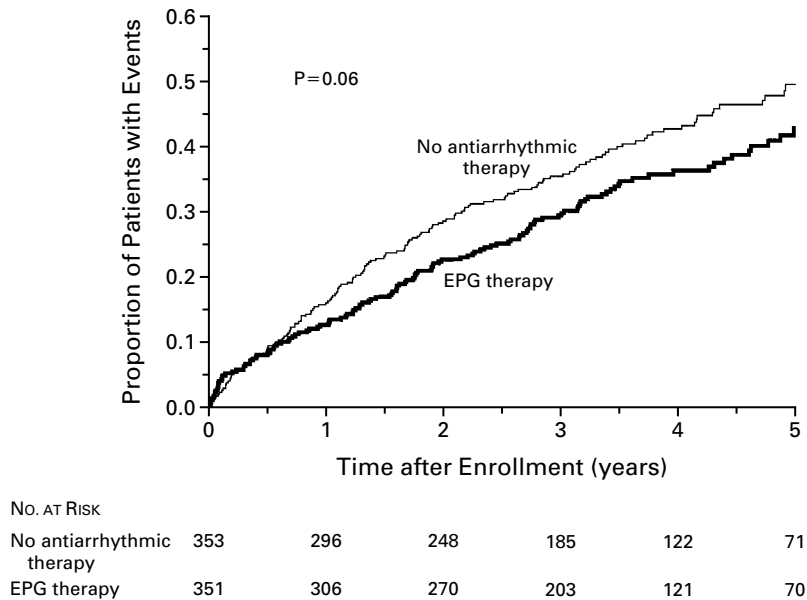


Figure 2. Kaplan–Meier Estimates of the Rates of Death from All Causes. EPG denotes electrophysiologically guided.

The lower rates of arrhythmic events among the patients assigned to electrophysiologically guided therapy were largely attributable to the use of defibrillators. The five-year rate of cardiac arrest or death from arrhythmia was 9 percent among the patients assigned to electrophysiologically guided therapy who

received a defibrillator, as compared with 37 percent among those in this group who did not receive a defibrillator ($P < 0.001$) (Fig. 3). The overall mortality rates at five years were 24 percent among the patients who received defibrillators and 55 percent among those who did not (Fig. 4). The survival benefit as-

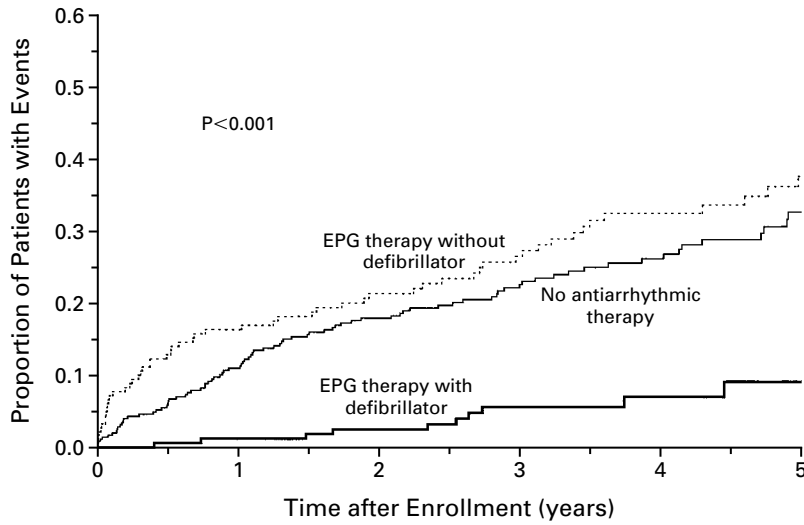


Figure 3. Kaplan–Meier Estimates of the Rates of Cardiac Arrest or Death from Arrhythmia According to Whether the Patients Received Treatment with a Defibrillator.

The P value refers to two comparisons: between the patients in the group assigned to electrophysiologically guided (EPG) therapy who received treatment with a defibrillator and those who did not receive such treatment, and between the patients assigned to electrophysiologically guided therapy who received treatment with a defibrillator and those assigned to no antiarrhythmic therapy.

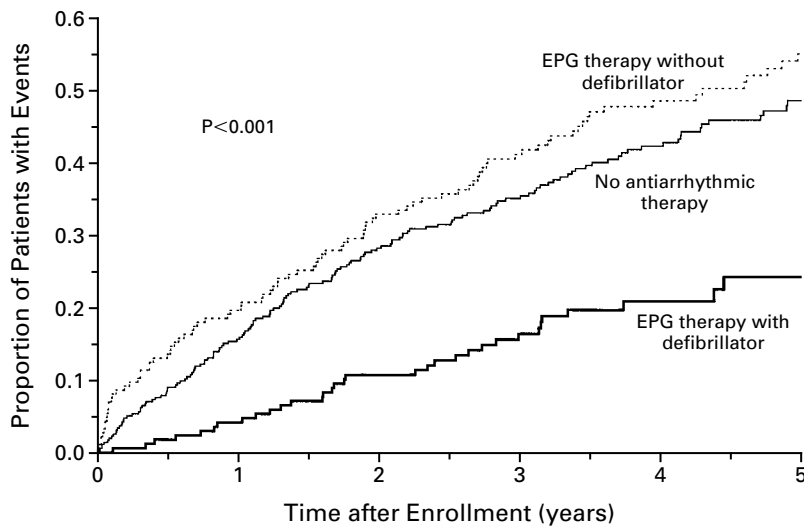


Figure 4. Kaplan–Meier Estimates of the Rates of Overall Mortality According to Whether the Patients Received Treatment with a Defibrillator.

The P value refers to two comparisons: between the patients in the group assigned to electrophysiologically guided (EPG) therapy who received treatment with a defibrillator and those who did not receive such treatment, and between the patients assigned to electrophysiologically guided therapy who received treatment with a defibrillator and those assigned to no antiarrhythmic therapy.

TABLE 2. EFFECTS OF DEFIBRILLATOR THERAPY.*

END POINT	NO ANTIARRHYTHMIC THERAPY	ELECTROPHYSIOLOGICALLY GUIDED THERAPY WITH DEFIBRILLATOR	ELECTROPHYSIOLOGICALLY GUIDED THERAPY WITHOUT DEFIBRILLATOR	RELATIVE RISK OF EVENT WITH DEFIBRILLATOR THERAPY (95% CI)			
				AS COMPARED WITH ELECTROPHYSIOLOGICALLY GUIDED THERAPY WITHOUT DEFIBRILLATOR		AS COMPARED WITH NO ANTIARRHYTHMIC THERAPY	
				<i>Unadjusted</i>	<i>Adjusted</i>	<i>Unadjusted</i>	<i>Adjusted</i>
		no. of events					
Cardiac arrest or death from arrhythmia	90	12	56	0.24 (0.13–0.43)	0.24 (0.13–0.45)	0.28 (0.16–0.49)	0.27 (0.15–0.47)
Death from all causes	158	35	97	0.42 (0.29–0.61)	0.40 (0.27–0.59)	0.49 (0.35–0.69)	0.45 (0.32–0.63)

*P<0.001 for both unadjusted and adjusted estimates of relative risk for each end point. CI denotes confidence interval.

sociated with defibrillator treatment remained significant (P<0.001) after Cox regression analysis, in which adjustments were made for all available prognostic clinical factors (Table 2). As compared with the patients who were assigned to electrophysiologically guided therapy and who did not receive defibrillators, those who received such treatment had an adjusted relative risk of arrhythmic events of 0.24 (95 percent confidence interval, 0.13 to 0.45), and an adjusted relative risk of overall mortality of 0.40 (95 percent confidence interval, 0.27 to 0.59) (Table 2).

DISCUSSION

We found that the risk of cardiac arrest or sudden death was substantial among patients with coronary artery disease, a left ventricular ejection fraction of 40 percent or less, spontaneous, unsustained ventricular tachycardia, and sustained tachyarrhythmia induced by programmed stimulation. Antiarrhythmic therapy guided by the results of electrophysiologic testing led to an absolute reduction in the risk of cardiac arrest or death from arrhythmia of 7 percent after five years of follow-up. The survival benefit associated with electrophysiologically guided therapy was due solely to the use of defibrillators, not to antiarrhythmic drugs. Defibrillators not only reduced the risks of cardiac arrest and sudden death from arrhythmia, but also improved overall survival.

The study included a diverse group of patients from many study sites throughout the United States and Canada, including private practices not affiliated with a university, medical schools, and Veterans Affairs hospitals. The electrocardiographic characteristics of the patients with unsustained ventricular tachycardia were virtually identical to those of patients enrolled in the Cardiac Arrhythmia Suppression Trial.^{17,18} Thus, in this regard, the patients enrolled in our trial were representative of all patients with unsustained ventricular tachycardia after myocardial infarction.

Electrophysiologic testing has been studied to predict the risk of sudden death in patients with a recent myocardial infarction and in patients who have unsustained ventricular tachycardia after myocardial infarction. Electrophysiologic testing after a recent myocardial infarction has been reported to induce tachyarrhythmia in 9 to 20 percent of patients.¹⁹⁻²¹ Arrhythmic events have occurred in 14 to 36 percent of patients with inducible, sustained tachyarrhythmia over a period of one to two years.¹⁹⁻²³ The rate of inducible ventricular tachyarrhythmia was higher in our study, suggesting that the presence of a reduced ejection fraction and unsustained ventricular tachycardia identifies patients who are more likely to have inducible tachyarrhythmia. The median time from acute myocardial infarction to enrollment in the current trial was longer than in the previous studies, but there was no effect of the length of time between myocardial infarction and enrollment on whether sustained ventricular tachyarrhythmia could be induced.²⁴ The rate of cardiac arrest or death from arrhythmia in the group that was assigned to no antiarrhythmic therapy (18 percent at two years) was similar to the rates in the earlier studies, in which use of antiarrhythmic drugs was variable.¹⁹⁻²³ The high rate of arrhythmic events observed in our study is remarkable, given that the median time between myocardial infarction and enrollment was 39 months.

Inducible sustained tachyarrhythmia in patients presenting with unsustained ventricular tachycardia and chronic coronary disease has previously been observed in 20 to 45 percent of cases, a finding similar to the rate of 35 percent that we observed.²⁵⁻²⁸ Previous studies reported rates of arrhythmic events of 11 to 88 percent over a period of 14 to 30 months among patients with inducible tachycardia. None of these earlier reports systematically included untreated patients. Our study demonstrated a risk of cardiac arrest or death from arrhythmia of 18 percent among patients with inducible sustained tachyarrhythmia

when no antiarrhythmic therapy was administered over a similar follow-up period.

The rate of response to antiarrhythmic drugs in our study, as ascertained by electrophysiologic testing, is consistent with the rates reported in previous studies.²³⁻²⁶ Such a response did not translate into a reduction in the risk of cardiac arrest or death from arrhythmia. In fact, the survival benefit associated with electrophysiologically guided therapy was due to the use of defibrillators. The patients who received defibrillators had at least one unsuccessful antiarrhythmic-drug test, suggesting that they might have had a poorer prognosis than those who did not receive defibrillators. However, the patients who received defibrillators had better rates of survival than those who did not receive such treatment. Previous studies have demonstrated that empirical antiarrhythmic-drug therapy and therapy guided by the results of Holter monitoring do not improve survival after myocardial infarction.²⁹⁻³² Our study demonstrates that antiarrhythmic-drug therapy guided by electrophysiologic testing does not improve survival either.

The reasons for the failure of this approach to improve survival are not clear. The criteria we used to ascertain drug response by electrophysiologic tests may have been inadequate.³³ Daily variability in the inducibility of tachycardia may result in false predictions of drug efficacy. The inconsistency of the effects of antiarrhythmic drugs (possibly owing to noncompliance) may contribute. Finally, progression of disease over the course of the trial may have altered the patients' responsiveness to the drugs.

The Multicenter Automatic Defibrillator Implantation Trial examined the efficacy of defibrillators in preventing sudden death in patients similar to those enrolled in our trial.³⁴ That small study (involving 196 patients) lacked a control group of untreated patients and involved an average follow-up period of only 27 months. The two-year mortality of 32 percent among the patients treated with antiarrhythmic drugs (primarily empirical therapy with amiodarone) in that study was slightly higher than the two-year mortality among our untreated patients (28 percent), but similar to the mortality among the patients in our study who were assigned to electrophysiologically guided therapy and who did not receive defibrillators (33 percent). The two-year mortality among the patients who received defibrillators was similar in both trials — approximately 10 percent. These similarities in survival are noteworthy, especially since the rate of beta-blocker use among the patients in our trial was about twice that of the patients in the earlier study.

Beta-blockers and angiotensin-converting-enzyme inhibitors have been proved to reduce mortality in patient populations similar to ours. Our patient population, with a median ejection fraction of approximately 29 percent, should benefit from both types of drugs. However, the benefits of beta-blockers more

than three years after myocardial infarction are unclear. The electrophysiologists participating in the study were not the patients' primary cardiologists in many cases, and there was widespread reluctance among primary physicians to administer beta-blocking agents to patients with markedly abnormal left ventricular function.

The primary end point in this trial was cardiac arrest or death from arrhythmia — which, as used in this study, meant instantaneous or unwitnessed death, except in the case of patients who died of incessant ventricular tachycardia or complications of antiarrhythmic therapy. We use this category for terminal events, but we can make no claim as to the mechanism by which such deaths occur. It is likely that some sudden deaths were due to acute ischemic events. We tried to minimize this possibility by requiring evaluation and appropriate therapy for myocardial ischemia before patients were enrolled. In addition, the proportion of arrhythmias mediated by ischemia should have been roughly equal between the treated and untreated groups.

The patients assigned to electrophysiologically guided therapy were not randomly assigned to drug therapy or defibrillator therapy. Thus, although the reductions in the relative risk of arrhythmic events and overall mortality in patients treated with defibrillators are large, caution should be used in interpreting the true magnitude of the benefit. Extensive analyses in which adjustments were made for potential prognostic factors that could have influenced outcome still demonstrate better survival among the patients given defibrillators than among those given drugs. This trial was not designed to test the efficacy of individual antiarrhythmic agents but rather the usefulness of electrophysiologic testing to guide antiarrhythmic therapy. Most patients discharged receiving antiarrhythmic drugs were treated with class I agents. It is not clear whether greater use of class III agents would have improved outcomes among the patients treated with antiarrhythmic drugs.

The results of this study establish that patients with coronary disease, an ejection fraction of 40 percent or less, asymptomatic, unsustained ventricular tachycardia, and inducible sustained ventricular tachyarrhythmia have substantial mortality due to arrhythmia. The rate of death among patients with inducible sustained tachyarrhythmia is reduced by the use of defibrillators but not by the use of antiarrhythmic-drug therapy based on the results of electrophysiologic testing. Thus, it is reasonable to perform electrophysiologic testing in patients who meet the entry criteria of this trial. If sustained ventricular tachyarrhythmia can be induced in a clinical setting similar to that of this study, implantation of a defibrillator is warranted. Further studies are necessary to clarify the mechanisms that cause sudden death among patients with coronary disease and to permit the development of improved, less costly treatments.

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APPENDIX

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CORRECTION

A Randomized Study of the Prevention of Sudden Death in Patients with Coronary Artery Disease

A Randomized Study of the Prevention of Sudden Death in Patients with Coronary Artery Disease . On page 1883, the sentence that begins four lines from the bottom of the left-hand column should have read, "Using these rates and an alpha level of 0.05, we determined that a total of 900 patients with inducible, sustained tachyarrhythmia would provide the study with more than 80 percent power to detect a reduction of at least 33 percent in the rate of events in the group assigned to electrophysiologically guided therapy if the event rate in the untreated group were 15 percent, and more than 90 percent power if the event rate in the untreated group were 20 percent."