ORIGINAL ARTICLE

Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy

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ABSTRACT

BACKGROUND

Patients with nonischemic dilated cardiomyopathy are at substantial risk for sudden death from cardiac causes. However, the value of prophylactic implantation of an implantable cardioverter–defibrillator (ICD) to prevent sudden death in such patients is unknown.

METHODS

We enrolled 458 patients with nonischemic dilated cardiomyopathy, a left ventricular ejection fraction of less than 36 percent, and premature ventricular complexes or nonsustained ventricular tachycardia. A total of 229 patients were randomly assigned to receive standard medical therapy, and 229 to receive standard medical therapy plus a single-chamber ICD.

RESULTS

Patients were followed for a mean ($\pm$SD) of 29.0$\pm$14.4 months. The mean left ventricular ejection fraction was 21 percent. The vast majority of patients were treated with angiotensin-converting–enzyme (ACE) inhibitors (86 percent) and beta-blockers (85 percent). There were 68 deaths: 28 in the ICD group, as compared with 40 in the standard-therapy group (hazard ratio, 0.65; 95 percent confidence interval, 0.40 to 1.06; P=0.08). The mortality rate at two years was 14.1 percent in the standard-therapy group (annual mortality rate, 7 percent) and 7.9 percent in the ICD group. There were 17 sudden deaths from arrhythmia: 3 in the ICD group, as compared with 14 in the standard-therapy group (hazard ratio, 0.20; 95 percent confidence interval, 0.06 to 0.71; P=0.006).

CONCLUSIONS

In patients with severe, nonischemic dilated cardiomyopathy who were treated with ACE inhibitors and beta-blockers, the implantation of a cardioverter–defibrillator significantly reduced the risk of sudden death from arrhythmia and was associated with a nonsignificant reduction in the risk of death from any cause.

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*Participants in the DEFINITE trial are listed in the Appendix.

PATIENTS WITH NONISCHEMIC DILATED cardiomyopathy often die suddenly.[1] Although therapy with angiotensin-converting–enzyme (ACE) inhibitors and beta-blockers has increased survival in clinical trials of patients with left ventricular dysfunction due to nonischemic and ischemic cardiomyopathies, such patients still have a substantial risk of sudden death from cardiac causes despite receiving adequate doses of both pharmacologic agents.[2,3] The implantable cardioverter–defibrillator (ICD) prevents sudden death in patients who have had an episode of ventricular tachycardia or cardiac arrest,[4] as well as in selected patients who have coronary disease and left ventricular dysfunction.[5-7] However, no large-scale studies have examined the role of the ICD in the primary prevention of sudden death in patients with nonischemic cardiomyopathy. Therefore, we tested the hypothesis that an ICD will reduce the risk of death in patients with nonischemic cardiomyopathy and moderate-to-severe left ventricular dysfunction.

METHODS

TRIAL DESIGN

The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial was a prospective, randomized, investigator-initiated study based on observational data[8] and was funded by St. Jude Medical, which did not have access to the data. Data collection and analysis were independently performed at Northwestern University under the supervision of the statistical primary investigator. The investigators had full access to the data and wrote the article.

Patients were randomly assigned to receive either standard oral medical therapy for heart failure or standard oral medical therapy plus an ICD. The primary end point of the study was death from any cause. Sudden death from arrhythmia was a prespecified secondary end point.[9]

The study was initially designed to have a statistical power of 85 percent based on a one-sided test, assuming two-year mortality rates of 15 percent in the standard-therapy group and 7.5 percent in the ICD group and the enrollment of 458 patients, with 56 deaths. In order to report results with the use of two-sided tests and 85 percent statistical power, we extended follow-up to include 68 deaths. Interim analyses were performed after 22, 34, 45, 50, and 56 deaths. The critical values for the interim and final analyses assumed an O'Brien–Fleming type of spending function.[10-12] For patients' safety, boundaries for stopping the study in favor of the null hypothesis of no effect of the ICD on the risk of death at each interim analysis were also defined according to the work of Whitehead and Stratton.[13] No boundaries were crossed at any of the five interim analyses. Hence, this report presents the results of the final analysis at the time of the 68th death. The P value required for significance at the final analy-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	All Patients (N=458)	Standard-Therapy Group (N=229)	ICD Group (N=229)
Age — yr			
Mean	58.3	58.1	58.4
Range	20.3–83.9	21.8–78.7	20.3–83.9
Male sex — no. (%)	326 (71.2)	160 (69.9)	166 (72.5)
Race or ethnic group — no. (%)†			
White	308 (67.2)	154 (67.2)	154 (67.2)
Black	118 (25.8)	59 (25.8)	59 (25.8)
Hispanic	26 (5.7)	13 (5.7)	13 (5.7)
Pacific Islander	1 (0.2)	0	1 (0.4)
Asian	1 (0.2)	1 (0.4)	0
Other	4 (0.9)	2 (0.9)	2 (0.9)
History of diabetes — no. (%)	105 (22.9)	53 (23.1)	52 (22.7)
History of atrial fibrillation — no. (%)	112 (24.5)	60 (26.2)	52 (22.7)
Duration of heart failure — yr			
Mean	2.83	3.27‡	2.39
Range	0.0–38.5	0.0–38.5	0.0–21.33
NYHA class — no. (%)			
I	99 (21.6)	41 (17.9)	58 (25.3)
II	263 (57.4)	139 (60.7)	124 (54.2)
III	96 (21.0)	49 (21.4)	47 (20.5)
QRS interval — msec			
Mean	115.1	115.5	114.7
Range	78–196	79–192	78–196
Bundle-branch block — no. (%)			
Left	90 (19.7)	45 (19.7)	45 (19.7)
Right	15 (3.3)	7 (3.1)	8 (3.5)
Qualifying arrhythmia — no. (%)			
NSVT only	103 (22.5)	52 (22.7)	51 (22.3)
PVCs only	43 (9.4)	22 (9.6)	21 (9.2)
NSVT and PVCs	312 (68.1)	155 (67.7)	157 (68.6)
LVEF — %			
Mean	21.4	21.8	20.9
Range	7–35	10–35	7–35
Distance walked in 6 min — m			
Mean	319.4	328.3	311.2
Range	18–1317	18–1317	29–1143

* ICD denotes implantable cardioverter–defibrillator, NYHA New York Heart Association, NSVT nonsustained ventricular tachycardia, PVCs premature ventricular complexes, and LVEF left ventricular ejection fraction.
† Race and ethnic group were self-reported by the patients.
‡ P=0.04 for the comparison with the ICD group.

sis was 0.041, on the basis of a two-sided test. The first patient underwent randomization on July 9, 1998, and the 458th patient underwent randomization on June 6, 2002. The 68th death occurred on May 25, 2003.

The trial received annual approval from the institutional review board of Northwestern University as well as each of the study centers. Written informed consent was obtained from all patients.

PATIENT POPULATION

Inclusion criteria were a left ventricular ejection fraction of less than 36 percent, the presence of ambient arrhythmias,[14] a history of symptomatic heart failure, and the presence of nonischemic dilated cardiomyopathy. Ambient arrhythmias were defined by an episode of nonsustained ventricular tachycardia on Holter or telemetric monitoring (3 to 15 beats at a rate of more than 120 beats per minute) or an average of at least 10 premature ventricular complexes per hour on 24-hour Holter monitoring. The absence of clinically significant coronary artery disease as the cause of the cardiomyopathy was confirmed by coronary angiography or by a negative stress imaging study. Patients were excluded if they had New York Heart Association (NYHA) class IV congestive heart failure, were not candidates for the implantation of a cardioverter–defibrillator, had undergone electrophysiological testing within the prior three months, or had permanent pacemakers. Patients in whom cardiac transplantation appeared to be imminent, those with familial cardiomyopathy associated with sudden death, and patients with acute myocarditis or congenital heart disease were also excluded.

PHARMACOLOGIC THERAPY

All patients received ACE inhibitors unless they were contraindicated. Patients who were unable to tolerate ACE inhibitors received hydralazine or nitrates[15] or angiotensin II–receptor blockers. In addition, beta-blocker therapy was required unless patients were unable to tolerate it. Carvedilol was the beta-blocker of choice on the basis of data available when the study was designed.[16] The doses of ACE inhibitors and beta-blockers were adjusted to the levels recommended for patients with heart failure or to the highest tolerated doses. Digoxin and diuretics were used when necessary to manage clinical symptoms. The use of antiarrhythmic drugs such as amiodarone was discouraged. However, it was recognized that some patients had symptomatic

atrial fibrillation or supraventricular arrhythmias requiring treatment with amiodarone, and these conditions did not constitute exclusion criteria. No other antiarrhythmic drugs were used.

RANDOMIZATION AND FOLLOW-UP

Patients were randomly assigned to one of two treatment groups, with 229 patients in each group. Randomization was stratified according to center and to the use or nonuse of amiodarone for supraventricular arrhythmias. Patients who were randomly assigned to the ICD group received a single-chamber device approved by the Food and Drug Administration (St. Jude Medical). The ICDs were programmed to back up VVI pacing at a rate of 40 beats per minute and to detect ventricular fibrillation at a rate of 180 beats per minute. All patients were evaluated at three-month intervals. According to prespecified criteria, patients who were randomly assigned to standard therapy received an ICD if they had a cardiac arrest or an episode of unexplained syncope that was consistent with the occurrence of an arrhythmic event.

For patients who died, the cause of death was determined by an events committee (see the Appendix) whose members were unaware of patients' treatment assignments. The blinding process included editing any information from progress notes or laboratory reports that could have identified the presence of an ICD. The cause of death was determined

Table 2. Pharmacologic Therapy.*			
Agent	All Patients (N=458)	Standard-Therapy Group (N=229)	ICD Group (N=229)
	number of patients (percent)		
ACE inhibitor	392 (85.6)	200 (87.3)	192 (83.8)
Beta-blocker	389 (84.9)	193 (84.3)	196 (85.6)
Carvedilol	263 (57.4)	134 (58.5)	129 (56.3)
Metoprolol	102 (22.3)	43 (18.8)	59 (25.8)
Other	24 (5.2)	16 (7.0)	8 (3.5)
Diuretic	397 (86.7)	197 (86.0)	200 (87.3)
Angiotensin II–receptor blocker	51 (11.1)	20 (8.7)	31 (13.5)
Amiodarone	24 (5.2)	15 (6.6)	9 (3.9)
Digoxin	192 (41.9)	97 (42.4)	95 (41.5)
Nitrate	51 (11.1)	30 (13.1)	21 (9.2)

* ICD denotes implantable cardioverter–defibrillator, and ACE angiotensin-converting enzyme.

as suggested by Epstein et al.[17] In this classification, patients who had pump failure with progressive symptomatic deterioration who died of terminal ventricular fibrillation were not considered to have had sudden death from arrhythmia.

STATISTICAL ANALYSIS

The baseline characteristics of the two groups were compared with the use of two-sample t-tests for continuous variables and chi-square tests for categorical variables. The log-rank test was used to compare Kaplan–Meier survival curves in the two groups, and the Cox proportional-hazards model was used to adjust for covariates and to estimate the hazard ratio for death and corresponding 95 percent confidence interval in the ICD group as compared with the standard-therapy group.[18] All analyses were conducted according to the intention to treat. Data on patients who received a heart transplant were censored at the time of transplantation, as specified in the study protocol. The duration of follow-up was computed from the time of randomization to death for patients who died, and to the date of the 68th death for patients who did not die. All reported P values are two-tailed.
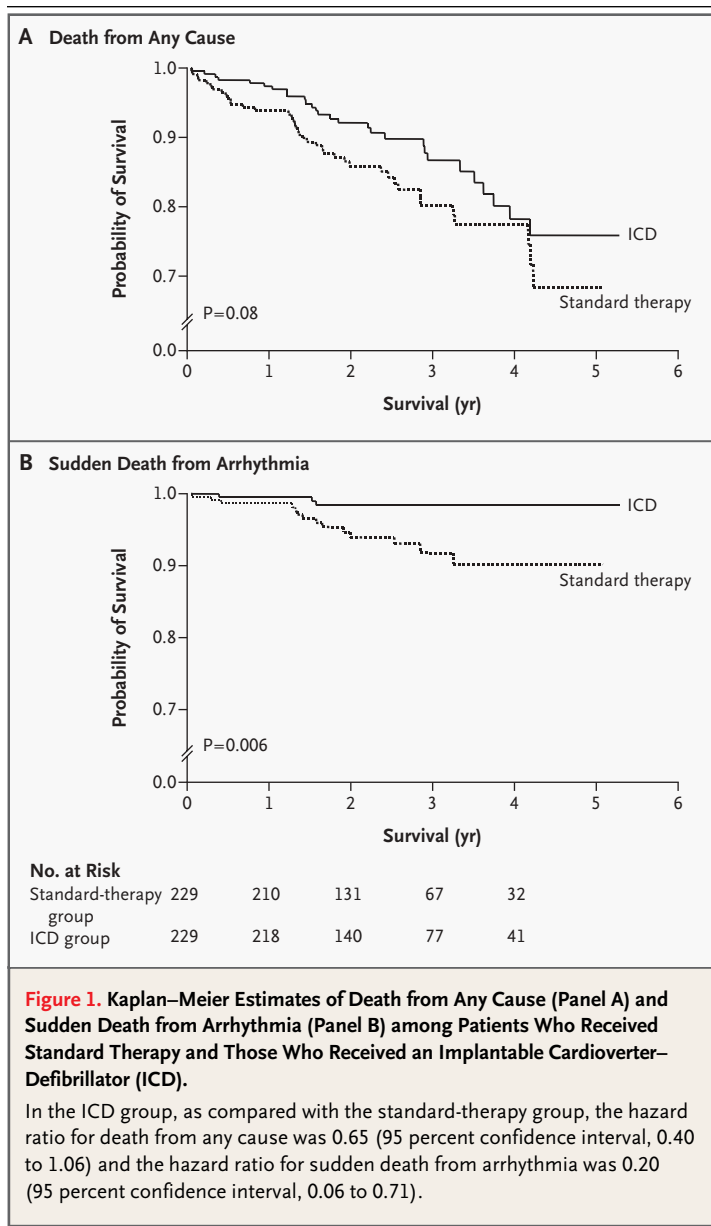
RESULTS

Follow-up lasted a mean (±SD) of 29.0±14.4 months. Baseline characteristics were similar in the two groups, except for the duration of heart failure (3.27 years in the standard-therapy group and 2.39 years in the ICD group, P=0.04) (Table 1).

THERAPY

The types of pharmacologic therapy used for heart failure are shown in Table 2. The majority of patients were treated with beta-blockers and ACE inhibitors. Of the 229 patients in the ICD group, 227 received a functioning ICD system. Two patients declined to undergo implantation of the ICD after providing consent and undergoing randomization. In addition, in response to the patients' requests, one patient had the ICD explanted and one patient had the device inactivated. All four patients were included in the ICD group according to the intention to treat.

There were three complications (1.3 percent) during the implantation of the ICD: one hemothorax, one pneumothorax, and one cardiac tamponade. There were no procedure-related deaths, and all complications resolved with medical therapy or drainage. There were 10 complications during follow-up (4.4 percent): 6 lead dislodgements or lead fractures, 3 cases of venous thrombosis, and 1 infection. Thirteen patients received ICD upgrades during follow-up; 2 received dual-chamber ICDs owing to the development of sinus-node dysfunction, and 11 received biventricular devices for NYHA class III or IV heart failure and a prolonged QRS interval. Of the 229 patients who were randomly assigned to standard therapy, 23 (10.0 percent) received ICDs during follow-up, primarily for syncope or heart failure with a prolonged QRS interval.
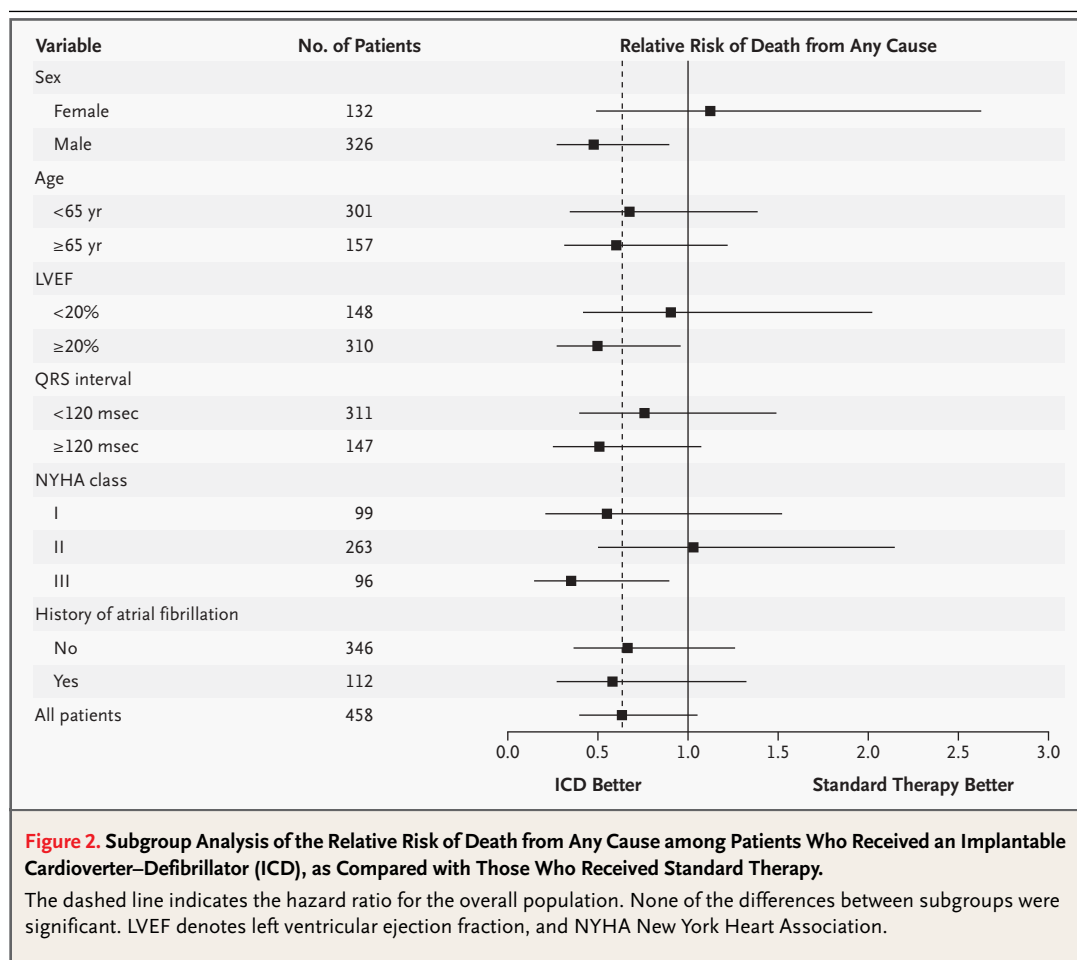

Figure 1. Kaplan–Meier Estimates of Death from Any Cause (Panel A) and Sudden Death from Arrhythmia (Panel B) among Patients Who Received Standard Therapy and Those Who Received an Implantable Cardioverter–Defibrillator (ICD).

In the ICD group, as compared with the standard-therapy group, the hazard ratio for death from any cause was 0.65 (95 percent confidence interval, 0.40 to 1.06) and the hazard ratio for sudden death from arrhythmia was 0.20 (95 percent confidence interval, 0.06 to 0.71).

OUTCOME

Fewer patients died in the ICD group than in the standard-therapy group (28 vs. 40), but the difference in survival was not significant (P=0.08 by the log-rank test) (Fig. 1). The unadjusted hazard ratio for death among patients who received an ICD, as compared with those who received standard therapy, was 0.65 (95 percent confidence interval, 0.40 to 1.06). The hazard ratio was unchanged (0.65) after adjustment for the duration of heart failure. On the basis of Kaplan–Meier survival curves, the rate of death from any cause at one year was 6.2 percent in the standard-therapy group and 2.6 percent in the ICD group. At two years, it was 14.1 percent in the standard-therapy group and 7.9 percent in the ICD group.

An analysis according to treatment actually received was also performed. The resulting hazard ratio was 0.66 (95 percent confidence interval, 0.40 to 1.08).

There were 3 sudden deaths from arrhythmia in the ICD group, as compared with 14 deaths in the standard-therapy group (hazard ratio, 0.20; 95 percent confidence interval, 0.06 to 0.71; P=0.006) (Fig. 1). There were 11 deaths due to heart failure in the standard-therapy group and 9 in the ICD group. One death in the standard-therapy group was thought to be from cardiac causes, but the events committee could not distinguish between arrhythmic and nonarrhythmic causes on the basis of the available information. Of the 26 deaths that were classified as noncardiac, 10 were due to cancer, 7 to pneumonia, 5 to stroke, and 1 each to a drug overdose, suicide, liver failure, and renal failure. With respect to the other four deaths (two in each group), there was not enough information to determine the cause of death. Some of these deaths could have been due to arrhythmia.

During the follow-up period, 41 patients received 91 appropriate ICD shocks. In addition, 49 patients

Variable	No. of Patients	Relative Risk of Death from Any Cause
Sex		
Female	132	
Male	326	
Age		
<65 yr	301	
≥65 yr	157	
LVEF		
<20%	148	
≥20%	310	
QRS interval		
<120 msec	311	
≥120 msec	147	
NYHA class		
I	99	
II	263	
III	96	
History of atrial fibrillation		
No	346	
Yes	112	
All patients	458	

Figure 2. Subgroup Analysis of the Relative Risk of Death from Any Cause among Patients Who Received an Implantable Cardioverter–Defibrillator (ICD), as Compared with Those Who Received Standard Therapy.

The dashed line indicates the hazard ratio for the overall population. None of the differences between subgroups were significant. LVEF denotes left ventricular ejection fraction, and NYHA New York Heart Association.

received inappropriate ICD shocks, primarily for atrial fibrillation or sinus tachycardia.

SUBGROUP ANALYSIS

Although the study was not powered to detect differences within subgroups, several prespecified analyses were performed regarding variables that could affect survival (Fig. 2). A Cox proportional-hazards model was used to analyze differences in survival in predefined subgroups. Men had a relative risk of death from any cause of 0.49 (95 percent confidence interval, 0.27 to 0.90; P=0.018) after the implantation of an ICD. Patients with NYHA class III heart failure had a relative risk of death of 0.37 (95 percent confidence interval, 0.15 to 0.90; P= 0.02) after receiving an ICD (Fig. 3).

DISCUSSION

Our results indicate that patients with left ventricular dysfunction due to nonischemic cardiomyopathy have an annual rate of death from any cause of about 7 percent when treated with standard medical therapy for heart failure. Therapy with an ICD significantly reduced the risk of sudden death from arrhythmia (hazard ratio, 0.20; P=0.006) and resulted
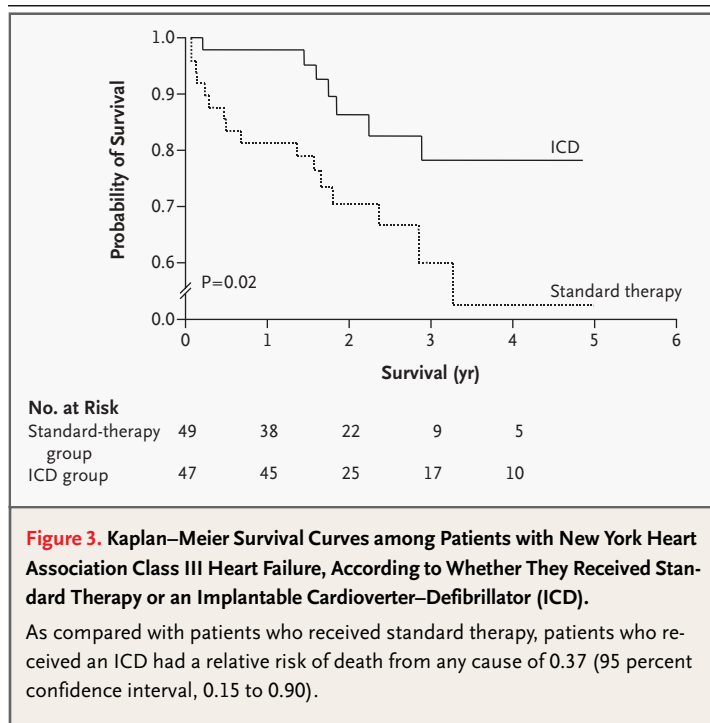
in a reduction in the risk of death from any cause that approached but did not reach statistical significance (hazard ratio, 0.65; P=0.08).

As in prior trials, the ICD was highly effective at preventing sudden death from cardiac causes.[4-7] The difference in mortality between the standard-therapy group and the ICD group was almost entirely due to a difference in the incidence of death from cardiac arrhythmia. On the basis of data available at the time the study was designed, more than 50 percent of the deaths were expected to be due to arrhythmia, and thus, the trial was powered to detect a 50 percent difference in the rates of death from any cause. However, only approximately one third of the deaths in the standard-therapy group were due to arrhythmia. Eighty-five percent of the patients in this study were treated with ACE inhibitors and beta-blockers — a higher compliance rate than in other studies.[4-7] The lower-than-expected rate of sudden death from arrhythmia may have been due to the high rate of use of beta-blockers and ACE inhibitors[19-23] and may thus have resulted in the nonsignificant reduction in deaths from any cause. Subgroup analyses revealed that the implantation of an ICD significantly reduced the risk of death among patients who had NYHA class III heart failure and among men. However, further studies will be required to determine whether these findings are clinically important.

Prior large-scale studies evaluating the effect of prophylactic implantation of an ICD for the prevention of sudden death have focused on patients with coronary disease.[5-7] Our trial was designed to evaluate the effect of an ICD on the risk of death among patients with nonischemic cardiomyopathy who were receiving standard therapy, usually including ACE inhibitors and beta-blockers. The second Multicenter Automatic Defibrillator Implantation Trial (MADIT II) reported a decrease in the relative risk of death from any cause of 31 percent among patients who received an ICD — which was similar to our finding of a 35 percent decrease.[7]

Two recent small studies have examined the use of ICDs in patients with nonischemic dilated cardiomyopathy.[24,25] Each of these studies randomly assigned only approximately 100 patients and failed to show a benefit of the ICD. However, the sample size of these studies was too small to show even a moderate effect of the ICD on the risk of death.[24,25]

Our study design did not include a group of patients who were treated with amiodarone. Several

Figure 3. Kaplan–Meier Survival Curves among Patients with New York Heart Association Class III Heart Failure, According to Whether They Received Standard Therapy or an Implantable Cardioverter–Defibrillator (ICD).

As compared with patients who received standard therapy, patients who received an ICD had a relative risk of death from any cause of 0.37 (95 percent confidence interval, 0.15 to 0.90).

previous studies have suggested that amiodarone therapy slightly reduces the risk of death, especially in patients with nonischemic cardiomyopathy.[26] However, those data alone cannot be used to support the use of amiodarone as standard therapy in this patient population.[25-27] Since the data supporting the use of beta-blockers to improve survival were clear at the time our study was designed, the use of amiodarone was specifically discouraged owing to concern that its use would limit the ability to titrate beta-blockers to therapeutic doses. Aldosterone antagonists were not used as standard therapy in this study, since no survival benefit of these agents had been demonstrated in patients with NYHA class I, II, or III heart failure due to nonischemic cardiomyopathy.[28,29]

On the basis of our results, the routine implantation of a cardioverter–defibrillator cannot be recommended for all patients with nonischemic cardiomyopathy and severe left ventricular dysfunction. However, our findings of a reduction in sudden death from arrhythmia and an apparent benefit of ICDs in subgroup analyses suggest that the use of these devices should be considered on a case-by-case basis.

APPENDIX

The following investigators and centers participated in the study: F. Abi-Samra, E. Faranceware, *Alton Ochsner Medical Foundation, New Orleans;* C. Albert, B. Kelly, *Massachusetts General Hospital, Boston;* A. Bhandari, B. Firth, *Heart Institute, Good Samaritan Hospital, Los Angeles;* B. Belhassen, *Ichilov Hospital, Tel Aviv, Israel;* H. Calkins, J. Bolt, *Johns Hopkins Hospital, Baltimore;* T. Chow, J. Everett, *Linder Clinical Trial Center, Cincinnati;* J. Conti, D. Leach, *University of Florida, Gainesville;* J. Cook, J. Provencher, *Baystate Medical Center, Springfield, Mass.;* S. Cossu, K. Mullinax, *Charlotte Heart Group, Port Charlotte, Fla.;* R. Damle, L. Stoune, *South Denver Cardiology, Littleton, Colo.;* J.P. Daubert, G. Head, *University of Rochester Medical Center, Rochester, N.Y.;* M. Eldar, *Sheba Medical Center, Tel Hashomer, Israel;* N.A.M. Estes III, S. Galvin, *New England Medical Center, Boston;* N. Freedberg, *Haemek Medical Center, Afula, Israel;* J. Goldberger, K. Acker, *Northwestern University, Chicago;* C. Gottlieb, F. Hoffman, *Abington Medical Specialists, Abington, Pa.;* M. Hazday, L. Jopperi, *Orlando Regional Medical Center, Orlando, Fla.;* B. Hook, L. Pimenta, *New England Heart Institute, Manchester, N.H.;* G. Horvath, E. Healy, *Berkeley Cardiovascular Medical Group, Berkeley, Calif.;* L.L. Horvitz, M. Cole-Ferry, *Cardiovascular Associates of the Delaware Valley, Cherry Hill, N.J.;* L. Kanter, P. Farrar, *Virginia Beach General Hospital, Virginia Beach;* A. Katz, *Soroka Medical Center, Beer Sheva, Israel;* S. Klein, D. Ricks, *LeBauer Cardiovascular Research Foundation, Greensboro, N.C.;* H.A. Kopelman, C. Griffith, *American Cardiovascular Research Institute, Atlanta;* C.S. Kuo, L. Withrow, *University of Kentucky Division of Cardiovascular Medicine, Lexington;* J.H. Levine, M. Ferrara, *Cardiac Arrhythmia and Pacemaker Center of St. Francis Hospital, Roslyn, N.Y.;* D. Man, B. Gardner, S. Gable, *Associated Cardiologists/Pinnacle Health Hospitals, Harrisburg, Pa.;* F. Marchlinski, G. Schott, *Hospital of the University of Pennsylvania, Philadelphia;* D. Martin, N. Todd, *Lahey Hitchcock Medical Center, Burlington, Mass.;* T. Mattioni, S. Welch, *Arizona Arrhythmia Consultants, Phoenix;* R. McCowan, C. Tignor, *Charleston Cardiology Group, Charleston, W.V.;* J.P. McKenzie, III, N. Magno, *California Cardiac Institute, Glendale;* J. Merrill, T. Dicken, *The Heart Center, Cardiovascular Associates, Kingsport, Tenn.;* W. Miles, M. Barr, *Southwest Florida Heart Group, Fort Myers;* A. Natale, D. Holmes, *Cleveland Clinic Foundation, Cleveland;* B. Pavri, K. Henry, *Thomas Jefferson University Hospital, Philadelphia;* J. Pennington III, L. Bittner, *Christiana Health Care Systems, Newark, Del.;* E. Rashba, M. Mclane, *University of Maryland School of Medicine, Baltimore;* S. Rothbart, J. McCarthy, *Newark Beth Israel Medical Center, Newark, N.J.;* D. Rubenstein, C. Bell, *Arrhythmia Consultants, Greenville, S.C.;* S. Saba, D. Parkinson, *University of Pittsburgh Medical Center, Pittsburgh;* W.E. Sanders, C.A. Sueta, M.C. Herbst, *University of North Carolina at Chapel Hill, Chapel Hill;* A. Shalaby, K. Hickey, *Veterans Affairs Pittsburgh Healthcare System, Pittsburgh;* J. Szwed, J. Jackson, *The Care Group, Indianapolis;* T. Talbert, L. Wright, *Diagnostic Center, Chattanooga, Tenn.;* R.K. Thakur, L. Blaske, *Thoracic and Cardiovascular Healthcare Foundation, Lansing, Mich.;* S.L. Winters, K. Wain, *Morristown Memorial Hospital, Morristown, N.J.;* J. Zebede, S. Tong, *Mt. Sinai Hospital, Miami Beach, Fla.;* **Events Committee** — J.P. Daubert, *University of Rochester Medical Center, Rochester, N.Y.;* S. Murali, *University of Pittsburgh Medical Center, Pittsburgh;* B. Pavri, *Hospital of the University of Pennsylvania, Philadelphia;* S.L. Winters, *Morristown Memorial Hospital, Morristown, N.J.*

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