

## Prophylactic Use of an Implantable Cardioverter–Defibrillator after Acute Myocardial Infarction

Stefan H. Hohnloser, M.D., Karl Heinz Kuck, M.D., Paul Dorian, M.D., Robin S. Roberts, M.Tech., John R. Hampton, M.D., Robert Hatala, M.D., Eric Fain, M.D., Michael Gent, D.Sc., and Stuart J. Connolly, M.D., on behalf of the DINAMIT Investigators\*

### ABSTRACT

#### BACKGROUND

Implantable cardioverter–defibrillator (ICD) therapy has been shown to improve survival in patients with various heart conditions who are at high risk for ventricular arrhythmias. Whether benefit occurs in patients early after myocardial infarction is unknown.

#### METHODS

We conducted the Defibrillator in Acute Myocardial Infarction Trial, a randomized, open-label comparison of ICD therapy (in 332 patients) and no ICD therapy (in 342 patients) 6 to 40 days after a myocardial infarction. We enrolled patients who had reduced left ventricular function (left ventricular ejection fraction, 0.35 or less) and impaired cardiac autonomic function (manifested as depressed heart-rate variability or an elevated average 24-hour heart rate on Holter monitoring). The primary outcome was mortality from any cause. Death from arrhythmia was a predefined secondary outcome.

#### RESULTS

During a mean ( $\pm$ SD) follow-up period of  $30\pm 13$  months, there was no difference in overall mortality between the two treatment groups: of the 120 patients who died, 62 were in the ICD group and 58 in the control group (hazard ratio for death in the ICD group, 1.08; 95 percent confidence interval, 0.76 to 1.55;  $P=0.66$ ). There were 12 deaths due to arrhythmia in the ICD group, as compared with 29 in the control group (hazard ratio in the ICD group, 0.42; 95 percent confidence interval, 0.22 to 0.83;  $P=0.009$ ). In contrast, there were 50 deaths from nonarrhythmic causes in the ICD group and 29 in the control group (hazard ratio in the ICD group, 1.75; 95 percent confidence interval, 1.11 to 2.76;  $P=0.02$ ).

#### CONCLUSIONS

Prophylactic ICD therapy does not reduce overall mortality in high-risk patients who have recently had a myocardial infarction. Although ICD therapy was associated with a reduction in the rate of death due to arrhythmia, that was offset by an increase in the rate of death from nonarrhythmic causes.

From J.W. Goethe University, Frankfurt (S.H.H.), and St. Georg's Hospital, Hamburg (K.H.K.) — both in Germany; St. Michael's Hospital, Toronto (P.D.), and Hamilton Civic Hospitals Research Center (R.S.R., M.G.) and McMaster University (S.J.C.), Hamilton, Ont. — all in Canada; University Hospital, Nottingham, United Kingdom (J.R.H.); Slovak Cardiovascular Institute, Bratislava, Slovak Republic (R.H.); and St. Jude Medical, Sunnyvale, Calif. (E.F.). Address reprint requests to Dr. Hohnloser at the Department of Medicine, Division of Cardiology, J.W. Goethe University, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany, or at hohnloser@em.uni-frankfurt.de.

\*The investigators and study sites participating in the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) are listed in the Appendix.

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**P**ROPHYLACTIC USE OF AN IMPLANTABLE cardioverter–defibrillator (ICD) has been shown to prolong life in several populations of patients with serious heart disease and reduced left ventricular function. Previous trials, however, have included relatively few patients who have recently had a myocardial infarction.<sup>1,2</sup> The first 6 to 12 months after myocardial infarction constitute a period during which there is a particularly high risk of death from arrhythmia,<sup>3–5</sup> and pharmacologic therapies other than beta-blockers have not been shown to be effective in counteracting this risk.

The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) was designed to test whether prophylactic implantation of an ICD would reduce mortality in survivors of a recent myocardial infarction who are at high risk for ventricular arrhythmias.<sup>6</sup> Because several large studies have shown that markers of impaired autonomic function are associated with increased mortality,<sup>7–11</sup> only survivors of infarction who had severe left ventricular dysfunction as well as depressed heart-rate variability or an elevated 24-hour heart rate were eligible for the trial.

## METHODS

### ORGANIZATION OF THE TRIAL

The DINAMIT trial was initiated by the investigators. The study protocol was approved by the institutional review boards of all 73 participating investigational sites in 12 countries worldwide. All the patients gave written informed consent before randomization. An external data and safety monitoring committee independently reviewed the results at regular intervals throughout the trial. A description of the design and study protocol has been published previously.<sup>6</sup>

### PATIENT POPULATION

Patients aged 18 to 80 years were eligible if they had recently had a myocardial infarction (6 to 40 days previously) and if they had a left ventricular ejection fraction of 0.35 or less, as assessed by angiography, radionuclide scanning, or echocardiography. Patients also had to have a standard deviation of normal-to-normal RR intervals of 70 msec or less or a mean RR interval of 750 msec or less (heart rate, 80 beats per minute or greater) over a 24-hour period,<sup>8–12</sup> as assessed by 24-hour Holter monitoring performed at least three days after the infarction.

The following exclusion criteria were applied:

congestive heart failure or New York Heart Association class IV at the time of randomization; noncardiac disease that limited life expectancy; coronary artery bypass grafting performed since the qualifying infarction or planned to be performed within four weeks after randomization; three-vessel percutaneous coronary intervention performed since the qualifying infarction; name on a waiting list for a heart transplant; current, ongoing ICD therapy; prior implantation of a permanent pacemaker; requirement for an ICD (i.e., sustained ventricular tachycardia or fibrillation more than 48 hours after the qualifying infarction); low probability that the study ICD could be implanted within seven days after randomization; and expected poor compliance with the protocol.

### STUDY DESIGN

Patients were stratified according to clinical center and underwent central randomization, which was performed at the study coordinating and methods center (Hamilton Civic Hospitals Research Centre, Hamilton, Ont., Canada). Patients were randomly assigned in a 1:1 ratio either to receive an ICD (the ICD group) or not to receive an ICD (the control group). The randomization sequence was stratified according to center and balanced within randomly varying blocks of two, four, or six patients.

The study protocol mandated that patients receive the best conventional medical therapy. Investigators were encouraged to treat all study patients with angiotensin-converting–enzyme inhibitors, beta-blockers, aspirin, and lipid-lowering drugs, as appropriate. Reasons for not giving these medications were documented.

Patients who were randomly assigned to receive an ICD were required to undergo implantation of a market-approved, single-chamber ICD (St. Jude Medical, Sunnyvale, Calif.) within one week after randomization. Implanted leads were required to achieve an R wave of more than 4.9 mV, a pacing threshold of less than 2.1 V at 0.5 msec, and a defibrillation threshold with a safety margin of at least 10 J. Postoperatively, the ICD was set to detect ventricular tachycardia and fibrillation. The detection rate for tachycardia was set at 175 or more beats per minute for at least 16 beats. The device was programmed to deliver all discharges at maximal output in the ventricular-fibrillation zone (200 beats per minute or greater). Bradycardia pacing was programmed for activation at a minimum of 40 beats

per minute. Antitachycardia pacing within the ventricular-tachycardia zone (175 to 200 beats per minute) could be activated to deliver four bursts of 6 to 10 beats beginning at 81 percent of the tachycardia cycle length, with 10-msec decrements between bursts.

#### FOLLOW-UP

Patients were followed with respect to all outcomes for a maximum of four years, beginning on the date of randomization. The study commenced in April 1998, and follow-up ended in September 2003, about 15 months after the last patient had been recruited. Follow-up visits were scheduled to take place three and six months after randomization and at six-month intervals thereafter.

#### STUDY OUTCOMES

The primary outcome in DINAMIT was death from any cause. Death due to cardiac arrhythmia was the secondary outcome. Ascertainment of the cause of death of patients in the trial was the responsibility of the local investigators. Documentation of the cause of death was based on information obtained from witnesses, family members, death certificates, hospital records, and autopsy reports, when available, but not from ICD telemetry.

The blinded central validation committee independently reviewed information on all deaths. Classification of each death based on the surrounding circumstances was agreed on by these reviewers. The committee classified deaths as either arrhythmic or nonarrhythmic in nature on the basis of criteria originally developed by Hinkle and Thaler<sup>12</sup> and previously validated in the Canadian Implantable Defibrillator Study<sup>13</sup> and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial.<sup>14</sup> These criteria are based on the clinical circumstances of death and do not rely on ICD information.

#### STATISTICAL ANALYSIS

Data analysis was performed at Hamilton Civic Hospitals Research Center by two of the authors (Mr. Roberts and Dr. Gent). All investigators had full access to the data. The primary study outcome was evaluated according to the intention-to-treat principle. The cumulative risks of death from any cause and from specific causes over time were estimated separately for each treatment group with use of the Kaplan-Meier procedure<sup>15</sup> and were compared between groups with use of the Mantel-

Haenszel test.<sup>16</sup> On the basis of mortality data from similar populations of patients,<sup>9</sup> it was anticipated that the control group would have a three-year mortality rate of 30.0 percent and that 40.0 percent of these deaths would be accounted for by deaths due to arrhythmia. The net effect of preventing 80.0

**Table 1. Characteristics of the Patients at Baseline.\***

Characteristic	ICD Group (N=332)	Control Group (N=342)
Male sex — no. (%)	252 (75.9)	262 (76.6)
Age — yr	61.5±10.9	62.1±10.6
Prior MI — no. (%)	123 (37.0)	111 (32.5)
Prior CABG — no. (%)	25 (7.5)	24 (7.0)
Prior PTCA — no. (%)	49 (14.8)	38 (11.1)
Diabetes mellitus — no. (%)	102 (30.7)	98 (28.7)
Hypertension — no. (%)	155 (46.7)	154 (45.0)
Location of index MI — no. (%)		
Anterior	239 (72.0)	247 (72.2)
Other	93 (28.0)	95 (27.8)
QRS duration (msec)	107±24	105±23
Peak creatine kinase — U/liter	2329±3837	2138±2349
New Q-wave infarction — no. (%)	240 (72.3)	256 (74.9)
Congestive heart failure with index MI — no. (%)	156 (47.0)	167 (48.8)
NYHA class I	21 (13.5)	20 (12.0)
NYHA class II	95 (60.9)	98 (58.7)
NYHA class III	40 (25.6)	49 (29.3)
Left ventricular ejection fraction	0.28±0.05	0.28±0.05
SD of normal-to-normal RR intervals — msec	61±21	61±22
24-hr RR interval — msec	745±106	747±105
In-hospital therapy for MI — no. (%)		
Any	208 (62.7)	212 (62.0)
PTCA only	87 (26.2)	92 (26.9)
Thrombolysis only	88 (26.5)	76 (22.2)
Both PTCA and thrombolysis	33 (9.9)	44 (12.9)
None	115 (34.6)	111 (32.5)
Unknown	9 (2.7)	19 (5.6)
Beta-blockers — no. (%)	289 (87.0)	296 (86.5)
ACE inhibitors — no. (%)	315 (94.9)	323 (94.4)
Antiplatelet agents — no. (%)	306 (92.2)	315 (92.1)
Lipid-lowering agents — no. (%)	255 (76.8)	272 (79.5)

\* Plus-minus values are means ±SD. There were no significant differences between the groups in baseline characteristics. Because of rounding, not all percentages total 100. ICD denotes implantable cardioverter-defibrillator, MI myocardial infarction, CABG coronary-artery bypass grafting, PTCA percutaneous transluminal coronary angioplasty, NYHA New York Heart Association, and ACE angiotensin-converting enzyme.

percent of these deaths due to arrhythmia with use of an ICD would reduce the total mortality rate to 20.4 percent — a reduction considered biologically plausible and clinically relevant. Based on a one-sided test at an alpha level of 0.05, we determined that 525 patients would be required in order for the study to have 80 percent power to identify a difference between the groups. Because mortality rates were lower than expected during the study, the target enrollment was increased to 674 patients.

A single interim analysis of efficacy was performed by an external safety and efficacy monitoring committee after 66 deaths — about half the anticipated number — had occurred. A one-sided P value of less than 0.001 would have resulted in early termination of the study. Before unblinding, a decision was made to use two-sided statistical testing.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 674 patients were enrolled; 332 were randomly assigned to the ICD group and 342 to the control group. Twenty of the patients who were randomly assigned to receive an ICD subsequently refused to have one implanted. The baseline demographic characteristics of the two groups are provided in Table 1. Most patients had new Q-wave infarctions, and 72.1 percent were anterior in loca-

tion. Two thirds of the patients had received thrombolytic therapy, had undergone acute percutaneous intervention, or both. The mean left ventricular ejection fraction was 0.28. In a subgroup of 321 patients in whom assessment of the left ventricular ejection fraction was repeated six to eight weeks after randomization, there was a mean ( $\pm$ SD) increase of  $0.02\pm 0.11$ . The average time from myocardial infarction to randomization was 18 days and was similar in the two groups.

There was excellent adherence to optimal medical therapy (Table 1). Amiodarone was prescribed to 27 of the patients who had been randomly assigned to receive an ICD (8.1 percent) and to 46 of the control patients (13.5 percent) ( $P=0.04$ ). During the course of the study, percutaneous or surgical coronary revascularization was performed in 33 ICD recipients (9.9 percent), as compared with 50 patients in the control group (14.6 percent) ( $P=0.08$ ). Only partial follow-up was available for four patients (all members of the control group).

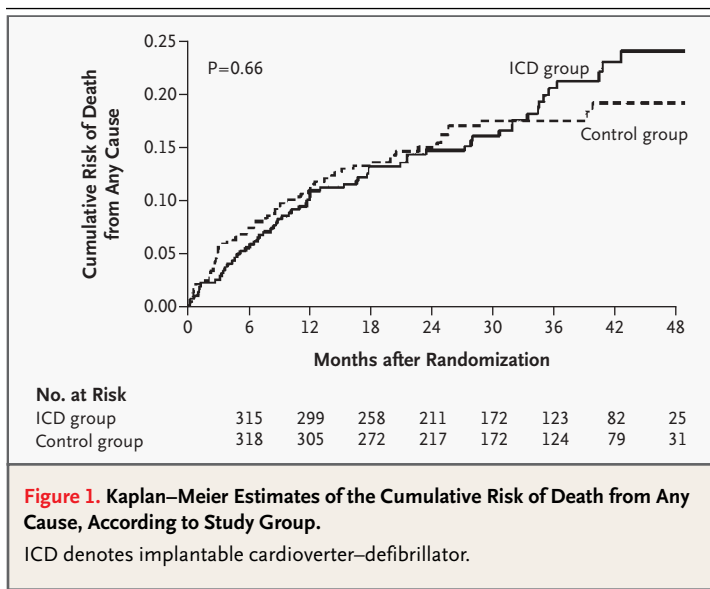
DEATH FROM ANY CAUSE

The cumulative-mortality curves for the two groups are shown in Figure 1. During an average observation period of  $30\pm 13$  months, 120 patients died, 62 in the ICD group and 58 in the control group (hazard ratio, 1.08; 95 percent confidence interval, 0.76 to 1.55; two-sided  $P=0.66$ ) (Table 2). The annual mortality rates were 7.5 and 6.9 percent, respectively. The adjudicated causes of death are listed in Table 2. Two patients who had been randomly assigned to the ICD group died before they received an ICD.

A set of baseline clinical features was examined for potential subgroup effects (Fig. 2). For each feature, the ICD effect remained consistent and did not differ significantly between or among subgroups.

DEATH FROM ARRHYTHMIC AND NONARRHYTHMIC CAUSES

In the ICD group, there were 12 deaths due to arrhythmia, as compared with 29 in the control group (annual rate, 1.5 percent and 3.5 percent, respectively) (Fig. 3A). This difference was highly statistically significant (hazard ratio, 0.42; 95 percent confidence interval, 0.22 to 0.83; two-sided  $P=0.009$ ). There were 50 deaths due to nonarrhythmic causes in the ICD group, as compared with 29 in the control group (hazard ratio, 1.75; 95 percent confidence



interval, 1.11 to 2.76;  $P=0.02$ ) (Fig. 3B). Of the three prespecified subcategories of deaths from nonarrhythmic causes, the only one found to occur at a significantly increased rate in the ICD group was death from cardiac, nonarrhythmic causes ( $P=0.05$ ) (Table 2). Of the 50 deaths from nonarrhythmic causes in the ICD group, 39 (78 percent) were cardiovascular in nature (i.e., due to cardiac, nonarrhythmic or vascular, noncardiac causes); in the control group, 23 of 29 deaths from nonarrhythmic causes (79 percent) were cardiovascular in nature.

#### COMPLICATIONS OF ICD THERAPY

The average time between randomization and ICD implantation was  $6.3\pm 7.3$  days. Of the 332 patients assigned to receive an ICD, 310 actually received a device. The time between ICD implantation and discharge from the hospital averaged  $4.7\pm 6.4$  days. In-hospital device-related complications occurred in 25 patients; the most common of these complications were lead dislodgment, pneumothorax, and inappropriate shocks. There were no deaths related to device implantation. To prevent inappropriate pacing, bradycardia pacing was typically programmed to 40 to 45 beats per minute (maximum, 55 beats per minute).

#### DISCUSSION

In this randomized trial of high-risk patients who had recently had a myocardial infarction, overall survival was not improved by prophylactic implan-

tation of an ICD. The study groups were well balanced with respect to their baseline clinical characteristics and the early use of reperfusion therapy. There was a high rate of use of appropriate medical therapy. It is unlikely that the similarity between the two groups in the rate of death from all causes represents a false negative result due to inadequate sample size. The 95 percent confidence interval of the hazard ratio for death from any cause rules out a reduction in mortality of 25 percent or greater.

The ICD group, as compared with the control group, had a large, statistically significant reduction (by more than 50 percent) in the risk of death due to arrhythmia; however, this effect was offset by a significant increase, of similar magnitude, in the rate of death from nonarrhythmic causes. The ICD is expected to reduce mortality by preventing sudden cardiac deaths due to ventricular fibrillation without any effect on death from nonarrhythmic causes. This pattern has been consistently observed in previous trials of ICD therapy in patients at high risk. In several trials of ICD therapy—the Canadian Implantable Defibrillator Study, the Antiarrhythmics versus Implantable Defibrillators trial, and the Cardiac Arrest Study Hamburg—there was a 50 percent reduction in the rate of death from arrhythmia and almost no effect on the rate of death from other causes; the net effect was a 25 percent reduction in overall mortality.<sup>17</sup> In the Multicenter Automatic Defibrillator Implantation Trial I (MADIT I) and MADIT II,<sup>1,2</sup> which evaluated prophylactic ICD therapy in patients with chronic ischemic heart disease, the rate of death due to arrhythmia was mark-

**Table 2. Mortality Rates.\***

Cause of Death	ICD Group		Control Group		Hazard Ratio (95% CI) <sup>†</sup>	P Value <sup>‡</sup>
	No. of Deaths	Rate %/yr	No. of Deaths	Rate %/yr		
Any cause	62	7.5	58	6.9	1.08 (0.76–1.55)	0.66
Arrhythmia	12	1.5	29	3.5	0.42 (0.22–0.83)	0.009
Nonarrhythmic causes	50	6.1	29	3.5	1.75 (1.11–2.76)	0.02
Cardiac, nonarrhythmic	34	4.1	20	2.4	1.72 (0.99–2.99)	0.05
Vascular, noncardiac	5	0.6	3	0.4	1.69 (0.40–7.06)	0.47
Nonvascular	11	1.3	6	0.7	1.85 (0.68–5.01)	0.22

\* The data were analyzed with use of the Cox model. ICD denotes implantable cardioverter-defibrillator, and CI confidence interval.

<sup>†</sup> Hazard ratios are for the ICD group as compared with the control group.

<sup>‡</sup> P values are two-sided.

edly reduced and the rate of death from other causes was not increased.

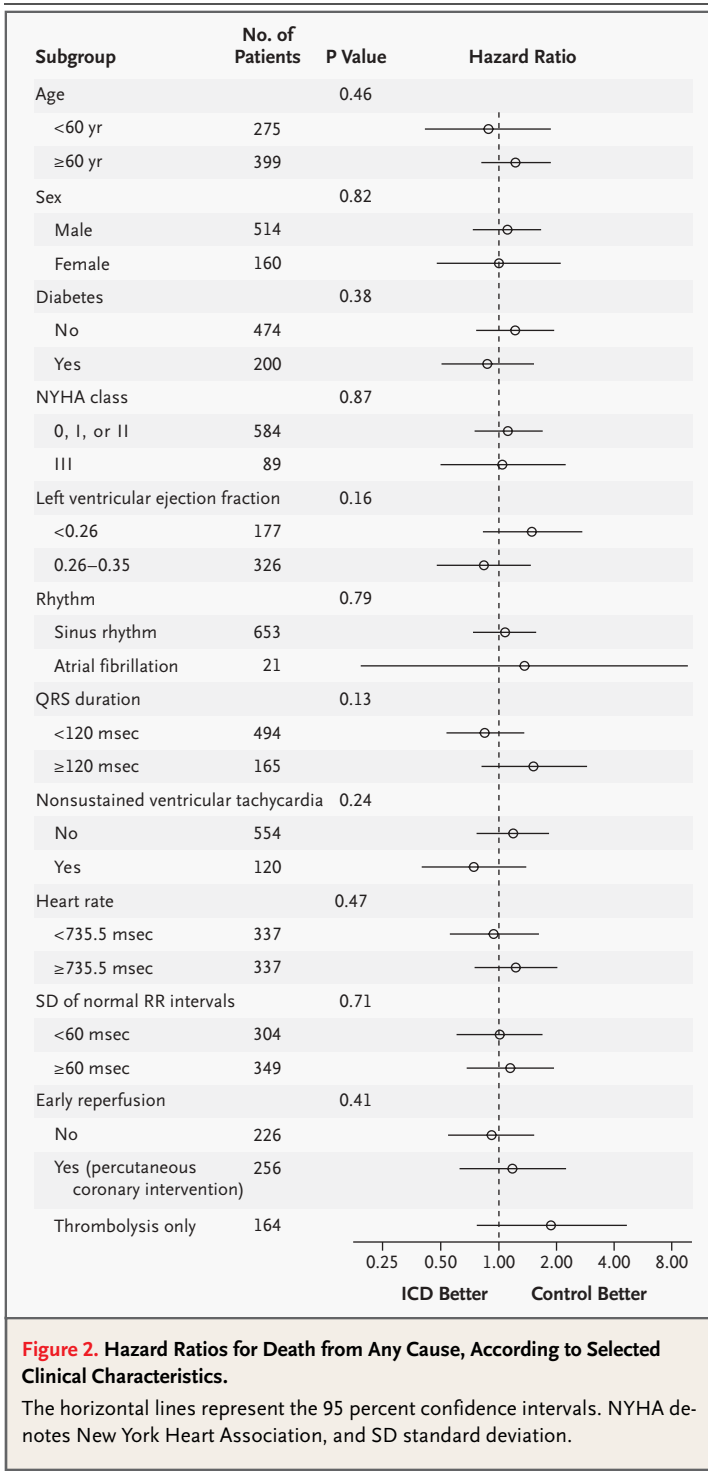
In DINAMIT, the reduction in the rate of arrhythmia-related death was very similar to that observed in previous trials of ICD therapy. However, in con-

trast to the previous trials, DINAMIT revealed a statistically significant increase in the rate of death from nonarrhythmic causes among patients assigned to receive an ICD. Most of these deaths (78 percent) were cardiovascular in nature. It appears that in this trial, as in previous trials of ICD therapy, the ICD prevented death from ventricular fibrillation. However, preventing death from ventricular fibrillation did not reduce overall mortality in these patients.

The reason for the unexpected and unprecedented increase in mortality from causes other than arrhythmia in patients assigned to receive an ICD is not clear. The most likely explanation is that the patients “saved” from an arrhythmia-related death by ICD therapy are also at high risk for death from other cardiac causes. There was no sign of an increased rate of death in association with the surgical procedure or complications with the use of the ICD. It is unlikely that the increased rate of deaths from cardiac, nonarrhythmic causes were due to excessive pacing, as in the Dual-Chamber and VVI Implantable Defibrillator Trial,<sup>18</sup> because the backup pacing was programmed at a very low rate in almost all the patients in the ICD group.

It has been speculated that ICDs might, by shocking ventricular fibrillation, merely transform sudden death to eventual death from pump failure, without significantly prolonging life, especially when ventricular fibrillation is occurring in a patient with end-stage heart failure or a large acute myocardial infarction. There is some evidence that such a possibility may have factored into the results of the Coronary Artery Bypass Graft Patch Trial,<sup>19</sup> and it provides a reasonable hypothesis for the results of DINAMIT.

The mean left ventricular ejection fraction in DINAMIT was significantly reduced (at 0.28) and did not increase appreciably six weeks later. However, the mean ejection fraction was somewhat higher than that in MADIT II (0.23)<sup>2</sup> — a difference that may explain the higher overall mortality observed in MADIT II. The main differences between patients in DINAMIT and those in previous trials is the temporal proximity to acute infarction and the abnormal results of autonomic-function tests at baseline. In DINAMIT, the ratio of death due to arrhythmia to death from any cause was 34 percent, similar to the ratio in other ICD trials. A recent analysis of the MADIT II trial, which also enrolled patients with a previous myocardial infarction, supports the main finding of DINAMIT — that patients who have recently had an infarction do not



**Figure 2. Hazard Ratios for Death from Any Cause, According to Selected Clinical Characteristics.**

The horizontal lines represent the 95 percent confidence intervals. NYHA denotes New York Heart Association, and SD standard deviation.

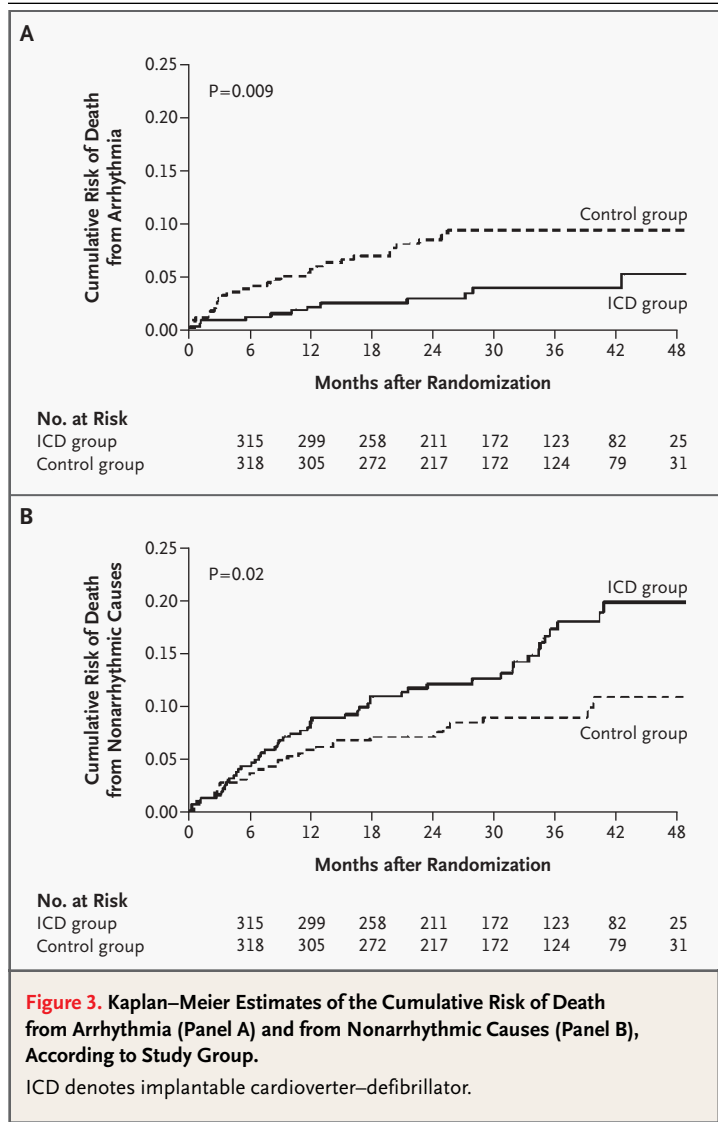
benefit from ICD.<sup>20</sup> In MADIT II, the mean time from the most recent infarction to enrollment in the study was 6.5 years; the subgroup of patients with the most recent infarction did not benefit at all from ICD therapy.<sup>20</sup> This finding was in marked contrast to the outcome in patients whose infarction had occurred in the remote past, in whom the benefit from the ICD was large.

Although several clinical studies had indicated that the results of tests of autonomic function carry prognostic implications after myocardial infarction,<sup>7-11</sup> the recently published Azimilide Post Infarct Survival Evaluation,<sup>21</sup> which provided definitive information on the prognostic value of heart-rate variability, has demonstrated that impaired heart-rate variability is associated with increased mortality but not specifically mortality from arrhythmic causes. Nonetheless, the proportion of deaths in the DINAMIT control group that were attributable to arrhythmia was 50 percent — as high as in any previous trial of ICD therapy for secondary or primary prevention.

Use of amiodarone was more common in the control group than it was in the ICD group. Most likely, this difference is a reflection of physicians' desire in this unblinded study to provide additional optimal therapy in the absence of an ICD. However, as recently demonstrated in a large, randomized trial, amiodarone does not offer any survival benefit if given for primary prevention in patients with ischemic or nonischemic cardiomyopathy and reduced ventricular function.<sup>22</sup> Most likely, amiodarone had no effect on survival in our trial as well.

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Drs. Hohnloser, Kuck, Dorian, and Connolly report that they are consultants to and have received lecture fees from St. Jude Medical. Dr. Fain reports that he is an employee of St. Jude Medical.



**Figure 3. Kaplan-Meier Estimates of the Cumulative Risk of Death from Arrhythmia (Panel A) and from Nonarrhythmic Causes (Panel B), According to Study Group.**

ICD denotes implantable cardioverter-defibrillator.

APPENDIX

**Steering committee** — S.J. Connolly (Hamilton, Canada), P. Dorian (Toronto), E. Fain (Sunnyvale, Calif.), M. Gent (Hamilton, Canada), J.R. Hampton (Nottingham, United Kingdom), R. Hatala (Bratislava, Slovakia), S.H. Hohnloser (chair; Frankfurt, Germany), K.H. Kuck (Hamburg, Germany), and R.S. Roberts (Hamilton, Canada). **Central validation committee** — M. Gent (Hamilton, Canada), M. Gardner (Halifax, Canada), H. Kottkamp (Leipzig, Germany), and P. Blomström (Uppsala, Sweden). **External safety and efficacy monitoring committee** — J.T. Bigger (New York), S. Pocock (London), and H.J.J. Wellens (Maastricht, the Netherlands). **Clinical study sites, Canada** — Hamilton Health Sciences, Hamilton (S. Connolly); St. Michael's Hospital, Toronto (P. Dorian); Victoria Heart Institute, Victoria (L.D. Sterns); Institut de Cardiologie de Montréal, Montréal (D. Roy); Queen Elizabeth II Health Sciences Centre, Halifax (M. Gardner); Cambridge Memorial Hospital, Cambridge (S. Vize); Campus Notre-Dame du Centre Hospitalier Universitaire de Montréal, Montréal (C. Guimond); Montréal General Hospital, Montréal (T. Hadjis); Hôpital Cité de la Santé de Laval, Vimont (R. Gendreau); Welland County General Hospital 1, Welland (E.G. Abraham); Guelph General Hospital, Guelph (J. Misternski); Toronto East General Hospital, Toronto (G. Rewa); Kawartha Cardiology Clinic, Peterborough (W.G. Hughes); Hôpital Laval, Sainte-Foy (F. Philippon); Oakville Trafalgar Memorial Hospital, Oakville (D.R. McConachie); Welland County General Hospital 2, Welland (J. Vedova); Hôpital du Sacré Coeur, Montréal (T.K. Kus); Foothills Hospital, Calgary (L.B. Mitchell); Ottawa Heart Institute, Ottawa (M. Green); Hôtel-Dieu De Lévis, Lévis (F. Grondin); Sunnybrook Health Science Centre, Toronto (Z. Wulffhart); University Hospital, Edmonton (S.K.M. Kimber); Centre Hospitalier Universitaire, Sainte-Foy (M. Samson); Hôpital de L'Enfant Jésus, Québec City (G. Houde); and Healthcare Corporation of St. John's, St. John's (S. Connors). **Clinical study sites, Germany** — Allgemeines Krankenhaus St. Georg, Hamburg (K.H. Kuck); Johann Wolfgang Goethe Universität, Frankfurt (S.H. Hohnloser); Städtische Kliniken, Kassel (J. Neuzner); Universitätsklinikum Herzzentrum, Leipzig (H. Kottkamp); St. Josefs-Hospital, Wiesbaden (W. Kasper); Städtisches Klinikum, Brandenburg (M. Oeff); Kreiskrankenhaus, Leer (E. Stammwitz); Kerckhoff Klinik, Bad Nauheim (J. Sperzel); Robert-Bosch-Krankenhaus, Stuttgart (U. Sechtem); Kliniken der Medizinischen Hochschule, Hannover (H. Drex-

ler); Klinikum Weisser Hirsch, Dresden (S.G. Spitzer); Zentralkrankenhaus Links der Weser, Bremen (J. Siebels); Westfälische Wilhelms-Universität, Münster (G. Breithardt); Herzzentrum, Bad Krozingen (D. Kalusche); Universitätsklinikum, Aachen (P. Hanrath); Krankenhaus der Barmherzigen Brüder, Trier (C. Drobjig); Medizinische Klinik und Poliklinik, Homburg-Saar (J. Jung); Friederich-Wilhelms-Universität, Bonn (B. Lüderitz); Julius-Maximilians-Universität, Würzburg (W. Bauer); Klinikum Süd, Nürnberg (K.J. Göhl); and Klinikum Konstanz, Zentrum für Innere Medizin, Konstanz (F. Haman). **Other clinical study sites** — *United Kingdom*: Wordsley Hospital, Stourbridge (P. Forsey); the Glenfield Hospital National Health Service Trust, Leicester (W.D. Toff); Regional Medical Cardiology Centre, Belfast, Northern Ireland (P.P. McKeown); and the Queen Elizabeth Hospital, Birmingham (M.J. Griffith); *Slovakia*: Slovak Cardiovascular Institute, Bratislava (R. Hatala); and F.D. Roosevelt Hospital, Banská Bystrica (G. Kaliska); *Poland*: Grochowski Hospital, Warsaw (L. Ceremuzynski); I Klinika Kardiologii, Katowice (M. Trusz-Gluza); Institute of Cardiology, Warsaw (H. Szwed); and I Pomeranian Academy of Medicine, Szczecin (Z. Kornacewicz); *France*: Hôpital Louis Pradel, Lyons (P. Touboul); Centre Hospitalier Universitaire Nancy, Nancy (E. Aliot); Centre Hospitalier Universitaire de Rennes, Rennes (P. Mabo); Hôpital Arnaud de Villeneuve, Montpellier (J. Davy); Centre Hospitalier Bon Secours, Bon Secours (K. Khalife); Hôpital Lariboisière, Paris (A. Leenhardt); Hôpital Maillot, Briey (M. Parisot), and Centre Hospitalier Général, Bodlio (J. Le Potier); *Czech Republic*: Institute for Clinical and Experimental Medicine, Prague (J. Bytesnik); *Austria*: Rehabilitationsszentrum Grossgmain, Grossgmain (F. Schnöll); and Wilhelminenspital der Stadt Wien, Wien (G. Jakl); *Switzerland*: Kantonsspital Basel, Basel (S. Osswald); *Sweden*: University Hospital, Uppsala (P. Blomström); and Huddinge University Hospital, Huddinge (B. Eriksson); *Italy*: Ospedale di Bentivoglio, Bologna (B. Sassone); and *United States*: Fort Sanders Parkwest Hospital, Knoxville, Tenn. (J.R. Gimbel); and North Mississippi Medical Center, Tupelo (K. Crossen).

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