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Cardiac-Resynchronization Therapy for Mild-to-Moderate Heart Failure

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ABSTRACT

BACKGROUND

Cardiac-resynchronization therapy (CRT) benefits patients with left ventricular systolic dysfunction and a wide QRS complex. Most of these patients are candidates for an implantable cardioverter–defibrillator (ICD). We evaluated whether adding CRT to an ICD and optimal medical therapy might reduce mortality and morbidity among such patients.

METHODS

We randomly assigned patients with New York Heart Association (NYHA) class II or III heart failure, a left ventricular ejection fraction of 30% or less, and an intrinsic QRS duration of 120 msec or more or a paced QRS duration of 200 msec or more to receive either an ICD alone or an ICD plus CRT. The primary outcome was death from any cause or hospitalization for heart failure.

RESULTS

We followed 1798 patients for a mean of 40 months. The primary outcome occurred in 297 of 894 patients (33.2%) in the ICD–CRT group and 364 of 904 patients (40.3%) in the ICD group (hazard ratio in the ICD–CRT group, 0.75; 95% confidence interval [CI], 0.64 to 0.87; P<0.001). In the ICD–CRT group, 186 patients died, as compared with 236 in the ICD group (hazard ratio, 0.75; 95% CI, 0.62 to 0.91; P=0.003), and 174 patients were hospitalized for heart failure, as compared with 236 in the ICD group (hazard ratio, 0.68; 95% CI, 0.56 to 0.83; P<0.001). However, at 30 days after device implantation, adverse events had occurred in 124 patients in the ICD-CRT group, as compared with 58 in the ICD group (P<0.001).

CONCLUSIONS

Among patients with NYHA class II or III heart failure, a wide QRS complex, and left ventricular systolic dysfunction, the addition of CRT to an ICD reduced rates of death and hospitalization for heart failure. This improvement was accompanied by more adverse events. (Funded by the Canadian Institutes of Health Research and Medtronic of Canada; ClinicalTrials.gov number, NCT00251251.)

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The use of implantable cardioverter–defibrillators (ICDs) improves survival among patients who have New York Heart Association (NYHA) class II or III heart failure with left ventricular systolic dysfunction despite optimal medical therapy.[1] Cardiac-resynchronization therapy (CRT) improves symptoms of heart failure, quality of life, exercise capacity,[2-6] and left ventricular function[7] when used in patients with NYHA functional class III or ambulatory class IV heart failure with a wide QRS complex. CRT has also been shown to reduce mortality among patients not receiving an ICD.[8] However, studies have not shown a survival benefit of CRT in patients with NYHA class II or III heart failure, left ventricular dysfunction, and a wide QRS complex who have been treated with optimal medical therapy and an ICD. Recent studies have shown that the use of CRT improves heart function in patients with mild (NYHA class I or II) heart failure and reduces the rate of hospitalization (or medical encounters) for heart failure.[9,10] It is reasonable to hypothesize that CRT may slow the progression of heart failure and reduce mortality and morbidity among such patients.

We conducted a multicenter, double-blind, randomized, controlled study, called the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT), to determine whether the addition of CRT to an ICD and optimal medical therapy would reduce mortality and the rate of hospitalization for heart failure, as compared with an ICD and optimal medical therapy alone, among patients with NYHA class II or III symptoms, left ventricular systolic dysfunction, and a wide QRS complex.[11]

Methods

Patients

We enrolled patients at 24 centers in Canada, 8 centers in Europe and Turkey, and 2 centers in Australia. Eligible patients had NHYA class II or III symptoms of heart failure despite receiving optimal medical therapy, with a left ventricular ejection fraction of 30% or less from ischemic or nonischemic causes, an intrinsic QRS duration of 120 msec or more or a paced QRS duration of 200 msec or more, sinus rhythm or permanent atrial fibrillation or flutter with a controlled ventricular rate (≤60 beats per minute at rest and ≤90 beats per minute during a 6-minute walk test) or planned atrioventricular-junction ablation after device implantation), and planned ICD implantation for indicated primary or secondary prevention of sudden cardiac death. Patients with a major coexisting illness or a recent cardiovascular event were excluded, as described previously.[11]

Initially, patients with NYHA class II or III heart failure were enrolled in the study. After clinical-trial data suggested a mortality benefit for CRT in patients with NYHA class III heart failure who had not undergone implantation of an ICD[8] and subsequent guideline changes,[12,13] the protocol was revised in February 2006 to include patients in NYHA class II only. All patients provided written informed consent.

Study Procedures

At baseline, all patients underwent a history taking and physical examination, including 12-lead electrocardiography, a 6-minute walk test, a quality-of-life assessment, and a medication evaluation to ensure that they were receiving optimal medical therapy with a beta-blocker, an angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker, spironolactone, aspirin, and statins, when appropriate.

Eligible patients were randomly assigned in a 1:1 ratio to receive an ICD or an ICD with CRT and were stratified according to clinical center, atrial rhythm (atrial fibrillation or flutter or sinus–atrial pacing), and a planned implantation of a single- or dual-chamber ICD.

We used commercially available transvenous leads and devices (Medtronic). A standard implantation technique was used with an emphasis on placing the left ventricular lead to the lateral or posterolateral wall of the left ventricle whenever possible. Programming of the device was standardized to minimize ventricular pacing in the ICD group, maximize ventricular pacing in the ICD–CRT group, and provide uniform arrhythmia detection and therapy. (Details regarding programming measures for the devices are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Patients were seen at follow-up visits 1 month after device implantation and then every 6 months for at least 18 months until the end of the trial.

At each follow-up visit, clinical assessment and device interrogation were performed.[11] The patients and the general health care providers, including the team that was responsible for heart-failure management and reporting of clinical events, were unaware of assignments to the two study groups. Only the arrhythmia team (physicians and caregivers) that performed the device implantation and device management were aware of study-group assignments.

OUTCOME MEASURES

The primary outcome was death from any cause or heart failure leading to hospitalization. Hospitalization for heart failure was defined as admission to a health care facility lasting more than 24 hours with symptoms of congestive heart failure and subsequent treatment for heart failure. Admissions for other medical problems that then developed into heart failure in the hospital were not classified as hospitalization for heart failure. An adjudication committee whose members were not aware of study-group assignments reviewed available documents and determined the cause of death and whether hospitalizations lasting more than 24 hours were due to the exacerbation of heart failure. All adverse events occurring within 30 days after ICD implantation were adjudicated as related or unrelated to the ICD.

The principal secondary outcomes included death from any cause at any time during the study, death from any cardiovascular cause, and hospitalization for heart failure among all patients, those with NYHA class II heart failure at baseline, and those with NYHA class III heart failure at baseline.

STUDY OVERSIGHT

The executive committee conceived and designed the trial and wrote the first draft of the manuscript. The University of Ottawa Heart Institute Cardiovascular Research Methods Center coordinated the study and maintained the database. We received a university–industry peer-reviewed grant from the Canadian Institutes of Health Research. Medtronic of Canada was the industry partner that provided funding and CRT components for the study but did not participate in the conduct of the trial, the reporting of the data, or the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the reported data, as well as the fidelity of the study to the protocol and statistical analysis plan, which are available at NEJM.org.

STATISTICAL ANALYSIS

All analyses were conducted according to the intention-to-treat principle. The study had a statistical power of 85% to detect a 25% relative reduction in the primary outcome, given a two-sided alpha value of 0.05 and taking into consideration the expected rate of loss to follow-up and crossover.[11] We used survival-analysis techniques to compare the two study groups with respect to the primary outcome and principal secondary outcomes. Survival in each of the two groups was summarized with the use of Kaplan–Meier product-limit estimates. We compared the survival curves using nonparametric log-rank tests. Hazard ratios and associated 95% confidence intervals were calculated with the use of the Cox proportional-hazards model.

We analyzed the primary and secondary outcomes for patients with NYHA class II or III heart failure separately, since patients in NYHA class III were enrolled only during the first part of the study, before the protocol was revised to include only patients in NYHA class II. Cox proportional-hazard models were used to test for interactions in the various planned subgroups. We used chi-square tests to compare the Kaplan–Meier (actuarial) rate of event-free survival at 5 years. We used the hazard ratio to calculate the number needed to treat in order to prevent one death or hospitalization for heart failure in one patient.[14] Underlying assumptions for these statistical procedures were assessed (in particular, the proportional-hazards assumption). Analyses were conducted with the use of SAS software, version 9.2 (SAS Institute). Two planned interim analyses were conducted for the data and safety monitoring board. An O'Brien–Fleming alpha spending function was used to adjust the sample size for these interim analyses.

RESULTS

PATIENTS

From January 2003 through February 2009, a total of 1798 patients were enrolled at 34 centers: 1617 patients in Canada, 137 in Europe and Turkey, and 44 in Australia. The clinical characteris-

tics of the patients at baseline were similar in the two groups (Table 1). The mean (±SD) follow-up period was 40±20 months for all patients and 44±18 months for surviving patients.

Of 904 patients in the ICD group, 899 (99.4%) underwent device implantation. Reasons for nonimplantation included 4 cases in which the patient or physician declined to participate and 1 case in which there was a lack of venous access. Of 894 patients in the ICD–CRT group, 888 (99.3%) underwent device implantation. Reasons for nonimplantation included 4 cases in which the patient died and 2 cases in which the patient or physician declined to participate. In the ICD–CRT group, a left ventricular lead was successfully implanted in 841 patients (94.7%) — in 802 during an initial attempt and in 39 during a subsequent attempt. Five patients (0.6%) in the ICD group either withdrew (4 patients) or were lost to follow-up (1 patient); 10 patients (1.1%) in the ICD–CRT group either withdrew (8 patients) or were lost to follow-up (2 patients).

Table 1. Characteristics of the Patients at Baseline.*

Variable	ICD (N=904)	ICD–CRT (N=894)
Age — yr	66.2±9.4	66.1±9.3
Male sex — no. (%)	732 (81.0)	758 (84.8)
Underlying heart disease — no. (%)		
Ischemic heart disease	587 (64.9)	614 (68.7)
Nonischemic heart disease	317 (35.1)	280 (31.3)
NYHA class — no. (%)		
Class II	730 (80.8)	708 (79.2)
Class III	174 (19.2)	186 (20.8)
Left ventricular ejection fraction — %	22.6±5.1	22.6±5.4
Atrial rhythm — no. (%)		
Permanent atrial fibrillation or flutter	115 (12.7)	114 (12.8)
Sinus or atrial paced	789 (87.3)	780 (87.2)
Hypertension — no. (%)	397 (43.9)	402 (45.0)
Diabetes mellitus — no. (%)	313 (34.6)	293 (32.8)
Previous percutaneous coronary intervention — no. (%)	208 (23.0)	220 (24.6)
Previous CABG — no. (%)	313 (34.6)	293 (32.8)
Current cigarette smoking — no. (%)	127 (14.0)	121 (13.5)
Peripheral vascular disease — no. (%)	90 (10.0)	88 (9.8)
Hospitalization for heart failure in the previous 6 mo — no. (%)	223 (24.7)	238 (26.6)
QRS duration		
Intrinsic		
No. of patients	837	826
Mean — msec	158.3±24.0	157±23.6
Paced		
No. of patients	67	68
Mean — msec	210.3±18.3	206.5±24.0
QRS morphologic type — no. (%)		
Right bundle-branch block	93 (10.3)	68 (7.6)
Left bundle-branch block	643 (71.1)	652 (72.9)
NIVCD	101 (11.2)	106 (11.9)
Ventricular paced	67 (7.4)	68 (7.6)

Table 1. (Continued.)

Variable	ICD (N=904)	ICD–CRT (N=894)
Medication — no. (%)		
Beta-blocker	805 (89.0)	808 (90.4)
ACE inhibitor or ARB	878 (97.1)	859 (96.1)
Spironolactone	378 (41.8)	372 (41.6)
Digoxin	319 (35.3)	301 (33.7)
Aspirin	622 (68.8)	584 (65.3)
Warfarin	298 (33.0)	310 (34.7)
Clopidogrel	145 (16.0)	134 (15.0)
Statin	618 (68.4)	607 (67.9)
Diuretic	756 (83.6)	757 (84.7)
Calcium-channel blocker	83 (9.2)	101 (11.3)
Amiodarone	124 (13.7)	140 (15.7)
Other antiarrhythmia drug	8 (0.9)	12 (1.3)
Distance on 6-minute walk test		
No. of patients	765	789
Mean — m	354.9±110.1	351.3±106.7
Estimated glomerular filtration rate		
No. of patients	897	885
Mean — %	60.8±21.9	59.5±19.8
Rate — ml/min/1.73 m^2		
<30 — no. (%)	63 (7.0)	57 (6.4)
30–59 — no. (%)	383 (42.7)	398 (45.0)
≥60 — no. (%)	451 (50.3)	430 (48.6)

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, CABG coronary-artery bypass grafting, CRT cardiac-resynchronization therapy, ICD implantable cardioverter–defibrillator, and NIVCD nonspecific intraventricular conduction delay.

A total of 12 patients underwent cardiac transplantation during the course of the study (5 in the ICD group and 7 in the ICD–CRT group) before reaching the primary outcome. In the ICD group, the numbers of patients who crossed over and received CRT in addition to an ICD were 36 (4.0%) before the occurrence of a primary outcome and 60 (6.6%) after hospitalization for heart failure. In the ICD–CRT group, 53 patients (6.0%) did not receive CRT (47 in whom the left ventricular lead failed and 6 in whom the lead malfunctioned). Details about the study groups are provided in the Supplementary Appendix.

OUTCOMES

The primary outcome, death or hospitalization for heart failure, occurred in 364 of 904 patients (40.3%) in the ICD group, as compared with 297 of 894 patients (33.2%) in the ICD–CRT group. The time to the occurrence of the primary outcome was significantly prolonged in the ICD–CRT group (hazard ratio, 0.75; 95% confidence interval [CI], 0.64 to 0.87; P<0.001) (Table 2 and Fig. 1A).

During the course of the trial, 422 of the 1798 patients in the two study groups (23.5%) died. In the ICD–CRT group, the 5-year actuarial rate of death was 28.6%, as compared with 34.6% in the ICD group. The time until death was significantly prolonged (relative risk reduction, 25%) in the ICD–CRT group (hazard ratio, 0.75; 95% CI, 0.62 to 0.91; P=0.003) (Table 2 and Fig. 1B). These findings meant that 14 patients would need to be treated for 5 years with ICD and CRT

Table 2. Risk of Death or Hospitalization for Heart Failure among All Patients and According to New York Heart Association (NYHA) Category.

Outcome	ICD (N=904)	ICD–CRT (N=894)	Hazard Ratio (95% CI)	P Value
	no. (%)			
All patients				
Primary outcome: death or hospitalization for heart failure	364 (40.3)	297 (33.2)	0.75 (0.64–0.87)	<0.001
Secondary outcomes				
Death from any cause	236 (26.1)	186 (20.8)	0.75 (0.62–0.91)	0.003
Death from cardiovascular cause	162 (17.9)	130 (14.5)	0.76 (0.60–0.96)	0.02
Hospitalization for heart failure	236 (26.1)	174 (19.5)	0.68 (0.56–0.83)	<0.001
Patients in NYHA class II				
No. of patients	730	708		
Primary outcome: death or hospitalization for heart failure	253 (34.7)	193 (27.3)	0.73 (0.61–0.88)	0.001
Secondary outcomes				
Death from any cause	154 (21.1)	110 (15.5)	0.71 (0.56–0.91)	0.006
Death from cardiovascular cause	100 (13.7)	74 (10.5)	0.73 (0.54–0.99)	0.04
Hospitalization for heart failure	159 (21.8)	115 (16.2)	0.70 (0.55–0.89)	0.003
Patients in NYHA class III				
No. of patients	174	186		
Primary outcome: death or hospitalization for heart failure	111 (63.8)	104 (55.9)	0.76 (0.58–0.99)	0.04
Secondary outcomes				
Death from any cause	82 (47.1)	76 (40.9)	0.79 (0.58–1.08)	0.14
Death from cardiovascular cause	62 (35.6)	56 (30.1)	0.77 (0.54–1.10)	0.15
Hospitalization for heart failure	77 (44.3)	59 (31.7)	0.63 (0.45–0.88)	0.006

in order to prevent 1 death. Similarly, we observed a 24% relative reduction in the risk of death from a cardiovascular cause among patients in the ICD–CRT group (hazard ratio, 0.76; 95% CI, 0.60 to 0.96; P=0.02).

A total of 1018 patients (56.6%) were hospitalized at least once during follow-up (509 patients in each group); the majority of these hospitalizations were for cardiovascular reasons. A total of 404 patients in the ICD group and 423 in the ICD–CRT group were hospitalized for a cardiac cause (hazard ratio for the ICD–CRT group, 1.04; P=0.56). The number of patients who were hospitalized for heart failure was lower in the ICD–CRT group, with 174 patients hospitalized (19.5%), as compared with 236 (26.1%) in the ICD group (hazard ratio, 0.68; 95% CI, 0.56 to 0.83; P<0.001). These findings meant that 11 patients would need to be treated for 5 years with an ICD and CRT to prevent 1 hospitalization for heart failure. However, the number of device-related hospitalizations was higher in the ICD–CRT group, with 179 hospitalizations (20.0%), as compared with 110 (12.2%) in the ICD group (hazard ratio, 1.68; 95% CI, 1.32 to 2.13; P<0.001).

SUBGROUP ANALYSES

We conducted prespecified analyses of the relationship between outcome and NYHA class. Overall, 20% of patients had NYHA class III heart failure at study entry. Among patients with NYHA class II heart failure and among those with class III heart failure, the two study interventions were associated with similar reductions in the risk of death or hospitalization for heart

failure (P=0.91 for interaction), death from any cause, and hospitalization for heart failure (Table 2 and Fig. 2).

The effects of treatment on 11 prespecified subgroups are shown in Figure 3. There was a significant interaction between treatment and QRS duration (P=0.003), with ICD–CRT therapy being more effective in patients with an intrinsic QRS duration of 150 msec or more (hazard ratio, 0.59; 95% CI, 0.48 to 0.73) than in either patients with an intrinsic QRS duration of less than 150 msec (hazard ratio, 0.99; 95% CI, 0.77 to 1.27; P=0.002 for interaction) or patients with a paced QRS duration of 200 msec or more (hazard ratio, 1.07; 95% CI, 0.63 to 1.84; P=0.03 for interaction). There was also a weak interaction between treatment and QRS morphologic type (P=0.046) such that patients with left bundle-branch block appeared to have a greater benefit than patients with nonspecific intraventricular conduction delay (P=0.04 for interaction). Patients with ischemic or nonischemic causes of heart failure had a similar benefit from ICD–CRT.

ADVERSE EVENTS

One death from worsening heart failure occurred in the ICD group within 24 hours after device implantation. During the first 30 days after device implantation, there were 118 device- or implantation-related complications among the 888 patients receiving ICD–CRT, as compared with 61 of 899 patients in the ICD group (P<0.001). These complications included hemothorax or pneumothorax in 8 patients (0.9%) in the ICD group and 11 patients (1.2%) in the ICD–CRT group, device-pocket hematoma requiring intervention in 11 patients (1.2%) in the ICD group and 14 (1.6%) in the ICD–CRT group, device-pocket infection requiring intervention in 16 patients (1.8%) in the ICD group and 21 patients (2.4%) in the ICD–CRT group, lead dislodgement requiring intervention in 20 patients (2.2%) in the ICD group and 61 patients (6.9%) in the ICD–CRT group, device-pocket problems requiring revision in 1 patient (0.1%) in the ICD group and 4 patients (0.5%) in the ICD–CRT group, and coronary sinus dissection in 11 patients (1.2%) in the ICD–CRT group.

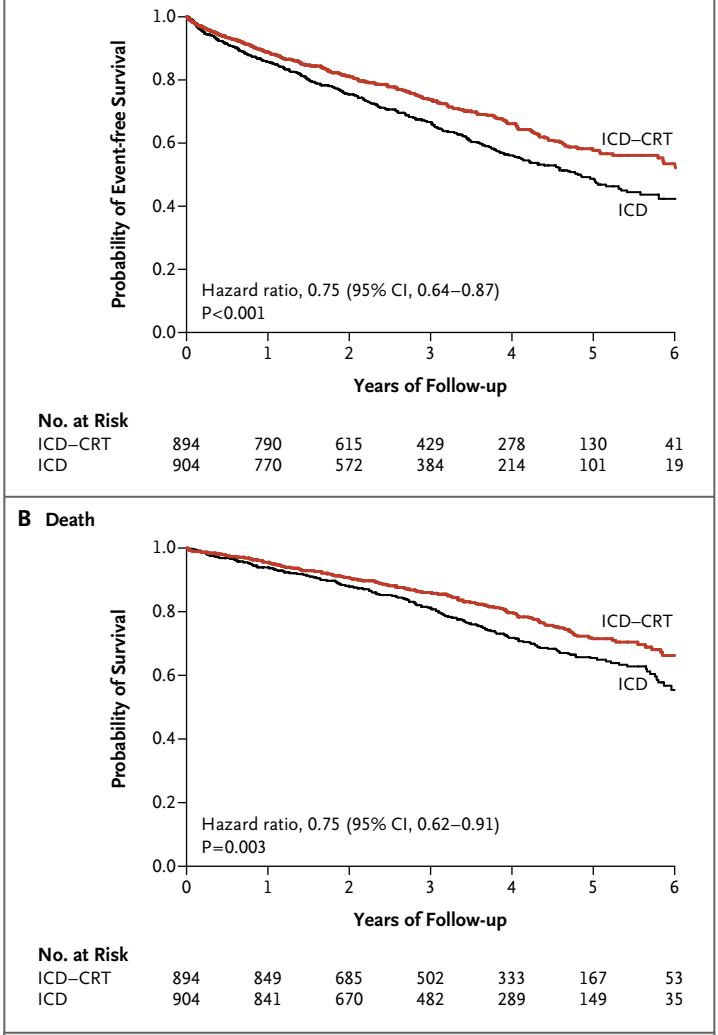

Figure 1. Kaplan–Meier Estimates of Death or Hospitalization for Heart Failure (Composite Primary Outcome) and Death from Any Cause.

Panel A shows the probability of the primary outcome among patients who were receiving optimal medical therapy along with cardiac-resynchronization therapy (CRT) plus an implantable cardioverter–defibrillator (ICD), as compared with those receiving an ICD alone. The probability of event-free survival at 5 years was 0.576 in the ICD–CRT group and 0.487 in the ICD group. Panel B shows the probability of death from any cause in each group, with a probability of survival at 5 years of 0.714 in the ICD–CRT group and 0.654 in the ICD group.

DISCUSSION

We found that the addition of CRT to an ICD and optimal medical therapy reduced rates of death and hospitalization for heart failure among patients with mild-to-moderate heart failure, a reduced left ventricular ejection fraction, and a wide QRS complex. Previous clinical trials have shown the benefits of CRT in patients who have more advanced heart failure with left ventricular systolic dysfunction and a wide QRS complex, including a reduction in symptoms, improvement in the quality of life and exercise capacity,[2-6] and

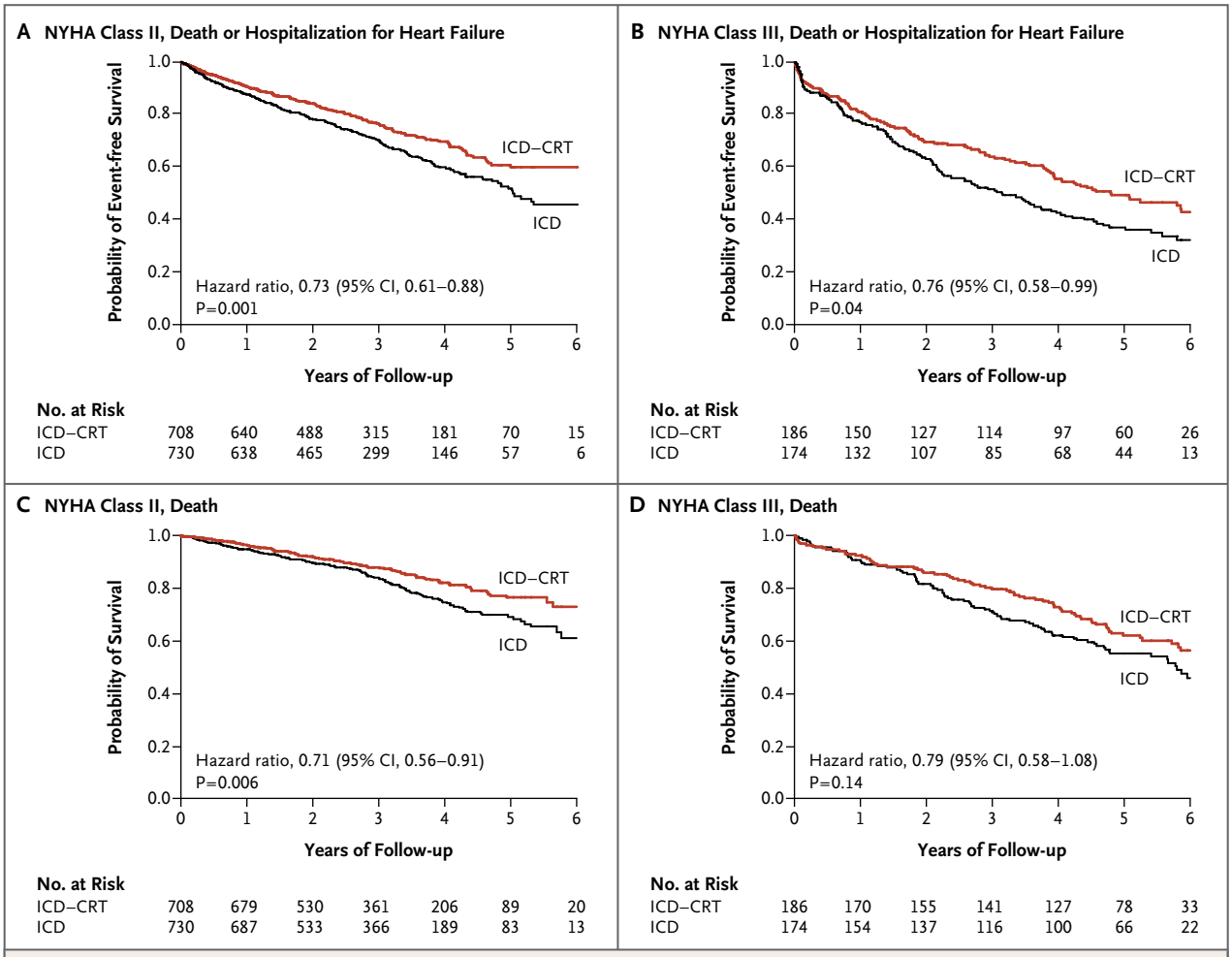

Figure 2. Kaplan–Meier Estimates of Death or Hospitalization for Heart Failure (Composite Primary Outcome) and Death from Any Cause among Patients with New York Heart Association (NYHA) Class II Heart Failure at Baseline and among Those with Class III Heart Failure.

Shown is the probability of the composite primary outcome for patients who were receiving optimal medical therapy along with cardiac-resynchronization therapy (CRT) plus an implantable cardioverter–defibrillator (ICD), as compared with those receiving an ICD alone, and who at baseline had either NYHA class II heart failure (Panel A) or class III heart failure (Panel B). Also shown is the probability of death from any cause among patients who at baseline had either NYHA class II heart failure (Panel C) or class III heart failure (Panel D).

a reduction in hospitalization for heart failure.[8,15] Furthermore, CRT can lead to left ventricular reverse remodeling in patients with advanced heart failure and those with milder heart failure, resulting in an improved ejection fraction,[9,10] a reduced left ventricular size,[7,16] and reduced mitral regurgitation[17] without increasing ventricular oxidative metabolism.[18,19] Three clinical trials have studied the effect of CRT on rates of death and heart-failure events among patients with heart failure. Two trials included patients with moderate-to-severe NYHA class III and ambulatory class IV heart failure, and the other trial included less symptomatic patients with NYHA class I or II heart failure.[8,15,20] In our trial, the primary outcome was a composite of death from any cause and hospitalization for heart failure, which was an adjudicated event. We believe this outcome measure is clinically relevant and allows assessment of the effect of the therapy on health care utilization.

Previously, three trials have had sufficient statistical power to examine the effect of CRT on mortality. In the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, patients with left ventricular dysfunction, a wide QRS complex, and severe heart-failure symptoms who received an ICD and CRT, in addition to optimal medical therapy, had a relative reduction of 36% in the rate of death,

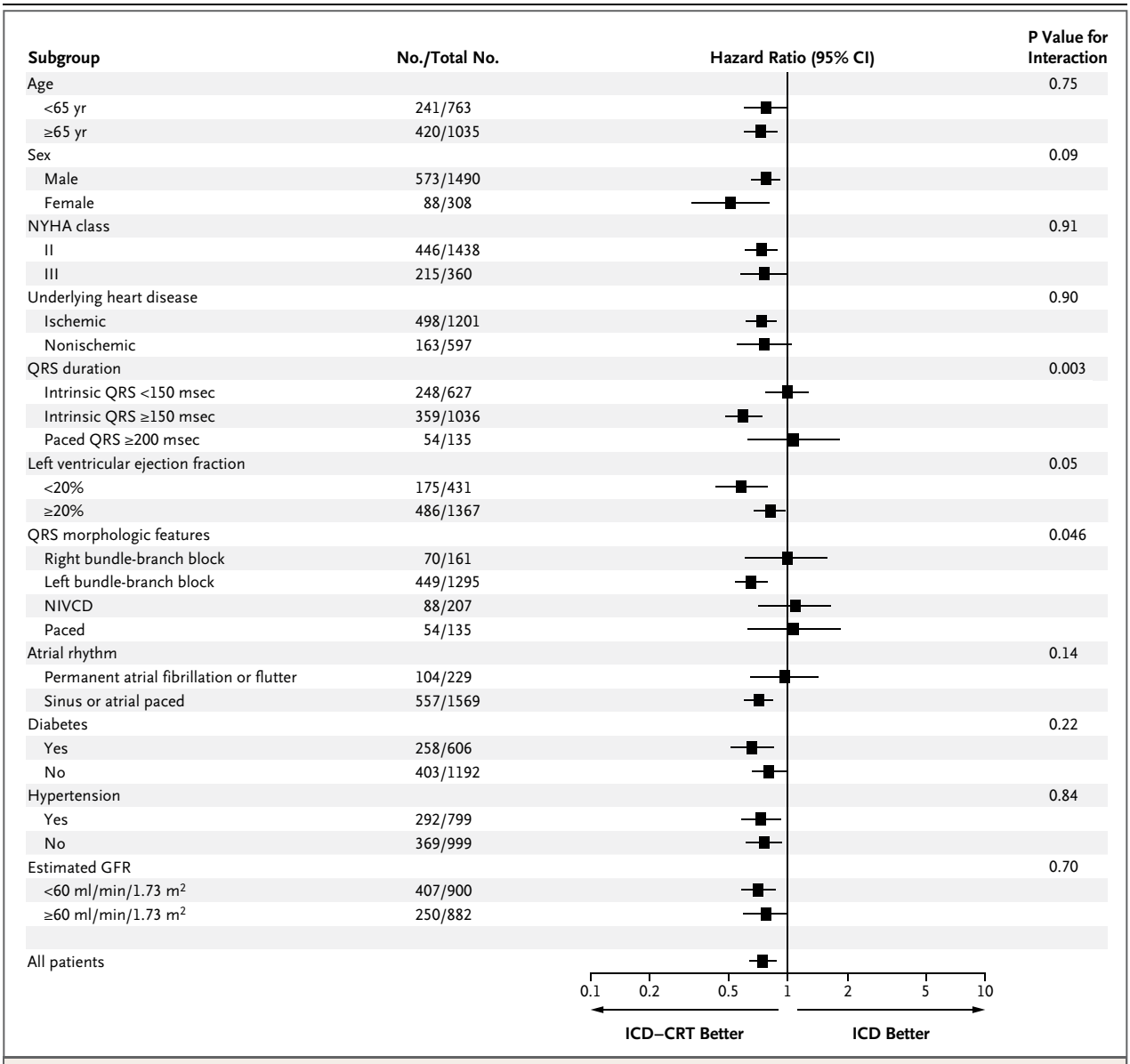

Figure 3. Subgroup Analyses of Death or Hospitalization for Heart Failure (Composite Primary Outcome).

Hazard ratios and 95% confidence intervals are shown for the primary outcome in each prespecified subgroup. GFR denotes glomerular filtration rate, NIVCD nonspecific intraventricular conduction delay, and NYHA New York Heart Association.

as compared with patients receiving optimal medical treatment alone (P=0.003). In the Cardiac Resynchronization–Heart Failure (CARE-HF) trial (ClinicalTrials.gov number, NCT00318357), the same relative reduction in the rate of death (36%) was observed among similar patients who had not undergone ICD implantation but who had received a CRT pacing device, as compared with those receiving optimal medical therapy (P=0.002). Until now there has been no evidence that CRT offers a survival benefit beyond that provided by an ICD. Since most patients with NYHA class II or III heart failure and left ventricular systolic dysfunction are also candidates for ICD therapy,[1,20-22] it would be important to know whether CRT can offer a survival benefit in addition to that provided by ICD.

We found a significant reduction in the rate of death from any cause associated with the use of CRT in addition to ICD and optimal medical therapy. The relative risk of death was reduced by 25%, resulting in an absolute mortality reduction

of 6 percentage points at 5 years. The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT–CRT; NCT00180271) did not show a survival benefit for CRT when used in addition to an ICD and optimal medical therapy in patients with mild NYHA class I or II heart failure, although a reduction in heart-failure medical encounters was observed with CRT.[10] Possible reasons for the differences in mortality between our study and MADIT–CRT are that our trial had more complete and longer follow-up and that patients in our trial had slightly more advanced disease with a slightly lower left ventricular ejection fraction, and a higher proportion of our patients had ischemic heart disease.

In our study, the only significant interaction between treatment and subgroup was the QRS duration, with an intrinsic QRS duration of 150 msec or more associated with an increased benefit of ICD combined with CRT. Although the results of this subgroup analysis should be interpreted with caution, our findings concur with those of MADIT–CRT and deserve further research. It is reassuring that the effect of CRT was similar for patients with NYHA class II heart failure and those with class III heart failure, with no statistical interaction between treatment and subgroup.

Our study also serves as a reminder that left ventricular lead implantation and ongoing care of patients with CRT are not without challenges. The rate of adverse events within 30 days after device implantation was significantly higher among patients in the ICD–CRT group than among those in the ICD group and was consistent with the rates in other studies.[23,24] Left ventricular lead dislodgement and an increased rate of infection remain significant problems. Although many of these adverse events did not have substantial long-term consequences, they may prolong hospitalization. Indeed, the rate of device-related hospitalization was higher in the ICD–CRT group than in the ICD group, in part because of more rapid battery drainage in the earlier models of ICD–CRT devices.

In conclusion, the addition of CRT to the use of an ICD and optimal medical therapy reduced rates of death and hospitalization for heart failure among patients who had NYHA class II or III heart failure with left ventricular systolic dysfunction and a wide QRS complex. These findings support the use of CRT along with an ICD and medical therapy in patients with NYHA class II or III heart failure, left ventricular systolic dysfunction, and a wide QRS complex.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37. [Erratum, N Engl J Med 2005;352:2146.]
2. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873-80.
3. Auricchio A, Stellbrink C, Sack S, et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol 2002;39:2026-33.
4. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845-53.
5. Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol 2003;42:1454-9.
6. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA 2003;289:2685-94.
7. Sutton MG, Plappert T, Hilpisch KE, et al. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). Circulation 2006;113:266-72.
8. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.
9. Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008;52:1834-43.
10. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329-38.
11. Tang AS, Wells GA, Arnold M, et al. Resynchronization/defibrillation for ambulatory heart failure trial: rationale and trial design. Curr Opin Cardiol 2009;24:1-8.
12. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005;112(12):e154-e235.
13. Arnold JM, Liu P, Demers C, et al. Canadian Cardiovascular Society consensus conference recommendations on heart

failure 2006: diagnosis and management. Can J Cardiol 2006;22:23-45. [Erratum, Can J Cardiol 2006;22:271.]
14. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ 1999;319:1492-5.
15. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.
16. Chan KL, Tang AS, Achilli A, et al. Functional and echocardiographic improvement following multisite biventricular pacing for congestive heart failure. Can J Cardiol 2003;19:387-90.
17. Ypenburg C, Lancellotti P, Tops LF, et al. Mechanism of improvement in mitral regurgitation after cardiac resynchronization therapy. Eur Heart J 2008;29:757-65.
18. Nelson GS, Berger RD, Fetics BJ, et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. Circulation 2000;102:3053-9. [Erratum, Circulation 2001;103:476.]
19. Ukkonen H, Beanlands RS, Burwash IG, et al. Effect of cardiac resynchronization on myocardial efficiency and regional oxidative metabolism. Circulation 2003; 107:28-31.
20. Moss AJ, Zareba W, Hall J, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-83.
21. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. Circulation 2008;117(21):e350-e408. [Erratum, Circulation 2009;120(5):e34-e35.]
22. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119:1977-2016.
23. León AR, Abraham WT, Curtis AB, et al. Safety of transvenous cardiac resynchronization system implantation in patients with chronic heart failure: combined results of over 2,000 patients from a multicenter study program. J Am Coll Cardiol 2005;46:2348-56.
24. Duray GZ, Schmitt J, Cicek-Hartvig S, Hohnloser SH, Israel CW. Complications leading to surgical revision in implantable cardioverter defibrillator patients: comparison of patients with single-chamber, dual-chamber, and biventricular devices. Europace 2009;11:297-302.

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