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Cardiac Resynchronization Therapy for the Treatment of Heart Failure in Patients With Intraventricular Conduction Delay and Malignant Ventricular Tachyarrhythmias

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OBJECTIVES This study was conducted to assess the safety and effectiveness of cardiac resynchronization therapy (CRT) when combined with an implantable cardioverter defibrillator (ICD).

BACKGROUND Long-term outcome of CRT was measured in patients with symptomatic heart failure (HF), intraventricular conduction delay, and malignant ventricular tachyarrhythmias (ventricular tachycardia/ventricular fibrillation [VT/VF]) requiring therapy from an ICD.

METHODS Patients (n = 490) were implanted with a device capable of providing both CRT and ICD therapy and randomized to CRT (n = 245) or control (no CRT, n = 245) for up to six months. The primary end point was progression of HF, defined as all-cause mortality, hospitalization for HF, and VT/VF requiring device intervention. Secondary end points included peak oxygen consumption (VO_2), 6-min walk (6 MW), New York Heart Association (NYHA) class, quality of life (QOL), and echocardiographic analysis.

RESULTS A 15% reduction in HF progression was observed, but this was statistically insignificant (p = 0.35). The CRT, however, significantly improved peak VO_2 (0.8 ml/kg/min vs. 0.0 ml/kg/min, p = 0.030) and 6 MW (35 m vs. 15 m, p = 0.043). Changes in NYHA class (p = 0.10) and QOL (p = 0.40) were not statistically significant. The CRT demonstrated significant reductions in ventricular dimensions (left ventricular internal diameter in diastole = −3.4 mm vs. −0.3 mm, p < 0.001 and left ventricular internal diameter in systole = −4.0 mm vs. −0.7 mm, p < 0.001) and improvement in left ventricular ejection fraction (5.1% vs. 2.8%, p = 0.020). A subgroup of patients with advanced HF (NYHA class III/IV) consistently demonstrated improvement across all functional status end points.

CONCLUSIONS The CRT improved functional status in patients indicated for an ICD who also have symptomatic HF and intraventricular conduction delay. (J Am Coll Cardiol 2003;42: 1454–9) © 2003 by the American College of Cardiology Foundation

Heart failure (HF) is a syndrome that affects an estimated five million Americans, with 400,000 to 700,000 new cases annually (1). Frequently, life-threatening ventricular arrhythmias may also accompany this condition (2). Heart failure may be compounded in patients with intraventricular conduction delay possibly due to a loss of ventricular synchrony (3). It has been hypothesized that biventricular cardiac stimulation could improve hemodynamics by resynchronizing the ventricles in patients with intraventricular conduction delays (4). To distinguish between pacing therapy for traditional indications and specific therapy for HF, the term "cardiac resynchronization therapy" (CRT) will be used to describe the therapy provided by these implanted systems.

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Published studies suggest that short-term improvements in hemodynamics (5,6) and long-term improvements in functional status are possible with CRT (7–9). Previously published studies have been restricted to patients with symptomatic HF but without conventional indications for an implantable cardioverter defibrillator (ICD) or had relatively small sample sizes and lacked a concurrent control group. This study is the first to describe the results of CRT in a double-blind, randomized controlled study in patients with both symptomatic HF and ventricular tachyarrhythmias.

METHODS

Study design. Major entry criteria for participation in the study include New York Heart Association (NYHA) class II to IV, left ventricular ejection fraction (LVEF) ≤35%, QRS interval ≥120 ms, and conventional indications for implant of an ICD. Patients could not be enrolled if they had atrial tachyarrhythmias or conventional indications for a permanent pacemaker. The full eligibility criteria have been

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Abbreviations and Acronyms

CRT = cardiac resynchronization therapy
HF = heart failure
HFEC = Heart Failure Events Committee
ICD = implantable cardioverter defibrillator
LV = left ventricle/left ventricular
LVEF = left ventricular ejection fraction
$LVID_d$ = left ventricular internal diameter in diastole
$LVID_s$ = left ventricular internal diameter in systole
NYHA = New York Heart Association classification
QOL = quality of life
VO_2 = oxygen consumption
VT/VF = ventricular tachycardia/ventricular fibrillation
6 MW = 6-min walk

previously described (10). Because of the immediate need for ICD therapy, investigators implanted the system first and then programmed the randomized therapy after a minimum 30-day period with no CRT. During this period, investigators were permitted to optimize pharmacologic therapy before initiating the randomized therapy. This step was added to reduce bias so that the observed changes could be attributed to CRT rather than changes in background medical therapy. The original study design (Phase I) was a crossover design with two three-month observation periods; its design and end point metrics of peak oxygen consumption (VO_2), 6-min walk (6 MW) distance, and quality of life (QOL) using the Minnesota Living with Heart Failure Questionnaire have been previously described (10).

The study design was later modified (Phase II) due to regulatory concerns over morbidity and mortality associated with CRT and the length of follow-up in the randomized mode. However, no changes were made to the study's eligibility criteria. Both designs are shown in Figure 1. The sponsor elected to change the primary end point from peak VO_2 to a composite end point driven by events associated with worsening HF, and the study was changed from a crossover to a parallel design. A Heart Failure Events Committee (HFEC) adjudicated all deaths and hospitalizations.

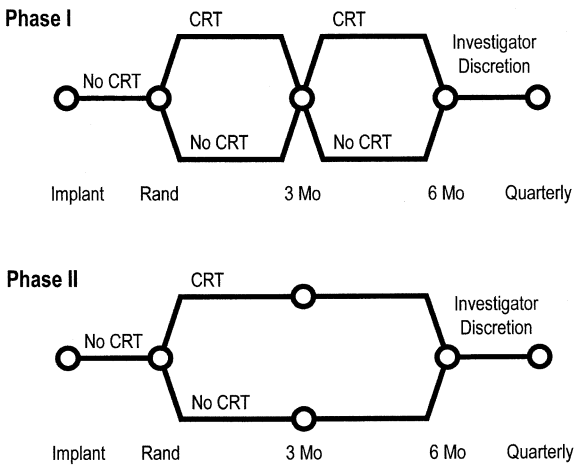

Figure 1. Study design for each phase. Phase I **(top)** was a crossover design (n = 248); Phase II **(bottom)** was a parallel design (n = 333). CRT = cardiac resynchronization therapy; Rand = randomization time.

Device description. The implanted system consisted of a pulse generator capable of providing both CRT and ICD therapy (Model 1822 Ventak CHF Automatic Implantable Cardioverter Defibrillator or Model 1823 Contak CD device, Guidant Corporation, St. Paul, Minnesota). Initially, the left ventricle (LV) was paced with a commercially available epicardial pace/sense lead (Model 4965 CapSure Epi pace/sense lead, Medtronic Corporation, Minneapolis, Minnesota). A lead (Model 4510/4511/4512/4513 Easytrak coronary venous pace/sense lead, Guidant Corporation, St. Paul, Minnesota) that could be placed transvenously under fluoroscopic guidance using over-the-wire techniques in the coronary venous vasculature was later introduced. A cardioversion/defibrillation lead (Model 0125 Endotak lead, Guidant Corporation, St. Paul, Minnesota) was implanted in the right ventricle, and a pace/sense lead was placed in the right atrium for this three-lead CRT system.

Statistical methods. The primary end point was progression of HF, defined as a composite of all-cause mortality, hospitalization for worsening HF, and ventricular tachyarrhythmias requiring device therapy. It was postulated that the therapy would reduce the overall incidence of these events by 25%. The primary end point was analyzed such that patients in Phase I contributed data from a three-month treatment phase and patients in Phase II contributed data from a six-month treatment phase. Cox proportional hazard models were fit for the combination of events with the treatment effect adjusted for covariates chosen by the HFEC before primary end point analysis. These covariates included NYHA class, QRS interval, ischemic etiology, LVEF, and bundle-branch morphology. The Wei method was used to calculate a composite effect of the treatment and covariates (11).

The longitudinal (repeated measures) analysis method was performed on continuous variables to compare the difference in the sample means. This method accounted for the patterns of missing data, took full advantage of the correlation structure, and used all the data to estimate the model parameters (12). Model parameters were estimated using maximum likelihood (SAS/STAT Version 8.1, SAS Institute, Inc., Cary, North Carolina). Values of $p < 0.05$ were considered to be significant for all tests.

RESULTS

Patient disposition. A total of 581 patients were enrolled at 47 investigational centers in the U.S. from February 1998 through December 2000. All patients enrolled provided written informed consent approved by each participating center's Institutional Review Board, and procedures were conducted in accordance with each participating investigator's institutional guidelines. All patients were indicated for implantation of an ICD in accordance with American College of Cardiology/American Heart Association guidelines (13).

Of the 581 patients enrolled in the study, 14 patients

Table 1. Baseline Characteristics

Characteristics	CRT (n = 245)	No CRT (n = 245)
Age (yrs)	66 ± 11	66 ± 11
Gender (male, %)	85	83
NYHA class (II/III/IV, %)	32/60/8	33/57/10
QRS interval (ms)	160 ± 27	156 ± 26
IVCD (LBBB/NS/RBBB, %)	54/32/14	55/33/12
Etiology (ischemic, %)	67	71
Diuretic (%)	88	83
ACE inhibitor/ARB (%)	86	89
Beta-blocker (%)	48	46
Digoxin (%)	69	68
Peak VO_2 (ml/kg/min)	13.8 ± 4.6	13.5 ± 3.8
QOL (points)	44 ± 25	40 ± 23
6 MW (m)	316 ± 119	320 ± 121
$LVID_d$ (mm)	71 ± 11	70 ± 10
$LVID_s$ (mm)	59 ± 11	58 ± 11
LVEF (%)	21 ± 7	22 ± 7

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; IVCD = intraventricular conduction delay; LBBB = left bundle-branch block; LVEF = left ventricular ejection fraction; $LVID_d$ = left ventricular internal diameter in diastole; $LVID_s$ = left ventricular internal diameter in systole; NS = non-specific; NYHA = New York Heart Association; QOL = quality of life; RBBB = right bundle-branch block; VO_2 = oxygen consumption; 6 MW = 6-min walk.

either withdrew informed consent or were determined not to meet eligibility criteria and were withdrawn by the investigator before an implant procedure. Another 66 patients did not receive an investigational system because of the inability to place the coronary venous lead; they received a conventional ICD system instead. Thus, 501 patients were implanted with the investigational system, with 448 (89%) receiving a transvenous system and 53 (11%) receiving a transthoracic system.

Of the transvenous leads, 242 (54%) were in a lateral vein, 142 (32%) were in an anterior vein, and 59 (13%) were posterior. Lead location was not recorded for the remaining five patients (1%). Of the leads placed transthoracically, 24 (45%) were placed apically, 14 (26%) were placed lateral, 11 (21%) were placed anterior, and 4 (8%) were implanted in a posterior position. Of the patients implanted, 222 were enrolled in Phase I (51 patients receiving transthoracic leads) and 279 were enrolled in Phase II (two patients receiving transthoracic leads).

Ten patients died and one withdrew within the 30-day post-implant recovery period before the randomized therapy could be programmed, leaving 490 patients available for analysis. Two of the 10 deaths were perioperative, with one death attributed to pulseless electrical activity resulting from defibrillation threshold testing and the other due to incessant ventricular tachycardia (VT) during the implant procedure. Of the remaining eight deaths, five were due to pump failure, two were attributed to cardiac causes unrelated to pump failure, and one was due to unknown cause as adjudicated by the HFEC. None of the latter eight deaths were attributed to the implant procedure. Patient demographics at the time of implant are reported in Table 1. The two randomized groups were balanced with no statistically significant differences with respect to baseline characteristics.

Table 2. Interaction Table for Functional Status by Covariate

Covariate	Peak VO_2	QOL	6 MW	NYHA Class
NYHA class III/IV	√√	√√	√√	√√
Wider QRS width	√	√	—	√√
LBBB/NSIVCD morphology	√√	—	—	√
Non-ischemic etiology	—	√	—	—
Lower LVEF	√√	—	—	—

√√ = Significant interaction ($p < 0.05$); √ = trend to significance ($0.05 \leq p < 0.10$); — = no significant interaction ($p \geq 0.10$).

NSIVCD = non-specific intraventricular conduction delay. Other abbreviations as in Table 1.

Influence of post-implant recovery period. All patients were in NYHA class II to IV at the time of entry into the study. During the post-implant recovery period, investigators were permitted to adjust or initiate HF medications to stabilize the patients' condition before implementing the randomized therapy. Many patients demonstrated significant symptomatic improvement with medical therapy during this period. Of the 328 patients who presented in NYHA class III/IV, 131 (40%) improved to NYHA class I or II, whereas 30 of 162 (19%) NYHA class II patients worsened to NYHA class III/IV during this period. Thus, after investigators had the opportunity to optimize medical therapy, 227 patients were in NYHA class III/IV and 263 were in NYHA class I/II before the office visit in which the randomized therapy was initiated.

Baseline predictors of improvement. Significant interactions of the five covariates chosen by the HFEC were found with the secondary end points (Table 2) as part of a post hoc analysis, but no interactions were found with the primary end point. The NYHA class, measured at the time of the randomization visit, was found to be the most consistent predictor of improvement with CRT across the functional status end points. Demographics for the NYHA class III/IV

Table 3. Baseline Characteristics (NYHA Class III/IV Post-Implant Recovery)

Characteristic	CRT (n = 117)	No CRT (n = 110)
Age (yrs)	66 ± 11	66 ± 11
Gender (male, %)	77	78
NYHA class (II/III/IV, %)	17/73/10	10/71/19
QRS interval (ms)	164 ± 27	152 ± 26
IVCD (LBBB/NS/RBBB, %)	50/32/18	54/34/12
Etiology (ischemic, %)	65	71
Diuretic (%)	92	86
ACE inhibitor/ARB (%)	81	89
Beta-blocker (%)	45	40
Digoxin (%)	72	68
Peak VO_2 (ml/kg/min)	12.0 ± 3.8	12.1 ± 3.4
QOL (points)	56 ± 22	49 ± 21
6 MW (m)	268 ± 123	269 ± 117
$LVID_d$ (mm)	73 ± 11	70 ± 10
$LVID_s$ (mm)	61 ± 11	58 ± 11
LVEF (%)	21 ± 6	21 ± 6

Abbreviations as in Table 1.

Table 4. Selected Secondary End Point Outcomes

End Point	All Patients			NYHA Class III/IV at Randomization			NYHA Class I/II at Randomization		
	CRT	No CRT	p Value	CRT	No CRT	p Value	CRT	No CRT	p Value
Peak VO_2 (ml/kg/min)	0.8 ± 0.3 (n = 216)	0.0 ± 0.3 (n = 201)	0.030	1.8 ± 0.4 (n = 96)	0.0 ± 0.4 (n = 80)	0.003	0.2 ± 0.3 (n = 120)	0.0 ± 0.3 (n = 121)	0.77
6 MW (m)	35 ± 7 (n = 224)	15 ± 7 (n = 220)	0.043	60 ± 12 (n = 99)	21 ± 13 (n = 90)	0.029	17 ± 9 (n = 125)	10 ± 9 (n = 130)	0.55
QOL (points)	−7 ± 2 (n = 234)	5 ± 2 (n = 225)	0.39	−16 ± 3 (n = 107)	−5 ± 3 (n = 96)	0.017	−1 ± 2 (n = 127)	−4 ± 2 (n = 129)	0.26
NYHA class (%)	(n = 109)	(n = 116)		(n = 45)	(n = 48)		(n = 64)	(n = 68)	
Improved 2 classes	11	2		27	4		—	—	
Improved 1 class	25	30	0.10	47	50	0.006	9	16	0.84
No change	51	51		22	38		72	60	
Worsened	13	17		4	8		19	24	
$LVID_d$ (mm)	−3.4 ± 0.6 (n = 228)	−0.3 ± 0.6 (n = 219)	< 0.001	−4.9 ± 1.0 (n = 104)	−0.2 ± 1.1 (n = 102)	0.001	−2.4 ± 0.8 (n = 124)	0.0 ± 0.8 (n = 117)	0.024
$LVID_s$ (mm)	−4.0 ± 0.7 (n = 228)	−0.7 ± 0.7 (n = 219)	< 0.001	−5.4 ± 1.1 (n = 104)	−0.6 ± 1.1 (n = 102)	0.002	−3.2 ± 0.8 (n = 124)	−0.5 ± 0.8 (n = 117)	0.014
LVEF (%)	5.1 ± 0.7 (n = 222)	2.8 ± 0.7 (n = 216)	0.020	6.0 ± 1.1 (n = 99)	2.3 ± 1.2 (n = 91)	0.029	4.7 ± 0.9 (n = 123)	2.9 ± 0.9 (n = 125)	0.16

Abbreviations as in Table 1.

patient population are presented in Table 3. Results for all patients are presented in Table 4 and are stratified by NYHA class I/II and NYHA class III/IV at the conclusion of the post-implant recovery period.

Progression of HF. Of the 245 patients randomized to CRT, a total of 79 events were observed, comprised of 11 deaths, 32 patients with at least one HF hospitalization, and 36 patients with at least one ventricular tachycardia/ventricular fibrillation (VT/VF) event. This result is compared with 94 events (16 deaths, 39 patients with at least one HF hospitalization, and 39 patients with at least one VT/VF event) observed in 245 patients randomized to no CRT. Relative reductions that were favorable to CRT were seen in all components. However, the overall relative reduction in composite HF progression of 15% with CRT was not statistically significant (p = 0.35). No statistically significant reductions were found when stratified into NYHA class I/II (12% reduction) or NYHA class III/IV (22% reduction). Kaplan-Meier curves illustrating time to event for both all-cause mortality and all-cause mortality plus HF hospitalization are shown in Figure 2.

Peak VO_2, 6 MW, QOL, and NYHA class. In the all-patients group (Table 4), CRT significantly improved peak oxygen consumption (p = 0.030) and 6MW distance (p = 0.043). The improvement in NYHA class did not achieve statistical significance (p = 0.10). The QOL improved more in those patients randomized to CRT than in patients randomized to control, but this change did not achieve statistical significance (p = 0.39).

Patients with NYHA class III/IV demonstrated improvement in peak VO_2 (p = 0.003), 6 MW distance (p = 0.029), NYHA class (p = 0.006), and QOL (p = 0.017). Patients with NYHA class I/II showed no significant improvement in any of these parameters.

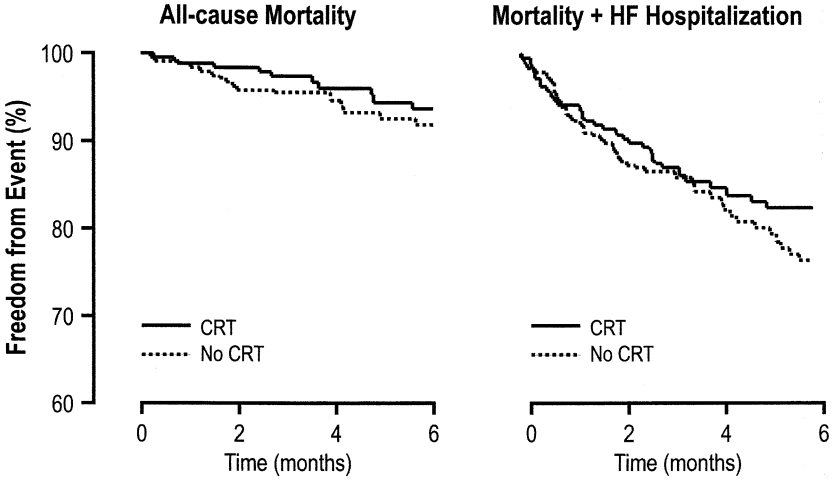

Figure 2. Kaplan-Meier curves for all-cause mortality **(left)** and all-cause mortality and heart failure (HF) hospitalization **(right)**. CRT = cardiac resynchronization therapy.

Echocardiographic data. Cardiac resynchronization therapy was associated with significant decreases in LV dimensions in the all-patients group. The $LVID_d$ was significantly improved ($p < 0.001$) as was left ventricular internal diameter in systole ($LVID_s$) ($p < 0.001$). The LVEF also significantly increased with CRT ($p = 0.020$). Decreases in LV dimensions were also noted in NYHA class III/IV patients with CRT in left ventricular internal diameter in diastole ($LVID_d$) ($p = 0.001$), $LVID_s$ ($p = 0.002$), and LVEF ($p = 0.029$). Patients in NYHA class I/II demonstrated significant reductions in $LVID_d$ ($p = 0.024$) and in $LVID_s$ ($p = 0.014$) with CRT.

All-cause mortality. A total of 109 deaths were reported throughout the study (27 deaths during the study treatment phase and 70 deaths during the long-term follow-up phase) and were adjudicated by an independent events committee. Of the 109 deaths, 47 (43%) were due to pump failure, 21 (19%) were non-cardiac, 9 (8%) were arrhythmic, 2 (2%) were ischemic, and 2 (2%) were cardiac in nature but of unknown etiology. The remaining 28 (26%) deaths had insufficient documentation for the committee to adjudicate cause of death. Operative mortality, defined as death from any cause within 30 days of the implant procedure, accounted for 12/567 (2%) of patients who underwent the implant procedure. Total survival at one, two, and three years was 85%, 74%, and 70%, respectively.

Spontaneous ventricular tachyarrhythmias. There was no statistically significant difference in the incidence or frequency of ventricular tachyarrhythmias when comparing CRT with no CRT. Of the 245 patients programmed to CRT, 36 (15%) received appropriate treatment of ventricular tachyarrhythmias with 25 (10%) having VT alone, 7 (3%) having VF alone, and 4 (2%) having both VT and VF. Of the 245 patients programmed to no CRT, 39 (16%) received appropriate device therapy. Ventricular tachycardia alone was reported in 27 (11%) patients, VF alone in 6 (2%) patients, and both VT and VF in 6 (2%) patients.

When excluding patients who had no VT/VF episodes, those patients randomized to CRT had a median of 2.5 episodes while those randomized to no CRT had a median of 2 episodes during the therapy evaluation phase. The device delivered antitachycardia pacing in a biventricular fashion. Spontaneous monomorphic VT was successfully treated with biventricular antitachycardia pacing in 927 of 1,053 (88%) episodes.

DISCUSSION

Progression of HF. The present study is the first report of CRT with an ICD in a double-blind, randomized, clinical study in a patient population with an ICD indication and symptomatic HF and intraventricular conduction delay. Although relative improvements in HF progression were observed that were favorable towards CRT, the magnitude of improvement was not statistically significant.

The primary end point analysis was based on an expected rate of HF events. The study was not adequately powered to detect a statistically significant difference because the actual event rate observed was approximately half that expected in the original study design. In addition to the relatively brief follow-up period of three months for Phase I patients, the widespread adoption of HF medications, such as beta-blockers and spironolactone, after the publication of positive clinical trial results and an evolution in HF management that focused on increased outpatient surveillance may have contributed to the reduction in expected events. Many patients responded positively once medical management was optimized before randomization. This improvement in status made it more difficult to show benefit in healthier patients while reducing the statistical power to show improvement in those who remained in NYHA class III/IV despite optimizing HF medications.

Secondary end points. Although this study was negative in terms of its primary end point, several important findings were observed about functional capacity, QOL, and reverse remodeling. Peak VO_2, which was the primary end point of the original study design, and 6 MW distance both demonstrated statistically significant improvements. Although angiotensin-converting enzyme inhibitors and beta-blockers have been proven to reduce mortality and hospitalization, these agents generally do not improve exercise tolerance (14–16). Thus, CRT appears to complement existing pharmacologic therapy by improving functional status without evidence for increased morbidity or mortality.

Echocardiographic analysis also revealed a statistically significant improvement in LV dimensions and LVEF. These findings are important because they provide evidence for reversal of the remodeling effects of HF. Interestingly, significant reductions in LV dimensions were noted in NYHA class I/II patients. Future studies may demonstrate benefit in patients with dyssynchrony but without overt symptoms by preventing remodeling.

Comparison with other studies. The results of two other studies, Multisite Insync Randomized Clinical Evaluation (MIRACLE) and InSync ICD (also referred to as "MIRACLE ICD"), have recently been publicized (17,18). These two studies enrolled patients with intraventricular conduction delay, LV dysfunction, and symptomatic HF while on stable HF medications. Patients without an ICD indication were enrolled in MIRACLE; those with an ICD indication were enrolled in InSync ICD.

The studies were similar in that CRT consisted of biventricular stimulation with LV stimulation from a lead placed in the coronary venous vasculature. All three designs called for patients to be randomized to CRT or no CRT for a six-month period, and all used similar methods for quantifying changes in functional status (peak VO_2, 6 MW, QOL, NYHA class, and echocardiography).

Dissimilarities in the studies were related to the patient populations (NYHA class II to IV in Contak CD and InSync ICD vs. NYHA class III to IV in MIRACLE) and how baseline testing was performed. Patients in the advanced HF subgroup of the Contak CD study most closely

correspond to the patient population in MIRACLE and the NYHA class III/IV subgroup of patients in InSync ICD for whom results were reported. In Contak CD, baseline testing was performed post-implant after a minimum 30-day waiting period, whereas the other two studies had most baseline tests performed pre-implant. Finally, the major difference in the studies was the use of mortality, hospitalization, and VT/VF events as the primary end point in the Contak CD study, whereas the MIRACLE and InSync ICD studies selected 6 MW, NYHA class, and QOL as co-primary end points.

All three studies showed directional improvement in mortality with CRT, but none achieved statistical significance or were powered to detect a difference. Similarly, all three studies demonstrated that CRT was safe. Improvements in functional capacity were highly consistent among the functional status end points when comparing the advanced HF subgroup with the results from the other two studies. Thus, the results of the published studies are highly concordant in demonstrating the safety and effectiveness of CRT across trials with similar patient populations.

Study limitations. Patients were studied in a randomized mode for only six months, with some patients followed for only three months. Ongoing studies with longer follow-up intervals, such as the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) and CArdiac REsynchronization in Heart Failure (CARE-HF) studies, are expected to determine long-term benefit (19,20). Applicability to patients with arrhythmias besides VT/VF is not well known, and it is unknown if the results can be generalized to patients with chronic atrial fibrillation, chronotropic incompetence, and sinus bradycardia. Furthermore, CRT was delivered in an atrial synchronous manner (i.e., VDD mode). The effects of atrial pacing as well as adaptive-rate pacing delivered with the DDD(R) modes were not studied.

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APPENDIX

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