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Patients With Recently Diagnosed Nonischemic Cardiomyopathy Benefit From Implantable Cardioverter-Defibrillators

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OBJECTIVES This study sought to determine whether the time from diagnosis to randomization was related to outcome in a clinical trial of implantable cardioverter-defibrillator (ICD) insertion in nonischemic cardiomyopathy.

BACKGROUND Whether the duration of nonischemic cardiomyopathy is related to arrhythmic risk and the possible benefit of ICD insertion is unknown.

METHODS The Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial randomized 458 patients with nonischemic dilated cardiomyopathy and a left ventricular ejection fraction <36% to receive standard medical therapy with or without an ICD. Patients were randomized regardless of the duration of known cardiomyopathy as long as a reversible cause of left ventricular dysfunction was not present. Patients were divided into recently and remotely diagnosed nonischemic cardiomyopathy groups based on the time from diagnosis of cardiomyopathy to randomization. To categorize patients, cut points of three and nine months were used.

RESULTS Patients with recently diagnosed cardiomyopathy who received an ICD had better survival than those treated with standard therapy at both cut points. This difference in survival was significant at three months ($p < 0.05$) and was borderline significant at nine months ($p = 0.058$). Patients with remotely diagnosed cardiomyopathy did not have a significant survival benefit with ICD insertion, but there were no significant differences between ICD benefit in the recent and remote diagnosis groups ($p = 0.17$ and 0.25).

CONCLUSIONS Patients who have a recent cardiomyopathy diagnosis do not have any less ICD benefit than those with a remote diagnosis. Thus, ICD therapy should be considered in such patients as soon as they are identified as long as a reversible cause of left ventricular dysfunction is excluded. (J Am Coll Cardiol 2006;47:2477–82) © 2006 by the American College of Cardiology Foundation

Patients with nonischemic dilated cardiomyopathy (NIDCM) have a heterogeneous group of disorders contributing to left ventricular dysfunction (1). The time course of progression of left ventricular dysfunction is variable, and the risk factors for sudden and nonsudden death may differ over time in patients with different etiologies of NIDCM (2,3). The Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial randomized patients with nonischemic dilated cardiomyopathy, New York Heart Association (NYHA) heart failure class I to III, left ventricular ejection fraction ≤0.35, and documented ambient ventricular arrhythmia to receive standard medical therapy or standard medical therapy plus an implantable cardioverter-defibrillator (ICD) (4). No specific duration of NIDCM was required before randomization in the DEFINITE trial, but physicians were asked to exclude patients in whom a reversible cause of left ventricular dysfunction was present. Recently, the Center for Medical Services approved ICD insertion for patients who had NIDCM of at least nine months in duration (5,6).

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Patients with NIDCM of three to nine months in duration may undergo ICD insertion if they are enrolled in a registry. Patients within three months of diagnosis do not qualify for ICD insertion. This recommendation was not based on the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) or the DEFINITE trial inclusion criteria (4,7,8). Whether the duration of nonischemic cardiomyopathy is related to possible ICD benefit is unknown. The purpose of the present study was to determine whether the time from diagnosis of cardiomyopathy to randomization is related to

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Abbreviations and Acronyms

CI	=	confidence interval
DEFINITE	=	Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation
HR	=	hazard ratio
ICD	=	implantable cardioverter-defibrillator
NIDCM	=	nonischemic dilated cardiomyopathy
NYHA	=	New York Heart Association
SCD-HeFT	=	Sudden Cardiac Death in Heart Failure Trial

prognosis and to estimate the degree of ICD benefit that patients receive using a post-hoc analysis of the DEFINITE trial data.

METHODS

The DEFINITE trial randomized 458 patients with nonischemic dilated cardiomyopathy to one of two groups: 1) standard medical therapy and 2) standard medical therapy plus a single-chamber ICD. Details of the overall trial have been previously published (4). Briefly, over 85% of patients in the trial were treated with beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The mean left ventricular ejection fraction was 0.21, and the mean age was 60 years. Patients randomized to the ICD had a 35% decrease in all-cause mortality—a difference that did not reach significance ($p = 0.08$). A significant reduction (80%) in sudden arrhythmic cardiac death was noted ($p < 0.05$). The DEFINITE trial protocol did not specify criteria for a minimum length of time from diagnosis of nonischemic cardiomyopathy to randomization. Physicians were instructed not to randomize patients if there was a reversible cause of cardiomyopathy, such as peripartum cardiomyopathy, myocarditis, or acute drug-induced cardiomyopathy. However, patients were randomized regardless of the duration of known cardiomyopathy as long as the treating physician did not think that a reversible cause of left ventricular dysfunction was present. The time from diagnosis of cardiomyopathy to randomization was reported to the nearest month. Most patients ($n = 350$; 76%) were classified as having idiopathic NIDCM. The number of patients with different etiologies of cardiomyopathy was too small to allow analysis of interactions between cause of cardiomyopathy and outcome.

Statistical methods. All 458 DEFINITE trial patients were stratified based on how long they had had the NIDCM diagnosis at the time of randomization. Three- and nine-month cut points were used for stratification. Baseline characteristics of the patients with shorter and longer NIDCM duration were compared using two-sample *t* tests for continuous variables and chi-square tests for categorical variables with one exception. Duration of NIDCM diagnosis at the time of randomization, although a continuous variable, was highly skewed toward longer time from diagnosis to randomization. Therefore, the nonparametric Wilcoxon rank-sum test was used to examine differences between treatment arms on this variable.

Kaplan-Meier survival curves were constructed and compared using the log-rank test. The Cox proportional hazards model was used to test and compare the impact of treatment assignment in recent and remote NIDCM duration strata at both cut points. The differences in all-cause mortality between recently and remotely diagnosed patients at both cut points were compared first. Subsequently, control for treatment assignment was implemented by adding this variable as a second predictor. Finally, an interaction term between NIDCM duration and treatment assignment was introduced to test for the difference between standard/ICD hazard ratios in recent and remote subgroups. The final model using the three predictors was further adjusted for the patient's NYHA functional class, white race, diabetes, and QRS duration. This dichotomized analysis was not prespecified in the initial protocol, and this article presents a post-hoc analysis. Variables used in adjustment were those that were different between treatment arms for patients in strata with recent or remote NIDCM diagnoses. A critical p value of 0.05 was used for all tests. The effect of treatment assignment on arrhythmic mortality for recently and remotely diagnosed patients was not tested because of a low number of events in the subgroups.

RESULTS

The mean time from diagnosis of cardiomyopathy to randomization was 2.9 ± 4 years. The range was from <1 month to 38.5 years (median 1 year, interquartile range 2 months to 4.6 years). There was a difference in time from diagnosis of cardiomyopathy to randomization between the ICD and standard therapy groups. As a rule, standard therapy patients were diagnosed more remotely (medians 20 and 8 months, respectively; $p = 0.032$ based on the Wilcoxon rank-sum test).

Patients were divided into recently and remotely diagnosed nonischemic cardiomyopathy based on the time from initial diagnosis of cardiomyopathy to randomization using cut points of three and nine months. Table 1 shows demographic characteristics of patients with recently diagnosed and remotely diagnosed cardiomyopathy for cut points of three and nine months. There were significant differences between patients with recently and remotely diagnosed cardiomyopathy in race, QRS duration, NYHA functional classification, and in the presence of diabetes (Table 1). Not surprisingly, those patients with more remotely diagnosed cardiomyopathy had a longer QRS duration, more severe heart failure, and a higher prevalence of diabetes than those with recently diagnosed cardiomyopathy.

Overall, survival was similar in patients with recently and remotely diagnosed cardiomyopathy. When a cut point of three months was used, 10.2% of patients with recently diagnosed cardiomyopathy were deceased at 2.5 years, as

Table 1. Demographic Characteristics of Patients With Recently and Remotely Diagnosed Cardiomyopathy: 3- and 9-Month Cut Points

	≤3 Mo; n = 150		>3 Mo; n = 308		≤9 Mo; n = 216		>9 Mo; n = 242	
	n	%	n	%	n	%	n	%
ICD group	82	54.7	147	47.7	120	55.6	109 *	45.0
Gender, male	109	72.7	217	70.5	153	70.8	173	71.5
Race, white	112	74.7	197*	64.0	162	75.0	147*	60.7
History of AF	31	20.7	81	26.3	44	20.4	68	28.1
NYHA functional class I	36	24.0	63	20.5	55	25.5	44*	18.2
NYHA functional class II	87	58.0	176	57.1	122	56.5	141	58.3
NYHA functional class III	27	18.0	69	21.0	39	18.1	57	23.6
Diabetes	20	13.3	85*	27.6	35	16.2	70*	28.9
Hypertension	12	8.0	37	12.0	21	9.7	28	11.6
Beta-blocker	128	85.3	260	84.4	189	87.5	200	82.6
ACE/ARB	142	94.7	291	94.5	206	95.4	227	93.8
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (yrs)	58.2	13.2	58.3	12.8	57.8	13.4	58.7	12.5
QRS (ms)	109.4	27.4	117.9*	28.9	111.2	27.8	118.6*	29.1
LVEF (%)	20.9	5.7	21.6	6.2	21.0	5.4	21.7	6.5

*$p < 0.050$, difference between recently and remotely diagnosed patients.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin-receptor blocker; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SD = standard deviation.

opposed to 16.0% of patients in remotely diagnosed group (hazard ratio [HR] 1.41; 95% confidence interval [CI] 0.82 to 2.41; p = 0.22). When a cut point of 9 months was used, 11.2% of patients with recently diagnosed cardiomyopathy were deceased at 2.5 years, as opposed to 16.8% of those with remotely diagnosed cardiomyopathy (HR 1.38; 95% CI 0.850 to 2.24; p = 0.194). Once assignment to ICD or standard therapy was controlled for in the entire sample, there was also no difference in overall survival between the recently and remotely diagnosed groups (HR 1.36; 95% CI 0.79 to 2.34; and HR 1.32; 95% CI 0.81 to 2.15 at three- and nine-month cut points; p = 0.26 at both cut points). Finally, when patients treated with standard therapy were considered alone, there was no difference in overall survival between the recently and remotely diagnosed patients (HR 1.00; 95% CI 0.51 to 1.96; p = 1.00 and HR 1.04; 95% CI 0.55 to 1.95; p = 0.91 for three- and nine-month cut points).

The ICD insertion was associated with a reduced risk of death for patients who had been diagnosed shortly before their enrollment in the study (Table 2, Figs. 1 and 2). A significant difference was found between treatment arms in patients with recently diagnosed cardiomyopathy when a cut point of three months was used (HR 0.37; 95% CI 0.14 to 0.998; p = 0.049) and the difference at nine months was borderline significant (HR 0.48; 95% CI 0.23 to 1.025; p = 0.058) for these patients. The ICD insertion was not significantly related to survival for patients who had been diagnosed with NIDCM for longer periods of time (HR 0.82; 95% CI 0.47 to 1.43; p = 0.48 and HR 0.86; 95% CI 0.46 to 1.94; p = 0.64 at three- and nine-month cut points). Despite the fact that treatment assignment was significantly related to improved survival in patients with shorter NIDCM duration but not in patients with longer duration, the association of treatment assignment with outcome was not significantly different in the two NIDCM duration groups as indicated by the nonsignificant interaction term (p = 0.17 and 0.25 at three- and nine-month cut points, respectively).

Adjusting for covariates that were different between patients with recently and remotely diagnosed cardiomyopathy did not substantially alter the findings of the unadjusted model. The hazard ratios for the effect of ICD therapy were still not significant in patients with longer NIDCM diagnosis times (HR 0.80; 95% CI 0.46 to 1.41; p = 0.44 and HR 0.86; 95% CI 0.46 to 1.61; p = 0.63 at three- and nine-month cut points). After adjustment, the hazard ratio for ICD treatment became significant in the recently diagnosed group at the nine-month cut point (HR 0.46; 95% CI 0.216 to 0.986; p = 0.046), and it remained

Table 2. All-Cause Mortality of Patients With Recently and Remotely Diagnosed Cardiomyopathy: 3- and 9-Month Cut Points

	≤3 Mo; n = 150		>3 Mo; n = 308		≤9 Mo; n = 216		>9 Mo; n = 242	
Deaths	n	%	n	%	n	%	n	%
All patients	18/150	12.0	50/308	16.2	28/216	13.0	40/242	16.5
Standard therapy	12/68	17.6	28/161	17.4	17/96	17.7	23/133	17.3
ICD	6/82*	7.3	22/147	15.0	11/120	9.2	17/109	15.6

*$p < 0.05$; rates in standard therapy and ICD groups are significantly different by Cox regression test.

Abbreviations as in Table 1.

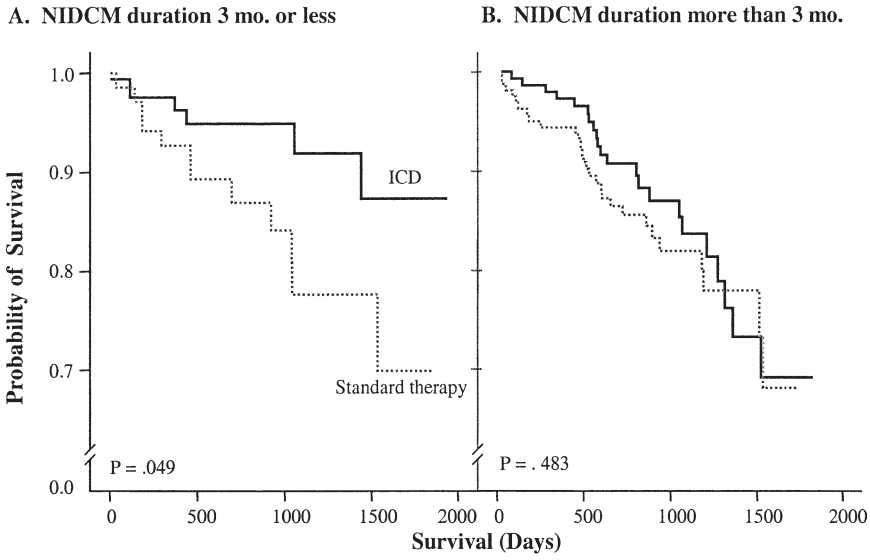

Figure 1. Kaplan-Meier estimates of death from any cause by treatment arm in patients with three months of nonischemic dilated cardiomyopathy (NIDCM) duration or less **(A)** and patients with more than three months of NIDCM duration **(B)**. ICD = implantable cardioverter-defibrillator.

unchanged for the same comparison with the three-month cutoff (HR 0.38; 95% CI 0.14 to 1.000; p = 0.050). As before adjustment, the impact of treatment did not significantly differ among patients with shorter and longer NIDCM diagnosis durations (p = 0.186 and 0.22 at three- and nine-month cut points, respectively). The outcomes were also generally similar when we used a subset of covariates that were prespecified in the original DEFINITE study; namely, gender, age, left ventricular ejection fraction, and NYHA functional class. The only notable difference, again, occurred in the analysis of the data with the nine-month split—the ICD benefit in the recently diagnosed cohort, which only showed trend levels in the original analysis, was now significant (HR 0.43; 95% CI 0.20 to 0.093; p = 0.032).

DISCUSSION

The primary finding of the present study is that patients who have a recent cardiomyopathy diagnosis do not have any less ICD benefit than those with a remote diagnosis. This result would not necessarily be expected because patients with recently diagnosed cardiomyopathy could potentially have reversible causes of left ventricular dysfunction and might be expected to have a lower risk of death. Patients with a clinical picture consistent with a reversible cause such as myocarditis, tachycardia-induced cardiomyopathy, or peripartum cardiomyopathy were excluded from randomization in the DEFINITE trial. Of patients who were randomized, whether the definition of recent diagnosis was set at three or nine months, those patients with more

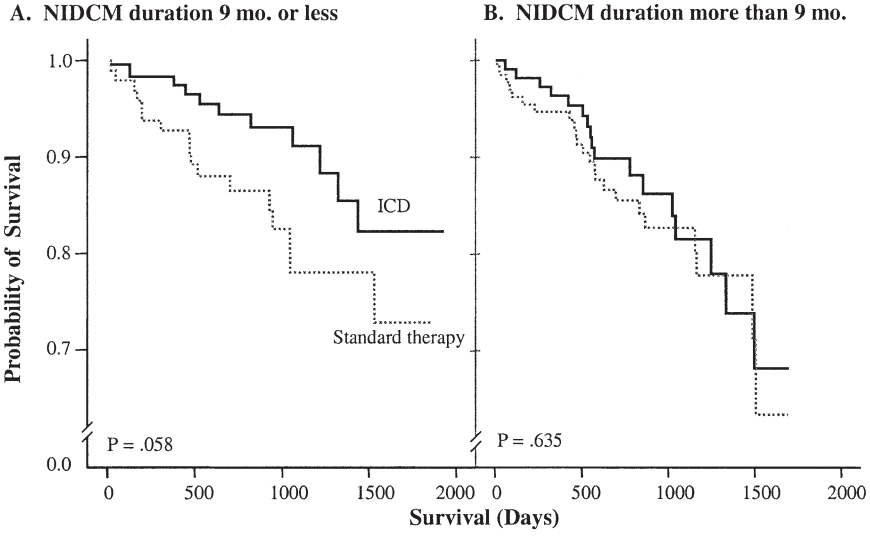

Figure 2. Kaplan-Meier estimates of death from any cause by treatment arm in patients with nine months of nonischemic dilated cardiomyopathy (NIDCM) duration or less **(A)** and patients with more than nine months of NIDCM duration **(B)**. ICD = implantable cardioverter-defibrillator.

recently diagnosed nonischemic cardiomyopathy had a significant benefit from the ICD when appropriate clinical covariates were controlled. The ICD benefit in the recently diagnosed group was not caused by death soon after randomization because the survival curves continue to diverge throughout the entire trial period. Although the ICD was related to significantly improved survival in patients with recently diagnosed cardiomyopathy but not in those with cardiomyopathy of a longer duration, the relative difference between the recent and remotely diagnosed groups for ICD benefit was not significant. Thus, based on these results, one cannot conclude that there is a difference in ICD benefit based on the duration of nonischemic cardiomyopathy.

The natural history of nonischemic cardiomyopathy is variable. The evolution and prognosis of the disease may be determined by the underlying cause of the cardiomyopathy. In one series of 1,230 patients referred for evaluation of unexplained cardiomyopathy, the etiology was found to be idiopathic (50%), myocarditis (9%), infiltrative myocardial disease, hypertension, human immunodeficiency virus, peripartum cardiomyopathy, connective tissue disease, substance abuse, doxorubicin-induced, and other causes (all <5%) (1). This series was published before the results of the more recent studies became available, suggesting that genetic disorders were a common cause of nonischemic cardiomyopathy (9). The patients randomized in the DEFINITE trial had a variety of etiologies of nonischemic cardiomyopathy, but the majority was classified as idiopathic. Perhaps a task force of heart failure experts should be established to develop a reliable list of reversible myopathic processes (myocarditis, severe obstructive outflow tract disease, paroxysmal atrial fibrillation, frequent ventricular ectopy, and so on) before a more aggressive approach to defibrillator implantation is considered in this patient population.

In the present study, patients with more recently diagnosed nonischemic cardiomyopathy had a similar survival compared with those with NIDCM of a longer duration. The ICD benefit seemed at least as prominent in those with recently diagnosed cardiomyopathy. One possible explanation is that as the duration of heart failure increases, the percentage of deaths caused by nonarrhythmic causes increase, leading to a less apparent ICD benefit.

In a prior analysis, using the time from diagnosis of cardiomyopathy to randomization did not significantly affect ICD benefit when it was used as a continuous variable in a covariate analysis (4). This conclusion is similar to that drawn from the nonsignificant interaction term between the time to diagnosis and ICD benefit. However, the trend toward a greater ICD benefit in those patients with recently diagnosed cardiomyopathy was accentuated by the dichotomous analysis. There is biological plausibility to dichotomizing this parameter. The time immediately after the development of cardiomyopathy may be a time when the disease process and consequent remodeling are in rapid evolution, and this process may stabilize after some time. Cardiomyopathy of 10 years' duration may be no different in risk from that of 2 years, yet a continuous variable analysis would seek to assign highly different risk values to these time points.

There were some differences in baseline characteristics between patients with recently and remotely diagnosed cardiomyopathy. Although the differences that reached statistical significance changed depending on which cut point was used (Table 1), in the case of NYHA functional class, in general, patients with remotely diagnosed cardiomyopathy had a longer QRS duration and a lower percentage of patients with NYHA class I heart failure. These differences might be expected in patients with a longer duration of heart failure. Patients with remotely diagnosed cardiomyopathy were more likely to have diabetes and were more likely to be nonwhite. These differences likely occurred by chance. Correcting for demographic differences between the two groups did not substantially alter the hazard ratio for ICD benefit for either the recently or the remotely diagnosed groups.

Prior studies. Three prior trials have examined the survival benefit of ICDs for the primary prevention of sudden death in nonischemic cardiomyopathy (7,10,11). Two meta-analyses have examined the use of ICDs for the secondary prevention of sudden death in patients with nonischemic cardiomyopathy (12,13). No prior studies have specifically examined whether ICD benefit varies depending on the time from diagnosis of cardiomyopathy to randomization.

Study limitations. The DEFINITE trial was not powered to examine the time from diagnosis of nonischemic cardiomyopathy to randomization, and the results of post-hoc studies should be interpreted with caution; however, the finding that patients with recently diagnosed cardiomyopathy benefited from ICD insertion did not significantly change after adjusting for covariates adds to the strength of these observations. There was a difference in the time from diagnosis of cardiomyopathy to randomization between the ICD and standard therapy groups, and somewhat different numbers of patients were randomized to each treatment assignment in recently and remotely diagnosed groups (Table 1). However, the Cox regression analysis does not require equal sample sizes, and thus the results of the analysis should be valid.

Although the main report of the DEFINITE trial suggested a 35% decrease in mortality with ICD therapy, these results did not reach significance. Therefore, the lack of a significant effect in some of the subgroups is not unexpected and cannot provide definite conclusions. However, a recent meta-analysis has shown the ICD to decrease mortality in NIDCM, and the subgroup findings in the present study also suggest that patients with recently diagnosed NIDCM may benefit from ICD insertion (12).

Conclusions. The risk of death seems high in patients with a recent diagnosis of cardiomyopathy, and ICD implantation seems to reduce this risk. Thus, if the ICD does provide benefit by improving survival in patients with nonischemic cardiomyopathy, as suggested by recent trials (12), ICD

therapy may be appropriate in such patients as soon as they are identified and reversible left ventricular dysfunction is excluded.

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