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Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events

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ABSTRACT

BACKGROUND

This trial was designed to determine whether cardiac-resynchronization therapy (CRT) with biventricular pacing would reduce the risk of death or heart-failure events in patients with mild cardiac symptoms, a reduced ejection fraction, and a wide QRS complex.

METHODS

During a 4.5-year period, we enrolled and followed 1820 patients with ischemic or nonischemic cardiomyopathy, an ejection fraction of 30% or less, a QRS duration of 130 msec or more, and New York Heart Association class I or II symptoms. Patients were randomly assigned in a 3:2 ratio to receive CRT plus an implantable cardioverter–defibrillator (ICD) (1089 patients) or an ICD alone (731 patients). The primary end point was death from any cause or a nonfatal heart-failure event (whichever came first). Heart-failure events were diagnosed by physicians who were aware of the treatment assignments, but they were adjudicated by a committee that was unaware of assignments.

RESULTS

During an average follow-up of 2.4 years, the primary end point occurred in 187 of 1089 patients in the CRT–ICD group (17.2%) and 185 of 731 patients in the ICD-only group (25.3%) (hazard ratio in the CRT–ICD group, 0.66; 95% confidence interval [CI], 0.52 to 0.84; P=0.001). The benefit did not differ significantly between patients with ischemic cardiomyopathy and those with nonischemic cardiomyopathy. The superiority of CRT was driven by a 41% reduction in the risk of heart-failure events, a finding that was evident primarily in a prespecified subgroup of patients with a QRS duration of 150 msec or more. CRT was associated with a significant reduction in left ventricular volumes and improvement in the ejection fraction. There was no significant difference between the two groups in the overall risk of death, with a 3% annual mortality rate in each treatment group. Serious adverse events were infrequent in the two groups.

CONCLUSIONS

CRT combined with ICD decreased the risk of heart-failure events in relatively asymptomatic patients with a low ejection fraction and wide QRS complex. (ClinicalTrials.gov number, NCT00180271.)

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Patients with cardiac disease and reduced left ventricular function are at increased risk for arrhythmia-related sudden death and heart failure. The placement of an implantable cardioverter–defibrillator (ICD) improves survival and reduces the risk of sudden death in appropriately selected patients with cardiac disease.[1-3] However, life-prolonging defibrillator therapy is associated with an increased risk of first and recurrent heart-failure events.[4] Cardiac-resynchronization therapy (CRT) with biventricular pacing is an effective adjunctive therapy to pharmacologic management in reducing the rate of hospitalization in symptomatic patients with advanced heart-failure symptoms (New York Heart Association [NYHA] class III or IV), an ejection fraction of 35% or less, and an intraventricular conduction delay of 120 msec or more.[5-7]

Findings from a recent study in patients with cardiac disease who have less advanced heart-failure symptoms suggest that CRT can improve cardiac structure and function through reverse left ventricular remodeling.[8] Our randomized study, called the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT), was designed to determine whether prophylactic CRT in combination with an ICD (CRT–ICD) would reduce the risk of death or nonfatal heart-failure events (whichever came first) in patients with an ejection fraction of 30% or less, a QRS duration of 130 msec or more, and NYHA class I or II symptoms, as compared with patients receiving only an ICD.[9]

Methods

Trial Design and Oversight

From December 22, 2004, through April 23, 2008, a total of 1820 patients were enrolled at 110 hospital centers: 1271 patients at 88 centers in the United States, 22 patients at 2 centers in Canada, and 527 patients at 20 centers in Europe. Follow-up continued thereafter until trial termination.

The protocol was approved by the institutional review board at each of the participating centers. The primary hypothesis was that CRT–ICD therapy would be associated with a reduced risk of death or nonfatal heart-failure events (whichever came first), as compared with ICD-only treatment. We anticipated a low annual mortality, since the enrolled patients would be in NYHA class I or II, and patients in both study groups would receive an ICD. All investigators agreed to abide by the conflict-of-interest guidelines described by Healy et al.[10] A description of the study design has been published previously.[9] All patients provided written informed consent. The trial's sponsor, Boston Scientific, was not involved in data collection or data analysis. The authors vouch for the accuracy and completeness of the reported findings.

Recruitment and Follow-up

Patients of either sex who were at least 21 years of age could participate in the study if they had ischemic cardiomyopathy (NYHA class I or II) or nonischemic cardiomyopathy (NYHA class II only), sinus rhythm, an ejection fraction of 30% or less, and prolonged intraventricular conduction with a QRS duration of 130 msec or more. All eligible subjects met the guideline indication for ICD therapy.[7] Patients were excluded from enrollment for a variety of reasons, including an existing indication for CRT; having an implanted pacemaker, ICD, or resynchronization device; NYHA class III or IV symptoms, previous coronary-artery bypass grafting, percutaneous coronary intervention, or an enzyme-positive myocardial infarction within 3 months before enrollment; atrial fibrillation within 1 month before enrollment; and other exclusion criteria, as reported previously[9] (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

Patients were seen in clinical follow-up at 1 month after randomization and then at 3-month intervals until the termination of the trial. Clinical evaluation and device testing were carried out at each follow-up visit. The treating physicians were aware of study-group assignments.

Randomization

A baseline clinical history, 12-lead electrocardiogram, and echocardiogram were obtained for each patient; we also performed a baseline physical examination and 6-minute walk test. The patients were randomly assigned in a 3:2 ratio to receive either CRT with an ICD (CRT–ICD group) or only an ICD (ICD-only group) and were stratified according to clinical center and ischemic status with the use of an algorithm that ensured near balance in each stratum.

Echocardiographic Studies

Two-dimensional echocardiography[11] was performed at baseline and at the 1-year follow-up to assess changes in the left ventricular volumes and ejection fraction in the two study groups. At 1 year,

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we evaluated 746 patients in the CRT–ICD group and 620 patients in the ICD-only group. The Food and Drug Administration initially required that CRT pacing be turned off during the 1-year echocardiography, but this requirement was subsequently reversed, and 746 paired echocardiographic studies were obtained in the CRT–ICD group with resynchronization on at 1 year. Volumes were estimated by averaging those derived from the two-chamber and four-chamber views according to Simpson's method, and the ejection fraction was calculated in the usual fashion.

THERAPY

Commercially available transvenous devices (Boston Scientific) were used in the trial. Standard techniques were used to implant the CRT–ICD and ICD-only devices. Device testing and programming were performed as reported previously,[9] along with the provision of optimal pharmacologic therapy for heart failure, in the two study groups. In the CRT–ICD group, the programmed mode was DDD with a lower rate of 40 bpm and hysteresis off. In the ICD-only group, the programmed pacing mode was VVI for single-chamber units and DDI for dual-chamber units, with lower rates of 40 bpm and hysteresis off in both single- and dual-chamber units.

PRIMARY END POINT

The primary end point was death from any cause or nonfatal heart-failure events, whichever came first. The diagnosis of heart failure, which was made by physicians who were aware of study-group assignments, required signs and symptoms consistent with congestive heart failure that was responsive to intravenous decongestive therapy on an outpatient basis or an augmented decongestive regimen with oral or parenteral medications during an in-hospital stay. Adjudication of the end points was carried out by an independent mortality committee and by a heart-failure committee that was unaware of study-group assignments, according to prespecified criteria, as described previously.[9]

STATISTICAL ANALYSIS

Data analysis was performed according to the intention-to-treat principle. We used a Wang–Tsiatis ($\Delta=0.1$ category) group-sequential design[12] with a power of 95% to detect a hazard ratio of 0.75 at a two-sided significance level of 0.05. The trial involved prespecified event monitoring by an independent data and safety monitoring board at up to 20 successive multiples of approximately 35 adjudicated events, precisely specified in terms of variance of the log-rank statistic, with stopping boundaries specified for termination of the trial in favor of CRT–ICD therapy, in favor of ICD-only therapy, or for no significant difference (Fig. 1). The analysis of the primary end point, which was based on the statistical log-rank test stratified according to study center and ischemia status, was used to evaluate statistical significance for the trial. A similarly stratified Cox proportional-hazards regression model[13,14] was used to estimate hazard ratios. Both of these analyses were adjusted for the group-sequential stopping rule and incorporated late reported events that occurred before

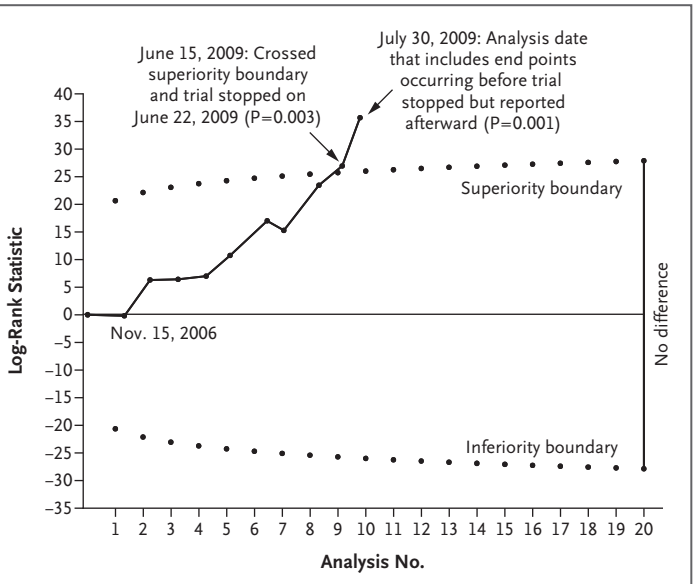

Figure 1. Sequential Monitoring in the Group-Sequential Design.

The log-rank statistic is the measure of the cumulative difference in occurrence of end-point events between the two study groups. The horizontal axis reflects 20 prespecified analyses, each requiring approximately 35 additional end-point events. Three stopping boundaries are shown: the upper row of dots indicates the superiority of cardiac-resynchronization therapy plus an implantable cardioverter–defibrillator (CRT–ICD), as compared with ICD only; the lower row of dots indicates the inferiority of CRT–ICD versus ICD only; and the vertical black line on the right indicates no difference between the two study groups. The plot is based on the number of adjudicated deaths or heart-failure events, whichever came first. The first scheduled analysis took place on November 15, 2006. The trial was stopped on June 22, 2009, shortly after the ninth scheduled interim analysis on June 15, 2009, crossed the upper boundary, indicating that the superiority of CRT–ICD was identified (P=0.003). The plot continues beyond the stopping point because of events that occurred before the stopping date but were not reported and adjudicated until afterward, with a final significance level of P=0.001. The trajectory had a relatively consistent path throughout the course of the trial.

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Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Variable	ICD-Only Group (N=731)	CRT-ICD Group (N=1089)
Age — yr	64±11	65±11
Male sex — no. (%)	553 (75.6)	814 (74.7)
Race — no./total no. (%)†		
White	657/724 (90.7)	979/1083 (90.4)
Black	56/724 (7.7)	87/1083 (8.0)
Other	11/724 (1.5)	17/1083 (1.6)
Cardiac history — no. (%)		
Ischemic heart disease		
NYHA class I	113 (15.5)	152 (14.0)
NYHA class II	288 (39.4)	446 (41.0)
Nonischemic heart disease		
NYHA class II	330 (45.1)	491 (45.1)
NYHA class III or IV >3 mo before enrollment — no. (%)	73 (10.0)	109 (10.0)
Cardiac risk factors — no./total no. (%)		
Treatment for hypertension	461/730 (63.2)	691/1085 (63.7)
Atrial fibrillation >1 mo before enrollment	90/717 (12.6)	118/1063 (11.1)
Diabetes mellitus	223/729 (30.6)	329/1088 (30.2)
Cigarette smoking	92/717 (12.8)	122/1069 (11.4)
Body-mass index ≥30‡	263/723 (36.4)	385/1072 (35.9)
Coronary-bypass surgery	208/730 (28.5)	317/1088 (29.1)
Cardiac findings at enrollment		
Blood pressure — mm Hg		
Systolic	121±18	124±17
Diastolic	71±10	72±10
Blood urea nitrogen ≥26 mg/dl (9.3 mmol/liter) — no./total no. (%)	177/721 (24.5)	260/1082 (24.0)
Creatinine — mg/dl	1.2±0.4	1.2±0.4
Left bundle-branch block — no./total no. (%)	520/729 (71.3)	761/1088 (69.9)
Right bundle-branch block — no./total no. (%)	92/729 (12.6)	136/1088 (12.5)
QRS duration ≥150 msec — no. (%)	476 (65.1)	699 (64.2)
Left ventricular ejection fraction	0.24±0.05	0.24±0.05
Six-minute walk distance — m	363±108	359±107
Echocardiographic or Doppler findings		
Left ventricular end-diastolic volume — ml	251±65	245±60
Left ventricular end-systolic volume — ml	179±53	175±48
Medications — no. (%)		
Aldosterone antagonist	226 (30.9)	352 (32.3)
Amiodarone	51 (7.0)	78 (7.2)
Angiotensin-converting–enzyme inhibitor	563 (77.0)	839 (77.0)
Angiotensin-receptor blocker	148 (20.2)	227 (20.8)
Beta-blocker	681 (93.2)	1016 (93.3)
Class I antiarrhythmic agent	3 (0.4)	12 (1.1)
Digitalis	177 (24.2)	291 (26.7)
Diuretic	533 (72.9)	824 (75.7)
Lipid-lowering statin	491 (67.2)	735 (67.5)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for creatinine to micromoles per liter, multiply by 88.4. CRT denotes cardiac-resynchronization therapy, ICD implantable cardioverter–defibrillator, and NYHA New York Heart Association.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

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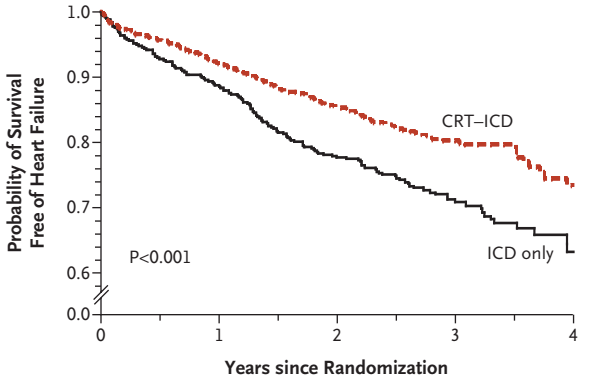
trial termination.[15] Additional primary analyses included Cox proportional-hazards regression for heart failure alone and for death at any time and evaluation of 10 prespecified categorical subgroups and treatment interactions. The homogeneity of treatment effect according to time period was likewise evaluated. All P values are two-tailed and have not been adjusted for the stopping rule, except for the primary end-point analysis.

Paired-sample t-tests were used to evaluate the absolute change in left ventricular volumes and the ejection fraction (as seen on echocardiography) between baseline and 1-year follow-up in patients from each study group who had paired baseline and 12-month recordings.

The executive committee stopped the trial on June 22, 2009, shortly after the 9th of 20 planned analyses, on the recommendation of the independent data and safety monitoring board, since the monitoring statistic had reached the prespecified efficacy boundary (Fig. 1). Study-group assignments were then unblinded, and all analyses were limited to events occurring before trial termination. In addition to the prespecified primary analyses, we outlined a plan for secondary analyses related to recurring heart-failure events and a number of tertiary analyses. Of the tertiary analyses, echocardiographic changes at 1 year are reported here. Analyses used version 2.0 of the database, which was released on July 30, 2009.



No. at Risk (Probability of Survival)

ICD only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT–ICD	1089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

Figure 2. Kaplan–Meier Estimates of the Probability of Survival Free of Heart Failure.

There was a significant difference in the estimate of survival free of heart failure between the group that received cardiac-resynchronization therapy plus an implantable cardioverter–defibrillator (CRT–ICD) and the group that received an ICD only (unadjusted P<0.001 by the log-rank test).

RESULTS

STUDY POPULATION

The clinical characteristics of the 1820 patients who underwent randomization are presented in Table 1. Baseline characteristics and the use of various cardiac medications at enrollment were similar in the two groups. Follow-up of patients in the trial averaged 2.4 years.

Of the 1089 patients who were assigned to the CRT–ICD group, 11 (1.0%) did not receive a device; of 731 patients who were assigned to the ICD-only group, 19 (2.6%) did not receive a device. Thus, implantation of a device was achieved in 98.4% of patients, with 95.4% of patients receiving the device to which they had been assigned. A total of 173 crossovers occurred: 91 patients who were assigned to the ICD-only group received a CRT–ICD device (12.4%) during the trial, 30 at the physician's discretion before reaching an end point and 61 after a heart-failure event; 82 patients who were assigned to the CRT–ICD group (7.5%) received an ICD-only device during the trial because of technical difficulties in positioning the CRT pacing lead in the coronary vein. Devices were removed during the trial for a variety of reasons in 14 patients in the CRT–ICD group (1.3%) and in 5 patients in the ICD-only group (0.7%). A total of 44 patients in the CRT–ICD group (4.0%) and 55 in the ICD-only group (7.5%) declined to continue participating in the study, were withdrawn by a physician, or were lost to follow-up.

PRIMARY END POINT

The primary end point occurred in 372 patients: 187 of 1089 patients in the CRT–ICD group (17.2%) and 185 of 731 patients in the ICD-only group (25.3%). These end-point events included 36 deaths (3.3%) and 151 heart-failure events (13.9%) in the CRT–ICD group and 18 deaths (2.5%) and 167 heart-failure events (22.8%) in the ICD-only group. A total of 276 of these heart-failure events occurred during hospitalization (136 in the CRT–ICD group and 140 in the ICD-only group), and 42 events occurred outside the hospital (15 in the CRT–ICD group and 27 in the ICD-only group). The remaining 54 events consisted of 36 deaths in the CRT–ICD group and 18 deaths in the ICD-only group. Kaplan–Meier estimates of event-free outcome in the two study groups are shown in Figure 2. The

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Table 2. Risk of Death or Heart Failure.*

Variable	ICD-Only Group	CRT–ICD Group	Hazard Ratio (95% CI)†	P Value
	no. (%)			
All patients	731	1089		
Death or heart failure‡	185 (25.3)	187 (17.2)	0.66 (0.52–0.84)§	0.001§
Heart failure only	167 (22.8)	151 (13.9)	0.59 (0.47–0.74)	<0.001
Death at any time¶	53 (7.3)	74 (6.8)	1.00 (0.69–1.44)	0.99
Patients with ischemic cardiomyopathy (NYHA class I or II)‖	401	598		
Death or heart failure‡	117 (29.2)	122 (20.4)	0.67 (0.52–0.88)	0.003
Heart failure only	105 (26.2)	96 (16.1)	0.58 (0.44–0.78)	<0.001
Death at any time¶	35 (8.7)	53 (8.9)	1.06 (0.68–1.64)	0.80
Patients with nonischemic cardiomyopathy (NYHA class II)‖	330	491		
Death or heart failure‡	68 (20.6)	65 (13.2)	0.62 (0.44–0.89)	0.01
Heart failure only	62 (18.8)	55 (11.2)	0.59 (0.41–0.87)	0.01
Death at any time¶	18 (5.5)	21 (4.3)	0.87 (0.44–1.70)	0.68

* The primary end point was death from any cause or nonfatal heart failure, whichever came first. CRT denotes cardiac-resynchronization therapy, ICD implantable cardioverter–defibrillator, and NYHA New York Heart Association.
† Hazard ratios are for patients in the CRT–ICD group as compared with those in the ICD-only group.
‡ This category excludes deaths that occurred after the first heart-failure event.
§ This value is for the primary analysis and takes into account the sequential stopping rule.
¶ This category includes all deaths, including those that occurred after the first heart-failure event.
‖ The difference in hazard ratios between patients with ischemic heart disease and those with nonischemic heart disease was not significant.

curves diverge within the first 2 months and continue their separate paths thereafter (P<0.001 in unadjusted analyses).

The number of primary end-point events and hazard ratios for the entire study population and for patients stratified according to ischemic or nonischemic cardiomyopathy are presented in Table 2. For the primary analysis, the hazard ratio of 0.66 indicates that there was a 34% reduction in the risk of death or nonfatal heart failure (whichever came first) among patients in the CRT–ICD group, as compared with those in the ICD-only group. Hazard ratios for the primary end point among patients with ischemic cardiomyopathy and nonischemic cardiomyopathy were similar. The hazard ratios for heart failure alone and for death at any time for the total population and in the ischemic and nonischemic subgroups indicate that the benefit from resynchronization therapy was driven by a 41% reduction in the risk of heart failure. During the study, there were 127 deaths at any time, with an annual rate of approximately 3% in each study group.

The effects of CRT–ICD therapy in seven prespecified subgroups are presented in Figure 3. Two interaction effects between subgroup and treatment were identified: CRT–ICD therapy was associated with a greater benefit in women (hazard ratio, 0.37; 95% confidence interval [CI], 0.22 to 0.61) than in men (hazard ratio, 0.76; 95% CI, 0.59 to 0.97; P=0.01 for interaction) and in patients with a QRS duration of 150 msec or more (hazard ratio, 0.48; 95% CI, 0.37 to 0.64) than in those with a QRS duration of less than 150 msec (hazard ratio, 1.06; 95% CI, 0.74 to 1.52; P=0.001 for interaction). No significant interaction effects were identified between the 37 centers with low enrollment (less than 10 patients) and the remaining 73 centers with higher enrollment or in patients with an elevated level of blood urea nitrogen (26 mg per deciliter [9.3 mmol per liter] or more) and those without an elevated level. Patients with ischemic cardiomyopathy and those with nonischemic cardiomyopathy had a similar benefit from CRT–ICD therapy (Table 2). Some caution in the interpretation of the subgroup interactions is needed because of multiple testing, but given the significance of the comparisons, the

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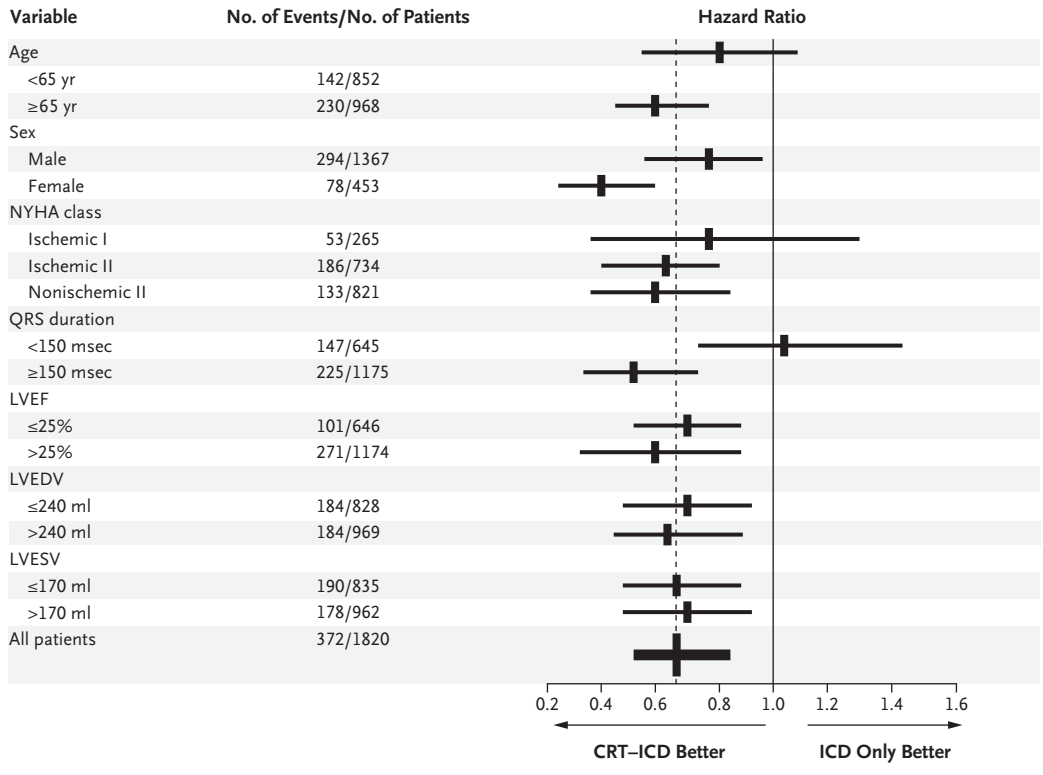

Figure 3. Risk of Death or Heart Failure, According to Selected Clinical Characteristics.

The hazard ratios for death or nonfatal heart failure (whichever came first) are shown for various subgroups among patients who received cardiac-resynchronization therapy plus an implantable cardioverter–defibrillator (CRT–ICD) and those who received an ICD only. The dashed vertical line represents the results for the entire study (hazard ratio in the CRT–ICD group, 0.66), and the horizontal lines indicate 95% confidence intervals. LVEDV denotes left ventricular end-diastolic volume, LVEF left ventricular ejection fraction, LVESV left ventricular end-systolic volume, and NYHA New York Heart Association. Two subgroup treatment interactions were identified, for sex (P=0.01) and QRS duration (P=0.001). All other interaction P values exceeded 0.10.

chance of getting two or more false positives is small, and the analyses showed a relatively constant treatment effect over time.

Exploratory analyses suggested that women but not men had a benefit from CRT–ICD therapy independent of the QRS duration. Among 182 patients who had NYHA class III or IV symptoms more than 3 months before enrollment and 213 patients with a history of atrial fibrillation more than a month before enrollment, CRT–ICD had less effect on outcome than in patients without these findings.

LEFT VENTRICULAR REMODELING

The changes from baseline to 1 year in left ventricular end-diastolic volume, end-systolic volume, and ejection fraction (as determined on echocardiography) are presented in Figure 4. The left ventricular volume was reduced and the ejection fraction was increased to a significantly greater degree in patients in the CRT–ICD group than in the ICD-only group.

ADVERSE EVENTS

One death (due to a pulmonary embolus documented on autopsy) occurred in the CRT–ICD group during hospitalization after device implantation. In the 30 days after device implantation, the following percentages of patients had serious adverse events: pneumothorax (1.7% in the CRT–ICD group and 0.8% in the ICD-only group), infection (1.1% in the CRT–ICD group and 0.7% in the ICD-only group), and pocket hematoma requiring evacuation (3.3% in the CRT–ICD group and 2.5% in the ICD-only group). During CRT–ICD implantation, coronary venous dissection with pericardial effusion occurred in 5 patients (0.5%), and the left ventricular coronary-vein lead was repositioned dur-

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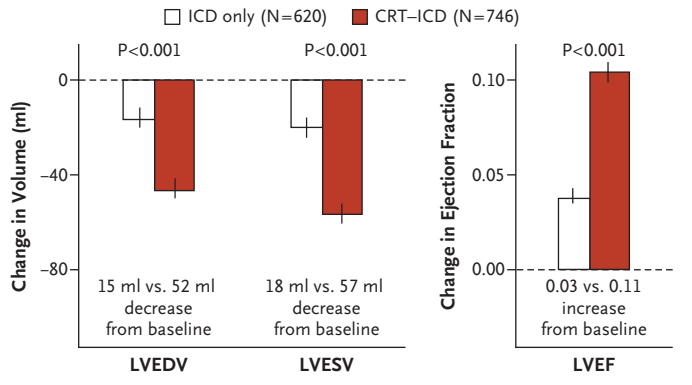

Figure 4. Changes in Mean Echocardiographic Left Ventricular Volumes and Ejection Fraction between Baseline and 1-Year Follow-up.

Paired-sample analyses involved 746 patients who received cardiac-resynchronization therapy plus an implantable cardioverter–defibrillator (CRT–ICD) and 620 patients who received an ICD only. LVEDV denotes left ventricular end-diastolic volume, LVEF left ventricular ejection fraction, and LVESV left ventricular end-systolic volume. The height of each bar indicates the average change in the measure from baseline to 1 year, the vertical lines represent 95% confidence intervals, and P values reflect the significances of the difference in average changes between the two groups.

ing the first 30 days for a variety of reasons in 44 patients (4.0%). During long-term follow-up after the first 30 days, serious device-related adverse events occurred with a frequency of 4.5 per 100 device-months in the CRT–ICD group and of 5.2 per 100 device-months in the ICD-only group.

DISCUSSION

In our study, the use of CRT combined with an ICD in asymptomatic or mildly symptomatic patients with heart disease and a reduced ejection fraction and wide QRS complex was associated with a 34% reduction in the risk of death or heart-failure events, as compared with the use of an ICD alone. The benefit was driven by a 41% reduction in the risk of heart-failure events, a finding that was evident primarily in a prespecified subgroup of patients with a QRS duration of 150 msec or more. The superiority of CRT was evident in patients with ischemic cardiomyopathy and in those with nonischemic cardiomyopathy. Echocardiographic studies showed substantial reductions in left ventricular end-diastolic and end-systolic volumes and improvement in the ejection fraction 1 year after the initiation of CRT–ICD therapy.

The use of a composite end point of death from any cause or nonfatal heart-failure events (whichever came first) is appropriate and widely used in heart-failure trials.[16] CRT has been shown to reduce symptoms and rates of hospitalization and death in patients with NYHA class III and IV heart failure.[5,6] In a recent study, CRT was associated with an improvement in a composite heart-failure score during 12 months of follow-up in 419 patients with resynchronization turned on in CRT devices, as compared with 191 patients with resynchronization turned off in CRT devices.[8] Our findings show the effectiveness of CRT in reducing the risk of heart-failure events in asymptomatic or mildly symptomatic patients.

The difference in the frequency of heart-failure events in the two study groups is not likely to be due to an increase in the rate of pacemaker-induced heart failure in the ICD-only group, since the demand pacing rate was programmed to 40 bpm, a backup bradycardia rate that has not been associated with an increased heart-failure rate.[17,18] The reduction in heart-failure events with CRT was not associated with a reduction in mortality in this prevention trial.

Members of the heart-failure adjudication committee were unaware of study-group assignments, but the investigators who decided on therapy or hospital admission for patients with heart failure were aware of such assignments. It is possible that the investigators' knowledge of study-group assignment contributed in some way to the lower frequency of heart failure in the CRT–ICD group. Another potential bias is that 201 patients in the CRT–ICD group underwent the 1-year echocardiographic evaluation with the CRT device turned off, and these patients were not included in the paired volume and ejection-fraction studies. This resulted in 746 paired studies in the CRT–ICD group, a large number but not randomly selected. In view of the size of the effects observed, we believe the general conclusions from these echocardiographic results are reliable.

In the 2008 guidelines for implantation of cardiac devices,[7] CRT with or without an ICD is a class I indication for patients with a left ventricular ejection fraction of 35% or less, a QRS duration of 120 msec or more, and sinus rhythm who have NYHA functional class III or ambulatory class IV heart-failure symptoms while receiving optimal medical therapy. Our study was designed to address a preventive indication for CRT–ICD therapy in relatively asymptomatic patients receiving appropriate medical treatment who have ischemic heart disease with class I or II symptoms or nonischemic heart disease with class II symp-

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toms, a reduced ejection fraction, a wide QRS complex, and sinus rhythm. All the patients in our study met the guideline indications for ICD therapy.[7] This study provides evidence that preventive CRT–ICD therapy decreases the risk of heart-failure events in vulnerable patients with ischemic or nonischemic heart disease who have minimal heart-failure symptoms but a wide QRS complex.

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APPENDIX

The following centers and investigators participated in the MADIT-CRT trial (listed in alphabetical order according to center): *Amarillo Heart Group, Amarillo, TX* — P. Desai; *Ark-La-Tex Cardiology, Shreveport, LA* — S. Wiggins; *Arkansas Cardiology, Little Rock* — G. Greer; *Arkansas Heart Hospital, Little Rock* — S. Beau; *Azienda Ospedaliera. Spedali Civili, Brescia, Italy* — A. Curnis; *Barzilai Medical Center, Ashkelon, Israel* — A. Katz; *Baystate Medical Center, Springfield, MA* — J. Cook; *Bridgeport Hospital, Bridgeport, CT* — C. McPherson; *Buffalo Cardiology and Pulmonary Associates, Williamsville, NY* — G. Rozmus; *Buffalo Medical Group, Williamsville, NY* — D. Switzer; *Cardiology Associates of North Mississippi, Tupelo* — J. Stone; *Cardiovascular Consultants Medical Group, Walnut Creek, CA* — P. Ludmer; *Carolinas Medical Center, Charlotte, NC* — P. Colavita; *Central Baptist, Lexington, KY* — G. Tomassoni; *Clarian Health Partners, Indianapolis* — B. Crevey, G. Nair; *Cleveland Clinic, Cleveland* — W. Saliba; *Deborah Heart and Lung Center, Browns Mills, NJ* — R. Corbisiero; *Duke University, Durham, NC* — F. Gilliam, P. Hranitzky; *Foothill Cardiology, Pasadena, CA* — M. Rashtian; *Genesis Heart Institute, Davenport, IA* — M. Giudici; *Gentofte University Hospital, Hellerup, Denmark* — P. Thomsen; *Good Samaritan Hospital, Los Angeles* — D. Cannom; *Hartford Hospital, Hartford, CT* — C. Clyne; *Heart Clinic of Southern Oregon, Medford* — E. Pena; *Heart Clinics Northwest, Spokane, WA* — T. Lessmeier; *Henry Ford Hospital, Detroit* — C. Schuger; *Herz- und Diabeteszentrum Nordrhein-Westfalen, Bad Oeynhausen, Germany* — J. Vogt; *Hôpital Cardiologique CHRU de Lille, Lille, France* — S. Kacet; *Hospital General Universitario Gregorio Maranon, Madrid* — J. Almendral; *Hospital General de Valencia, Valencia, Spain* — A. Quesada; *Institute for Clinical and Experimental Medicine, Prague, Czech Republic* — J. 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Rea; *Medical University of South Carolina, Charleston* — M. Gold; *Methodist Dallas Medical Center, Dallas* — A. Guttigoli; *Methodist Heart, Lung and Vascular Institute, Peoria, IL* — A. Adler, I. Singer; *Michigan Heart, Ypsilanti* — T. Shinn; *Midatlantic Cardiovascular Associates, Baltimore* — T. Guarnieri; *Midwest Heart Foundation, Downers Grove, IL* — C. Casey; *Milton S. Hershey Medical Center, Hershey, PA* — G. Naccarelli; *Minneapolis Heart Institute at Abbott Northwestern Hospital, Minneapolis* — C. Gornick; *Montreal Heart Institute, Montreal* — B. Thibault; *Nebraska Heart Institute, Lincoln* — S. Ackerman, K. Turk; *Newport Heart Medical Center, Newport Beach, CA* — N. Hunter; *Northeast Cardiology Associates, Bangor, ME* — J. Jentzer; *Northwest Ohio Cardiology Consultants, Toledo* — T. Bartlett, D. Glascock, K. Tamirisa; *Northwestern Memorial Hospital, Chicago* — J. Goldberger; *Oklahoma Heart Institute, Tulsa* — J. Coman, D. 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The following persons participated in the study: **Data and Safety Monitoring Board** — D. Oakes (chair), T. Pearson, F. Richeson, R. Pomerantz; **Mortality Events Committee** — R. Goldstein (chair), M. Haigney, R. Krone; **Heart Failure Events Committee** — E. Dwyer, Jr. (chair), M. Kukin, E. Lichstein; **Electrogram Analysis Core Laboratory** — P. Wang; **Echocardiogram Core Laboratory** — S. Solomon

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