The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 10, 2013 VOL. 369 NO. 15

Cardiac-Resynchronization Therapy in Heart Failure with a Narrow QRS Complex

Frank Ruschitzka, M.D., William T. Abraham, M.D., Jagmeet P. Singh, M.D., Ph.D., Jeroen J. Bax, M.D., Ph.D., Jeffrey S. Borer, M.D., Josep Brugada, M.D., Ph.D., Kenneth Dickstein, M.D., Ph.D., Ian Ford, M.D., Ph.D., John Gorcsan III, M.D., Daniel Gras, M.D., Henry Krum, M.B., B.S., Ph.D., Peter Sogaard, M.D., D.M.Sc., and Johannes Holzmeister, M.D., for the EchoCRT Study Group*

ABSTRACT

BACKGROUND

Cardiac-resynchronization therapy (CRT) reduces morbidity and mortality in chronic systolic heart failure with a wide QRS complex. Mechanical dyssynchrony also occurs in patients with a narrow QRS complex, which suggests the potential usefulness of CRT in such patients.

METHODS

We conducted a randomized trial involving 115 centers to evaluate the effect of CRT in patients with New York Heart Association class III or IV heart failure, a left ventricular ejection fraction of 35% or less, a QRS duration of less than 130 msec, and echocardiographic evidence of left ventricular dyssynchrony. All patients underwent device implantation and were randomly assigned to have CRT capability turned on or off. The primary efficacy outcome was the composite of death from any cause or first hospitalization for worsening heart failure.

RESULTS

On March 13, 2013, the study was stopped for futility on the recommendation of the data and safety monitoring board. At study closure, the 809 patients who had undergone randomization had been followed for a mean of 19.4 months. The primary outcome occurred in 116 of 404 patients in the CRT group, as compared with 102 of 405 in the control group (28.7% vs. 25.2%; hazard ratio, 1.20; 95% confidence interval [CI], 0.92 to 1.57; P=0.15). There were 45 deaths in the CRT group and 26 in the control group (11.1% vs. 6.4%; hazard ratio, 1.81; 95% CI, 1.11 to 2.93; P=0.02).

CONCLUSIONS

In patients with systolic heart failure and a QRS duration of less than 130 msec, CRT does not reduce the rate of death or hospitalization for heart failure and may increase mortality. (Funded by Biotronik and GE Healthcare; EchoCRT ClinicalTrials.gov number, NCT00683696.)

From the Clinic for Cardiology, University Hospital Zurich, Zurich, Switzerland (F.R., J.H.); the Division of Cardiovascular Medicine, Ohio State University Medical Center, Davis Heart and Lung Research Institute, Columbus (W.T.A.); Cardiac Arrhythmia Service, Massachusetts General Hospital, Harvard Medical School, Boston (J.P.S.); the Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands (J.J.B.); the Division of Cardiovascular Medicine and Howard Gilman and Ron and Jean Schiavone Institutes, State University of New York Downstate College of Medicine, New York (J.S.B.); Cardiology Department, Thorax Institute, Hospital Clinic, University of Barcelona, Barcelona (J.B.); University of Bergen, Stavanger University Hospital, Stavanger, Norway (K.D.); Robertson Centre for Biostatistics, University of Glasgow, Glasgow, United Kingdom (I.F.); University of Pittsburgh, Pittsburgh (J.G.); Nouvelles Cliniques Nantaises, Nantes, France (D.G.); Monash Centre of Cardiovascular Research and Education in Therapeutics, Melbourne, VIC, Australia (H.K.); and Aalborg University, Aalborg, Denmark (P.S.). Address reprint requests to Dr. Holzmeister at the Clinic for Cardiology, University Hospital Zurich, Raemistr. 100, CH-8091 Zurich, Switzerland, or at johannes.holzmeister@usz.ch.

Drs. Ruschitzka and Holzmeister and Drs. Abraham and Singh contributed equally to this article.

*Participating centers and investigators in the Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) study are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on September 3, 2013, at NEJM.org.

N Engl J Med 2013;369:1395-405.
DOI: 10.1056/NEJMoa1306687

Despite recent advances, heart failure remains a common cause of death and morbidity. According to current guidelines, cardiac-resynchronization therapy (CRT) is indicated for patients receiving stable medical therapy recommended by current guidelines who have moderate-to-severe heart failure, a left ventricular ejection fraction of 35% or less, and a QRS duration of 120 msec or more as assessed electrocardiographically.[1] However, many patients with heart failure have a QRS duration of less than 120 msec,[2] and it is currently not recommended that they receive CRT. Up to 50% of these patients show echocardiographic evidence of ventricular dyssynchrony[3,4] and hence might benefit from CRT.

Single-center studies have suggested that dyssynchrony criteria that are based on echocardiographic measurements can identify patients who can benefit from CRT,[5-7] resulting in frequent off-label use of CRT in patients with a narrow QRS complex.[8] Small, randomized clinical studies that were not powered to assess clinically relevant outcomes[9-14] have suggested the existence of true clinical equipoise, thereby setting the stage for a definitive outcome trial. We therefore initiated the Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) study to investigate the effect of CRT on morbidity and mortality among patients with symptomatic heart failure, a narrow QRS complex, and echocardiographic evidence of left ventricular dyssynchrony.

Methods

Study Design and Oversight

The EchoCRT study was an investigator-initiated, international, multicenter, randomized clinical trial. The trial was designed by the executive committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) and sponsored by Biotronik, with support for echocardiographic training and software provided by GE Healthcare. Biotronik was responsible for trial execution and monitoring. The trial protocol, available at NEJM.org, was approved by the institutional review board at each participating center. The study results were analyzed independently at the Robertson Centre for Biostatistics at the University of Glasgow. The first draft of the manuscript was written by the first author, with review by all the authors; there was no commercial involvement in the writing of the article. All the authors made the decision to submit the manuscript for publication. All the authors vouch for the accuracy and completeness of the reported findings and for the fidelity of this report to the trial protocol.

Patients

Eligible patients were 18 years of age or older, with New York Heart Association (NYHA) class III or IV heart failure; a left ventricular ejection fraction of 35% or less; a standard indication for an implantable cardioverter–defibrillator (ICD); stable medical therapy recommended by current guidelines; a QRS duration of less than 130 msec; a left ventricular end-diastolic diameter of 55 mm or more; and echocardiographic evidence of left ventricular dyssynchrony. Dyssynchrony was defined by means of color-coded tissue Doppler imaging as an opposing-wall delay in the peak systolic velocity of 80 msec or more in apical four-chamber or apical long-axis views or by means of speckle-tracking radial strain as a delay in the anteroseptal-to-posterior wall of 130 msec or more in the mid-left ventricular short-axis view.[15-18] Details of the echocardiographic evaluation of dyssynchrony are provided in the Supplementary Appendix.

Reasons for exclusion included acute decompensated heart failure, intravenous inotropic therapy, atrial fibrillation within the previous month, and bradycardia requiring pacing. Details of the inclusion and exclusion criteria are provided in the Supplementary Appendix. All the patients provided written informed consent.

CRT Device Implantation

Patients meeting all inclusion criteria and no exclusion criteria underwent implantation of a device with both CRT and ICD capability (CRT-D). Biotronik Lumax HF-T CRT-D systems were used exclusively. All the patients received atrial and right and left ventricular leads. Only transvenous lead systems legally marketed in the respective countries (regardless of manufacturer) were used. Details of device implantation are provided in the Supplementary Appendix. Patients who underwent an unsuccessful attempt at implantation received an ICD rather than a CRT-D and exited the study after enrolling in a 30-day safety registry.

Randomization, Device Programming, and Follow-up

Randomization occurred after successful implantation of the CRT-D system and the adjustment of

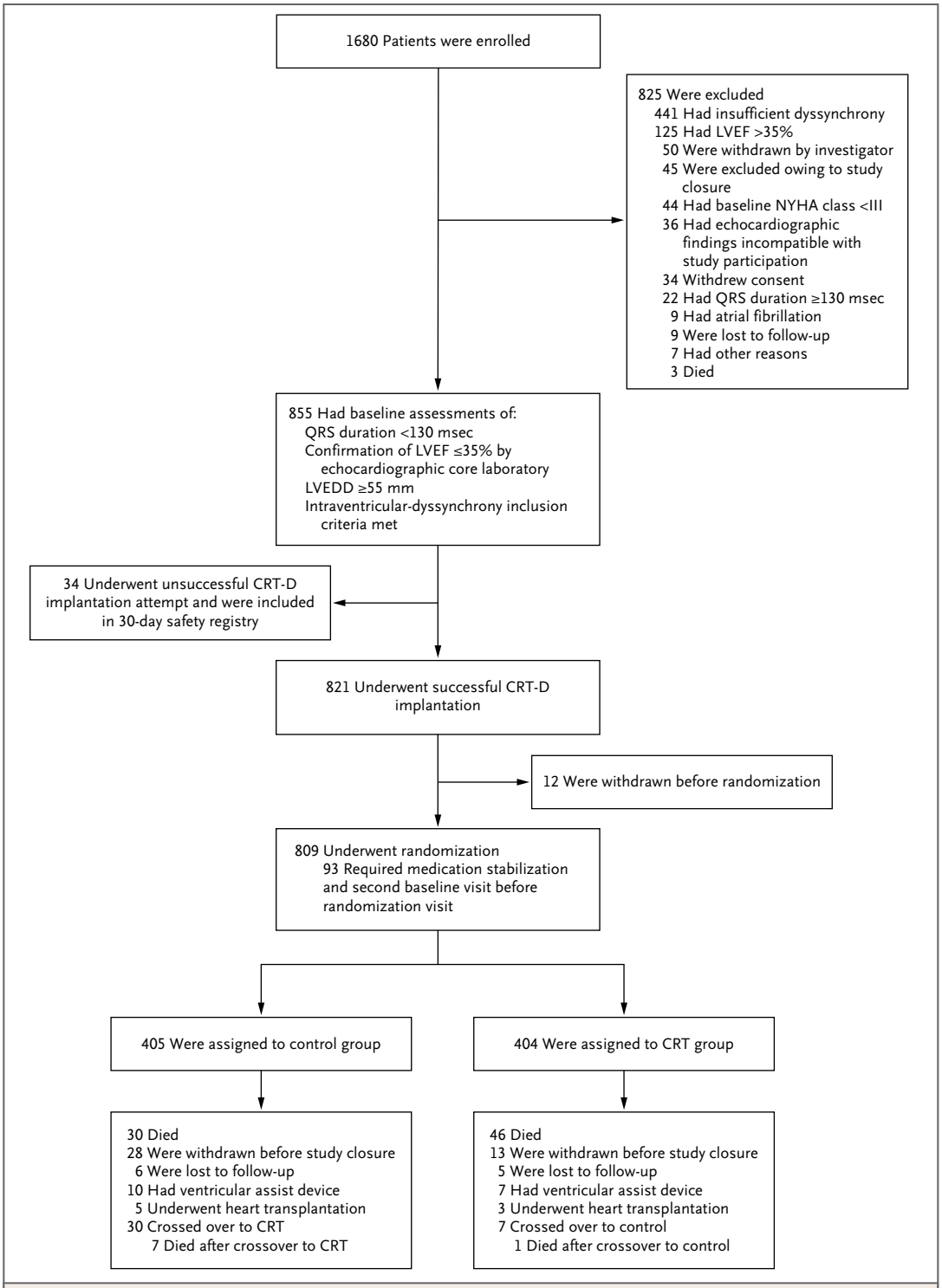

Figure 1. Study Enrollment, Randomization, and Follow-up.

At study termination on March 13, 2013, a total of 821 patients had undergone successful implantation of a device for cardiac-resynchronization therapy (CRT) with a defibrillator (CRT-D). A total of 809 patients underwent randomization (404 patients to CRT [CRT capability turned on] and 405 to control [CRT capability turned off]), and follow-up occurred at 1 month and 3 months and then every 3 months thereafter. LVEDD denotes left ventricular end-diastolic diameter, LVEF left ventricular ejection fraction, and NYHA New York Heart Association.

medical therapy for heart failure according to current guidelines. Patients were randomly assigned with the use of a Web-based electronic randomization system in a 1:1 ratio to have CRT capability turned on (the CRT group) or to have CRT capability turned off (the control group). Randomization was based on permuted blocks of four, stratified according to country. After randomization, ICD therapy was programmed on for all patients, and device programming was individualized to maximize the delivery of CRT in the CRT group and to minimize right ventricular pacing in those in the control group (see the Supplementary Appendix).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Control Group (N=405)	CRT Group (N=404)
Age — yr	58.3±12.6	57.6±12.9
Male sex — no. (%)	291 (71.9)	294 (72.8)
QRS duration — msec		
Reported by the study site	105.4±12.6	105.0±13.1
Reported by the core laboratory	105.5±12.1	106.1±13.1
6-Min walk distance — m	322.6±122.1	328.3±118.6
Quality-of-life score†	51.1±24.2	51.3±24.3
NYHA classification — no. (%)‡		
I	3 (0.7)	2 (0.5)
II	12 (3.0)	7 (1.7)
III	374 (92.3)	385 (95.3)
IV	16 (4.0)	10 (2.5)
Biomarker for heart failure		
Brain natriuretic peptide — pg/ml		
Median	275	241
Interquartile range	104–600	88–516
NT-proBNP — pg/ml		
Median	978	1275
Interquartile range	479–2028	488–2554
Blood pressure while sitting — mm Hg		
Systolic	120.1±19.1	117.5±19.6
Diastolic	73.0±11.9	72.6±12.1
Body-mass index	31.2±12.6	30.6±11.7
Ischemic cardiomyopathy — no./total no. (%)	214/404 (53.0)	218/404 (54.0)
Myocardial infarction >3 mo previously — no. (%)	155 (38.3)	167 (41.3)
PCI >3 mo previously — no. (%)	131 (32.3)	157 (38.9)
CABG >3 mo previously — no. (%)	74 (18.3)	77 (19.1)
Hypertension — no./total no. (%)	271/402 (67.4)	262/400 (65.5)
Congenital heart disease — no./total no. (%)	10/396 (2.5)	6/399 (1.5)
Prior ischemic stroke or TIA — no./total no. (%)	47/402 (11.7)	49/401 (12.2)
Diabetes — no./total no. (%)	153/404 (37.9)	167/402 (41.5)
Chronic lung disease — no./total no. (%)	79/401 (19.7)	70/401 (17.5)
Chronic kidney disease — no./total no. (%)	42/401 (10.5)	66/402 (16.4)
Left ventricular ejection fraction — %§	27.0±5.4	27.0±5.7
Left ventricular end-diastolic diameter — mm	66.1±7.4	66.7±7.7

Table 1. (Continued.)

Characteristic	Control Group (N=405)	CRT Group (N=404)
Dyssynchrony qualified with the use of tissue Doppler imaging, radial strain, or both — no./total no. (%)		
Tissue Doppler imaging	106/405 (26.2)	96/403 (23.8)
Radial strain	100/405 (24.7)	85/403 (21.1)
Tissue Doppler imaging and radial strain	199/405 (49.1)	222/403 (55.1)
Medication at randomization — no. (%)		
ACE inhibitor or ARB	384 (94.8)	383 (94.8)
Aldosterone antagonist	238 (58.8)	247 (61.1)
Beta-blocker	395 (97.5)	387 (95.8)
Diuretic agent	352 (86.9)	346 (85.6)

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline, except for chronic kidney disease (P=0.01). Data were missing for the following characteristics: QRS width as reported by the core laboratory (for 6 patients in the cardiac-resynchronization–therapy [CRT] group and for 3 in the control group), distance walked in 6 minutes (for 7 in the CRT group and for 10 in the control group), quality-of-life score (for 1 in the CRT group and for 2 in the control group), biomarker for heart failure (for 19 in the CRT group and for 12 in the control group), and body-mass index (the weight in kilograms divided by the square of the height in meters; for 1 in the CRT group). Additional details regarding baseline characteristics are provided in Table S1 in the Supplementary Appendix. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, CABG coronary-artery bypass grafting, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TIA transient ischemic attack.

† Quality of life was assessed with the use of the Minnesota Living with Heart Failure questionnaire.[19] Scores range from 0 to 105, with higher scores indicating worse function and a clinically significant difference considered to be approximately 5 points.

‡ Patients listed here with NYHA class I or II heart failure had class III or IV heart failure when they were enrolled in the study. The NYHA classification changed after medical therapy was tailored according to current guidelines and before randomization occurred and baseline values were assessed.

§ Left ventricular ejection fraction was assessed with the use of the biplane method.

After randomization, patients underwent follow-up at 1 month and 3 months and then every 3 months thereafter until the termination of the trial, always with clinical evaluation and device testing and with echocardiography at 6 months and 12 months. Device-implanting physicians were aware of the study-group assignments, but the patients, heart-failure physicians, and study personnel completing the follow-up assessments were unaware of the group assignments.

OUTCOME MEASURES

The primary efficacy outcome was the combination of death from any cause or first hospitalization for worsening heart failure. The primary safety outcome was freedom from complications related to the CRT-D system at 6 months for all patients undergoing an attempted implantation. Detailed definitions of the primary outcome measures are provided in the Supplementary Appendix.

The prespecified secondary outcomes were as follows: all hospitalizations for worsening heart failure throughout the study; changes in NYHA classification after 6 months; changes in quality of life, as measured by the Minnesota Living with Heart Failure questionnaire[19] (scores range from 0 to 105, with higher scores indicating worse function, and a clinically significant difference considered to be approximately 5 points) after 6 months; a study-specific score[20] based on the composite outcome of death, first hospitalization for worsening heart failure (up to 24 months), and change in the score on the Minnesota Living with Heart Failure questionnaire after 6 months (see the protocol for details); and all-cause mortality.

STATISTICAL ANALYSIS

To detect a 25% reduction in the hazard of a primary outcome with 80% power, we estimated that 381 first primary-outcome events were required. We based our estimate of expected event rates on data from the Cardiac Resynchronization–Heart Failure (CARE-HF) trial,[21] with adjustment for the expectation of a lower event rate among patients with a narrow QRS complex, as compared with patients with a wide QRS com-

plex. We calculated that 1132 patients would accrue the required number of events over an average follow-up of 2.5 years if the final primary event rate in the control group was equal to 38%.

We performed all analyses according to the intention-to-treat principle. Baseline characteristics were summarized as means and standard deviations for continuous variables and as counts and percentages for categorical variables and were compared with the use of two-sample t-tests and chi-square (or Fisher's exact) tests, respectively. P values for time-to-event analyses were based on log-rank tests (stratified according to country of recruitment) with hazard ratios for treatment effects and 95% confidence intervals calculated from Cox proportional-hazards models that included study group and country of recruitment as covariates. Interactions between treatment effects and subgroup levels were tested for in Cox models that included treatment and subgroup main effects and interaction terms. Time-to-event curves were estimated with the use of the Kaplan–Meier method.

Changes in NYHA class from baseline to 6 months were analyzed as a binary outcome (improved condition vs. no change or deteriorated condition) with the use of a logistic-regression model with adjustment for country of recruitment, providing odds ratios for improvement and corresponding 95% confidence intervals. The change in total score on the Minnesota Living with Heart Failure questionnaire (defined as the score at 6 months minus the score at baseline) was analyzed with the use of an analysis of covariance with adjustment for the baseline total score and country of recruitment, and adjusted mean differences between study groups and 95% confidence intervals were calculated. All P values in the efficacy analysis were two-sided.

The analysis of the primary safety outcome aimed to exclude a complication-free rate of 70% or less, on the basis of an exact one-sided binomial proportion test to show that the CRT-D system had similar complication-free rates as previously reported for comparable studies.[22,23]

RESULTS

PATIENT ENROLLMENT AND FOLLOW-UP

Beginning in August 2008, patients were enrolled at 115 centers in the United States, Canada, Israel, Australia, and Europe. On March 13, 2013, enrollment was stopped by the executive committee on the recommendation of the independent data and safety monitoring board, on the basis of futility with a potential for harm. No follow-up data were included after the study-closure date. A final clinical-status assessment and final device reprogramming to turn off CRT capability were conducted, when possible, and patients were subsequently returned to standard care.

At study termination, 1680 patients had consented to trial participation, and 809 had undergone randomization (404 patients to CRT and 405 to control) (Fig. 1). A total of 825 patients were excluded before implantation, the majority of whom did not meet the echocardiographic inclusion criteria according to either the local site or the core laboratory (602 patients). The echocardiographic core laboratory agreed with the findings of the local sites regarding dyssynchrony in 89.3% of the patients, excluding 10.7% whose degree of dyssynchrony could not be confidently confirmed. An additional 34 patients were excluded owing to unsuccessful implantation of a CRT-D (as described in the Supplementary Appendix), and 12 withdrew from the study before randomization.

The mean follow-up period was 19.4 months for all patients and 19.8 months for surviving patients. The study-visit compliance rate among patients was 95.5%; a total of 5324 of the 5575 required study visits were completed up to the date of patient withdrawal from the study. Details regarding patient withdrawal, loss to follow-up, and crossovers are provided in the Supplementary Appendix.

CHARACTERISTICS OF THE PATIENTS AT BASELINE

The baseline characteristics of the patients who underwent randomization are shown in Table 1, and Table S1 in the Supplementary Appendix. These characteristics were similar in the two groups, although chronic kidney disease was more prevalent in the CRT group. The mean QRS duration measured by the centers was 105.0 msec for the CRT group and 105.4 msec for the control group. The QRS width at baseline was independently measured at the electrocardiographic core laboratory and was repeated for crossover approval. The mean left ventricular ejection fraction and variables regarding left ventricular dyssynchrony did not differ significantly between the two groups.

EFFICACY OUTCOMES

The primary outcome, death from any cause or hospitalization for worsening heart failure, occurred in 116 of 404 patients (28.7%) in the CRT group, as compared with 102 of 405 (25.2%) in the control group (hazard ratio with CRT, 1.20; 95% confidence interval [CI], 0.92 to 1.57; P=0.15) (Table 2 and Fig. 2). During the trial, 45 of 404 patients (11.1%) in the CRT group died, as compared with 26 of 405 (6.4%) in the control group (hazard ratio, 1.81; 95% CI, 1.11 to 2.93; P=0.02) (Table 2). Table S2 in the Supplementary Appendix shows the causes of death, as originally adjudicated. There was an excess of deaths due to cardiovascular causes in patients randomly assigned to CRT (37 deaths, vs. 17 in the control group; P=0.004).

Of 809 patients, 418 (51.7%) were hospitalized at least once during follow-up (224 patients in the CRT group vs. 194 in the control group). Most of these hospitalizations were for cardiovascular reasons (147 patients in the CRT group vs. 137 in the control group; hazard ratio, 1.11; 95% CI, 0.88 to 1.40; P=0.36). The hospitalization rate for worsening heart failure did not differ significantly between the two groups (Table 2). A total of 229 hospital admissions for heart failure (35.6 admissions per 100 years of follow-up) occurred in the CRT group, as compared with 181 (27.6 per 100 years of follow-up) in the control group.

Changes from baseline to 6 months with respect to NYHA class and score on the Minnesota Living with Heart Failure questionnaire did not differ significantly between the study groups. There was also no difference between groups in the composite-outcome score that included death, first hospitalization for worsening heart failure, and change in score on the Minnesota Living with Heart Failure questionnaire. The details of these results are shown in Table S3 in the Supplementary Appendix.

SUBGROUPS

The effects of treatment on nine prespecified subgroups for the primary composite outcome and the component outcomes are shown in Figures S1A, S1B, and S1C in the Supplementary Appendix. There were no significant treatment-by-subgroup interactions for the primary out-

Table 2. Protocol-Specified Cardiovascular Outcomes.*

Outcome	Control Group (N=405)	CRT Group (N=404)	Adjusted Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary composite outcome				
Death from any cause or hospitalization for heart failure	102 (25.2)	116 (28.7)	1.20 (0.92–1.57)	0.15
Components of primary outcome				
Hospitalization for heart failure	90 (22.2)	99 (24.5)	1.16 (0.87–1.55)	0.25
Death from any cause	26 (6.4)	45 (11.1)	1.81 (1.11–2.93)	0.02
Other cardiovascular outcomes				
Hospitalization for cardiovascular event	137 (33.8)	147 (36.4)	1.11 (0.88–1.40)	0.36
Death				
Cardiovascular event	17 (4.2)	37 (9.2)	2.26 (1.27–4.01)	0.004
Heart failure	10 (2.5)	17 (4.2)	1.74 (0.80–3.81)	0.15
Follow-up data censored				
Owing to LVAD implantation	10 (2.5)	7 (1.7)	—	—
Owing to heart transplantation	5 (1.2)	3 (0.7)	—	—
Death after data were censored owing to LVAD implantation or heart transplantation†	4 (1.0)	1 (0.2)	—	—

* Hazard ratios were calculated by means of the Cox model with adjustment for country, and P values were calculated by the stratified log-rank test. LVAD denotes left ventricular assist device.

† Because these deaths occurred after LVAD implantation or heart transplantation, they were not included in the analysis of mortality.

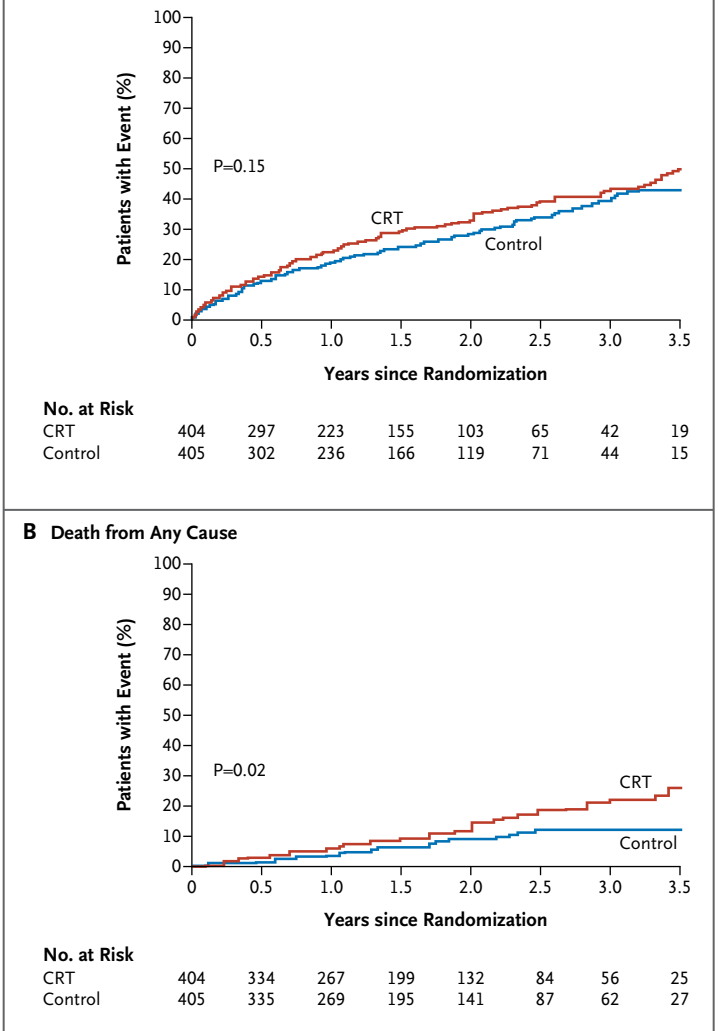

Figure 2. Kaplan–Meier Estimates for Primary-Outcome Events.
Panel A shows the Kaplan–Meier curves for the primary composite outcome of death from any cause or hospitalization for heart failure. Panel B shows the Kaplan–Meier curves for death from any cause.

come or for hospitalization for worsening heart failure. For all-cause mortality, there was one nominally significant treatment-by-subgroup interaction that suggested a greater harm with CRT in patients less than 65 years of age (Fig. S1C in the Supplementary Appendix) (P=0.02 for interaction).

SAFETY

The rate of freedom from complications related to the CRT-D system at 6 months was 89.6% for the population that included all patients who underwent an attempted implantation (binomial proportion, 0.90; 95% CI, 0.87 to 0.92; P<0.001 for excluding a rate ≤70%). A total of 50 patients (12.4%) in the CRT group had complications, as compared with 36 (8.9%) in the control group (P=0.11).

A total of 93 serious adverse events related to the device or implantation occurred in 70 of the 404 patients in the CRT group, and 50 such events occurred in 45 of the 405 patients in the control group (P=0.01) (Table 3). A total of 74 device-related serious adverse events after implantation occurred in 55 patients (13.6%) in the CRT group, and 32 events in 29 patients (7.2%) in the control group (P=0.003). This difference was largely driven by a difference of a factor of approximately three in the number of lead-related serious adverse events between the CRT and control groups (68 vs. 22). These events included dislodgement of the left ventricular lead in 14 patients (3.5%) in the CRT group and in 4 (1.0%) in the control group. Rates of implantation-related serious adverse events were similar between the two groups (19 events in 17 patients [4.2%] in the CRT group and 18 events in 16 patients [4.0%] in the control group).

The total number of patients receiving an ICD shock was similar between the study groups (occurring in 76 [18.8%] and 63 [15.6%] patients in the CRT and control groups, respectively). Inappropriate shocks were more prevalent in patients in the CRT group than in those in the control group (20 patients [5.0%] vs. 7 [1.7%], P=0.01).

DISCUSSION

In the EchoCRT study, the use of CRT did not reduce the rate of death from any cause or first hospitalization for heart failure among patients with symptomatic heart failure, a left ventricular ejection fraction of 35% or less, and a QRS duration of less than 130 msec. The observed excess mortality with CRT in this trial is of clinical concern. The excess mortality was due to a significant increase in the rate of death from cardiovascular causes among patients receiving CRT. There was a nonsignificant trend toward an increase in mortality related to heart failure, which was paralleled by a nonsignificant increase in hospitalization for heart failure. However, the interpretation of secondary outcomes in trials that fail to confirm the primary hypothesized outcome should be approached with great caution.

Mechanical dyssynchrony in our study was systematically assessed with the use of uniform

Table 3. Serious Adverse Events after Implantation, According to Study Group.*

Event	Control Group (N=405)		CRT Group (N=404)	
	no. of events	*no. of patients with event (%)*	*no. of events*	*no. of patients with event (%)*
All events	732	221 (54.6)	939	259 (64.1)
Cardiovascular event	423	160 (39.5)	499	182 (45.0)
Worsening heart failure	181	93 (23.0)	213	101 (25.0)
Atrial arrhythmia	35	25 (6.2)	34	27 (6.7)
Ventricular arrhythmia	29	22 (5.4)	36	26 (6.4)
Chest pain	26	21 (5.2)	31	16 (4.0)
Other	20	17 (4.2)	21	18 (4.5)
Dyspnea	12	11 (2.7)	16	16 (4.0)
Coronary artery disease	11	10 (2.5)	13	13 (3.2)
Noncardiovascular event	259	121 (29.9)	347	155 (38.4)
Infection	54	45 (11.1)	77	58 (14.4)
Gastrointestinal disorder	41	28 (6.9)	68	43 (10.6)
Other	55	36 (8.9)	54	40 (9.9)
Respiratory disorder	38	22 (5.4)	27	14 (3.5)
Renal disorder	19	16 (4.0)	38	28 (6.9)
Musculoskeletal disorder	18	15 (3.7)	32	25 (6.2)
Nervous system disorder	5	5 (1.2)	16	13 (3.2)
CRT-D–system related	32	29 (7.2)	74	55 (13.6)
ICD lead	13	13 (3.2)	26	23 (5.7)
Lead for right atrial pacing	5	5 (1.2)	21	18 (4.5)
Lead for left ventricular pacing	4	4 (1.0)	21	18 (4.5)
Implantation related	18	16 (4.0)	19	17 (4.2)

* Data for subcategories with an incidence of less than 3.0% are not shown. Patients could have more than one event. CRT-D denotes cardiac-resynchronization device with defibrillator, and ICD implantable cardioverter–defibrillator.

equipment and a core laboratory. In addition, advanced echocardiographic techniques were used to assess dyssynchrony, including tissue Doppler imaging and speckle-tracking radial strain, which have been associated with outcome when the QRS complex is wide.[16,18,24-26] Our results reinforce the notion that, at least until new methods of assessment are developed, QRS width (with or without mechanical dyssynchrony) remains the primary determinant of response to CRT.

Clinical-outcome trials may not be appropriately designed to elucidate the mechanisms of benefit or harm associated with a therapeutic intervention. However, they may provide insights that inform future research. Since CRT-induced proarrhythmia in patients with a narrow QRS complex could account in part for the increased mortality among patients randomly assigned to active therapy in this study, the numbers of appropriate and inappropriate ICD shocks were analyzed, both of which may contribute to an increase in mortality among patients who received an ICD or CRT-D.[27] Although the total number of patients receiving an ICD shock was similar between the study groups, inappropriate shocks were more prevalent in patients in the CRT group than in those in the control group.

Since unnecessary pacing may contribute to the development of heart failure, it is of note that ventricular pacing in the control group was negligible in this study. Patients with ischemic cardiomyopathy or suboptimal placement of the

left ventricular lead may be at greater risk for arrhythmic events with CRT, but subgroup analyses did not show evidence of any interactions between these factors and clinical outcomes. Although interactions of the location of the left ventricular lead with respect to activation or scar have not been examined, it is possible that this study did not show a benefit because the lead placement was not tailored to the mechanical abnormal substrate of patients with heart failure and normal or near-normal QRS duration or because the leads were placed in scar areas.[28,29]

Current guidelines do not recommend CRT for patients with a normal QRS duration.[1] The mean QRS width in the CARE-HF[21] trial was 160 msec, and the majority of patients included in many other major trials have had a QRS duration of more than 150 msec.[23,30,31] A recent meta-analysis evaluating the effect of QRS duration on the efficacy of CRT showed that CRT significantly reduced the rate of death from any cause or hospitalization among patients with a QRS duration of 150 msec or more, but the magnitude of effect and the certainty of benefit declined with shorter QRS duration.[32]

The excess risk of CRT among patients included in the EchoCRT study who had heart failure and a narrow QRS complex is of particular concern, because it serves as a reminder that the implantation of left ventricular leads and the ongoing care of patients treated with CRT (which may involve subsequent manipulation of the leads for improvement in pacing) are not without challenges. Indeed, the rate of adverse events after device implantation was significantly higher among patients in the CRT group than among those in the control group, a difference driven largely by a difference of a factor of three in the number of lead-related serious adverse events between the two groups.

In conclusion, we investigated the potential benefit of CRT-D in patients with systolic heart failure and a QRS duration of less than 130 msec. As compared with an ICD with inactivated CRT, a CRT-D did not reduce the rate of death from any cause or hospitalization for heart failure and may increase mortality among these patients.

Supported by Biotronik and GE Healthcare.
Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology: developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847. [Erratum, Eur Heart J 2013;34:158.]
2. Khan NK, Goode KM, Cleland JG, et al. Prevalence of ECG abnormalities in an international survey of patients with suspected or confirmed heart failure at death or discharge. Eur J Heart Fail 2007;9:491-501.
3. Yu CM, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart 2003;89:54-60.
4. Hawkins NM, Petrie MC, MacDonald MR, Hogg KJ, McMurray JJ. Selecting patients for cardiac resynchronization therapy: electrical or mechanical dyssynchrony? Eur Heart J 2006;27:1270-81.
5. Achilli A, Sassara M, Ficili S, et al. Long-term effectiveness of cardiac resynchronization therapy in patients with refractory heart failure and "narrow" QRS. J Am Coll Cardiol 2003;42:2117-24.
6. Bleeker GB, Holman ER, Steendijk P, et al. Cardiac resynchronization therapy in patients with a narrow QRS complex. J Am Coll Cardiol 2006;48:2243-50.
7. Yu CM, Chan YS, Zhang Q, et al. Benefits of cardiac resynchronization therapy for heart failure patients with narrow QRS complexes and coexisting systolic asynchrony by echocardiography. J Am Coll Cardiol 2006;48:2251-7.
8. Dickstein K, Bogale N, Priori S, et al. The European cardiac resynchronization therapy survey. Eur Heart J 2009;30:2450-60.
9. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. N Engl J Med 2007;357:2461-71.
10. Donahue T, Niazi I, Leon A, Stucky M, Herrmann K. Acute and chronic response to CRT in narrow QRS patients. J Cardiovasc Transl Res 2012;5:232-41.
11. Muto C, Solimene F, Gallo P, et al. A randomized study of cardiac resynchronization therapy defibrillator versus dual-chamber implantable cardioverter-defibrillator in ischemic cardiomyopathy with narrow QRS: the NARROW-CRT study. Circ Arrhythm Electrophysiol 2013;6:538-45.
12. Thibault B, Harel F, Ducharme A, et al. Cardiac resynchronization therapy in patients with heart failure and a QRS complex <120 milliseconds: the Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial. Circulation 2013;127:873-81.
13. Cazeau SJ, Daubert JC, Tavazzi L, Frohlig G, Paul V. Responders to cardiac resynchronization therapy with narrow or intermediate QRS complexes identified by simple echocardiographic indices of dyssynchrony: the DESIRE study. Eur J Heart Fail 2008;10:273-80.
14. Foley PW, Patel K, Irwin N, et al. Cardiac resynchronisation therapy in patients with heart failure and a normal QRS duration: the RESPOND study. Heart 2011;97:1041-7.
15. Delgado V, Ypenburg C, van Bommel RJ, et al. Assessment of left ventricular dyssynchrony by speckle tracking strain imaging comparison between longitudinal, circumferential, and radial strain in cardiac resynchronization therapy. J Am Coll Cardiol 2008;51:1944-52.
16. Gorcsan J III, Tanabe M, Bleeker GB, et al. Combined longitudinal and radial dyssynchrony predicts ventricular response after resynchronization therapy. J Am Coll Cardiol 2007;50:1476-83.
17. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J III. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to

cardiac resynchronization therapy. Circulation 2006;113:960-8.
18. van Bommel RJ, Tanaka H, Delgado V, et al. Association of intraventricular mechanical dyssynchrony with response to cardiac resynchronization therapy in heart failure patients with a narrow QRS complex. Eur Heart J 2010;31:3054-62.
19. Garin O, Ferrer M, Pont A, et al. Disease-specific health-related quality of life questionnaires for heart failure: a systematic review with meta-analyses. Qual Life Res 2009;18:71-85.
20. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351:2049-57. [Erratum, N Engl J Med 2005;352:1276.]
21. 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.
22. 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.
23. 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.
24. Gorcsan J III, Abraham T, Agler DA, et al. Echocardiography for cardiac resynchronization therapy: recommendations for performance and reporting — a report from the American Society of Echocardiography Dyssynchrony Writing Group endorsed by the Heart Rhythm Society. J Am Soc Echocardiogr 2008;21:191-213.
25. Gorcsan J III, Oyenuga O, Habib PJ, et al. Relationship of echocardiographic dyssynchrony to long-term survival after cardiac resynchronization therapy. Circulation 2010;122:1910-8.
26. Delgado V, van Bommel RJ, Bertini M, et al. Relative merits of left ventricular dyssynchrony, left ventricular lead position, and myocardial scar to predict long-term survival of ischemic heart failure patients undergoing cardiac resynchronization therapy. Circulation 2011;123:70-8.
27. Moss AJ, Schuger C, Beck CA, et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 2012;367:2275-83.
28. Khan FZ, Virdee MS, Palmer CR, et al. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. J Am Coll Cardiol 2012;59:1509-18.
29. Saba S, Marek J, Schwartzman D, et al. Echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy: results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region trial. Circ Heart Fail 2013;6:427-34.
30. 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.
31. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385-95.
32. Sipahi I, Carrigan TP, Rowland DY, Stambler BS, Fang JC. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Arch Intern Med 2011;171:1454-62. [Erratum, Arch Intern Med 2011;171:1429.]