Cardiac Resynchronization Therapy: A Review of Clinical Trials and Criteria for Identifying the Appropriate Patient

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Numerous clinical trials have evaluated the safety and efficacy of cardiac resynchronization therapy in patients with moderate or severe heart failure and ventricular dyssynchrony. Initial studies were observational or mechanistic in design and enrolled small numbers of patients. These investigations provided proof of concept in support of resynchronization therapy by demonstrating acute and chronic improvements in hemodynamics, echocardiographic measures of cardiac performance, and functional status. Of these early studies, the InSync Trial stands out as particularly important in suggesting the long-term clinical benefits of cardiac resynchronization therapy in advanced heart failure. Later, a series of randomized, controlled trials was initiated to definitively evaluate the effects of cardiac resynchronization on patient status and clinical outcomes. These landmark investigations included the MUSTIC, MIRACLE, MIRACLE ICD, and CONTAK CD trials. These studies consistently demonstrated statistically significant improvements in quality of life, New York Heart Association (NYHA) functional class ranking, exercise tolerance, and left ventricular reverse remodeling. Some studies suggested reductions in morbidity and mortality. This latter observation was confirmed by a recent, large-scale morbidity and mortality trial of cardiac resynchronization therapy in heart failure. Given these findings, cardiac resynchronization therapy should be routinely considered in eligible NYHA Class III and IV heart failure patients with ventricular dyssynchrony.
[Rev Cardiovasc Med. *2003;4(suppl 2):S30–S37*]

Key words: Heart failure • Cardiac resynchronization therapy • Biventricular pacing • MUSTIC trial • MIRACLE trial • CONTAK CD trial

There is now convincing evidence supporting the beneficial effects of cardiac resynchronization therapy for the treatment of heart failure. Numerous observational studies, as well as a series of randomized, controlled trials, have been recently completed, demonstrating the safety, efficacy, and long-term beneficial effects of cardiac resynchronization therapy for patients with chronic

Table 1
Landmark Randomized Controlled Trials of Cardiac Resynchronization Therapy in Heart Failure

Study (No. Randomized)	NYHA Class	QRS	Sinus	ICD?	Status
MIRACLE[17,18,28] (524)*	III, IV	≥130	Normal	No	Published
MUSTIC SR[16,30] (58)	III	>150	Normal	No	Published
MUSTIC AF[21] (43)	III	>200†	AF	No	Published
PATH CHF[12–14] (42)	III, IV	≥120	Normal	No	Published
CONTAK CD[19] (581)‡	III, IV	≥120	Normal	Yes	In press
MIRACLE ICD[27] (362)§	III, IV	≥130	Normal	Yes	In press
PATH CHF II[15] (89)	III, IV	≥120	Normal	No	Presented
COMPANION[23,26] (1520)	III, IV	≥120	Normal	No	Presented
PACMAN[29] (328)	III	≥150	Normal	Both	Enrolled
MIRACLE ICD II (186)	II	≥130	Normal	Yes	Completed
VecToR[29] (420)	II–IV	≥140	Normal	No	Enrolling
CARE HF[24] (800)	III, IV	≥120‖	Normal	No	Enrolled

LVEF ≤ 35% for all trials.
*Includes 71 patients enrolled in 3-month pilot study.
†Right ventricular paced QRS.
‡Includes 248 patients enrolled in 3-month cross-over phase.
§Excludes Class II patients.
‖Echo-based criteria for QRS < 150 msec.

systolic heart failure and ventricular dyssynchrony. Early observational studies supported the concept of resynchronization therapy by demonstrating acute and chronic improvements in hemodynamics, echocardiographic measures of cardiac performance, and functional status.[1–11] Since the completion of these initial studies, nearly 5000 patients have been evaluated in randomized single- or double-blinded controlled trials of cardiac resynchronization (Table 1). These studies consistently demonstrated statistically significant improvements in quality of life, New York Heart Association (NYHA) functional class ranking (Figure 1), exercise tolerance (Figure 2), and left ventricular reverse remodeling.[28,30] A comprehensive meta-analysis showed reductions in the risks of mortality and hospitalization from worsening heart failure.[25] The preliminary results from a recently completed, large-scale morbidity and mortality trial support the survival benefit of cardiac resynchronization therapy in heart failure (Table 2).[23,26] Among these landmark trials are the Pacing Therapies in Congestive Heart Failure (PATH CHF) trial,[12–14] PATH CHF II,[15] the Multisite Stimulation in Cardiomyopathy (MUSTIC) studies,[16,21,22] the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial,[17,18] MIRACLE ICD,[20] the VENTAK CHF/CONTAK CD trials,[19] the Cardiac Resynchronization in Heart Failure (CARE-HF) trial,[24] and the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial.[23,26] Selected trials are reviewed in detail below.

There is now convincing evidence supporting the beneficial effects of cardiac resynchronization therapy for the treatment of heart failure.

InSync Trial

The InSync trial[11] was a prospective, nonrandomized trial of cardiac resynchronization therapy for moderate to severe heart failure. Between August 1997 and November 1998, 103 NYHA Class III (68%) and IV (32%) heart failure patients were enrolled at 16 centers throughout Europe and Canada. Inclusion criteria mandated a left ventricular ejection fraction (LVEF) ≤ 35% and a QRS duration ≥ 150 ms, among other requirements. At baseline, the average LVEF was 22 ± 6% and the mean LV end diastolic dimension was 72 ± 10 mm. Patients were evaluated at baseline and at 1, 3, 6, and 12 months after the initiation of resynchronization therapy.

The primary objective of the InSync Trial was to evaluate the safety and effectiveness of cardiac resynchronization in these patients. Major end points included changes in quality-of-life score using the Minnesota Living with Heart Failure questionnaire, NYHA class ranking, and exercise capacity determined by 6-minute hall-walk distance. Each of these end points was significantly improved at 1 month, and the effects were sustained at 3, 6, and 12 months. For example, the NYHA class was improved by one full class ranking, on average, throughout the 12-month study period. The magnitude of benefit for this and other end points matched or exceeded

Table 2
Effect of CRT on Mortality and Morbidity

Study, No. randomized	Follow-Up, mo.	Treatment	Risk Reduction With CRT Versus Control, %				
			Mortality + Hospitalization	Mortality + HF Hospitalization	Mortality	HF Mortality	HF Hospitalization
COMPANION[26] (N = 1520)	12	CRT + ICD	19.3*	39.5*	43.4*	—	—
		CRT	18.6*	35.8*	23.9		
MIRACLE[2] (N = 453)	6	CRT		39.0*	27.0	—	50*
Meta-analysis[25] (N = 1634)†	3–6	CRT	—		23	51*	29*

*$P < .05$
†Includes MIRACLE.
CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; HF, heart failure.

that seen with drug therapies for heart failure, thus encouraging further randomized, controlled trials of cardiac resynchronization therapy as a treatment of chronic heart failure.

MUSTIC

The MUSTIC trial,[16,21,22] which began in March 1998, was designed to evaluate the safety and clinical efficacy of cardiac resynchronization therapy in patients with moderate heart failure associated with a dilated ischemic or non-ischemic cardiomyopathy and ventricular dyssynchrony. MUSTIC was distinctive at the time for being the first randomized, controlled trial of cardiac resynchronization employing the transvenous approach to left ventricular lead placement. MUSTIC included a group of heart failure patients in normal sinus rhythm (NSR) to test the efficacy of atrial-synchronized biventricular pacing or cardiac resynchronization therapy and a cohort of subjects in chronic atrial fibrillation to evaluate the effects of biventricular pacing alone. The results have been reported as two separate studies.[16,21]

The first study randomized 58 patients with NYHA class III heart failure, NSR, and a QRS duration ≥ 150 ms. All patients were implanted with a device, and after a run-in period, patients were randomized in a single-blind fashion to either active pacing or no pacing. After 12 weeks, patients were crossed over and remained in the alternate study assignment for 12 weeks. After completing this second 12-week period, the device was programmed to the patient's preferred mode of therapy.

The second MUSTIC study involved few patients with atrial fibrillation and a slow ventricular rate (either spontaneously or from radio frequency ablation) with a paced QRS duration ≥ 200 ms. A VVIR biventricular pacemaker and leads for each ventricle were implanted, and the same randomization procedure described above was applied; however, biventricular VVIR pacing versus single-site right ventricular VVIR pacing were compared in the atrial fibrillation group.

The primary end points for MUSTIC were exercise tolerance (assessed by measurement of peak VO_2 or the 6-minute hall-walk test) and quality of life (assessed using the Minnesota Living with Heart Failure questionnaire). Secondary end points included rehospitalizations and/or drug therapy modifications for worsening heart failure. During the active pacing phase in the NSR arm of MUSTIC, the mean distance walked in 6 minutes was 23% greater than during the inactive pacing phase (Figure 3). Significant improvement was also seen in quality of life and NYHA class. There were fewer hospitalizations during active resynchronization therapy. Similar results have been reported for the atrial fibrillation group, although the magnitude of benefit appeared to be somewhat smaller, and the statistical significance was somewhat less.

In the InSync trial, the NYHA class was improved by one full class ranking, on average, throughout the 12-month study period.

MIRACLE

MIRACLE[17,18] was the first prospective, randomized, double-blind, parallel-controlled clinical trial designed to validate the results of previous cardiac resynchronization studies and to further evaluate the therapeutic effi-

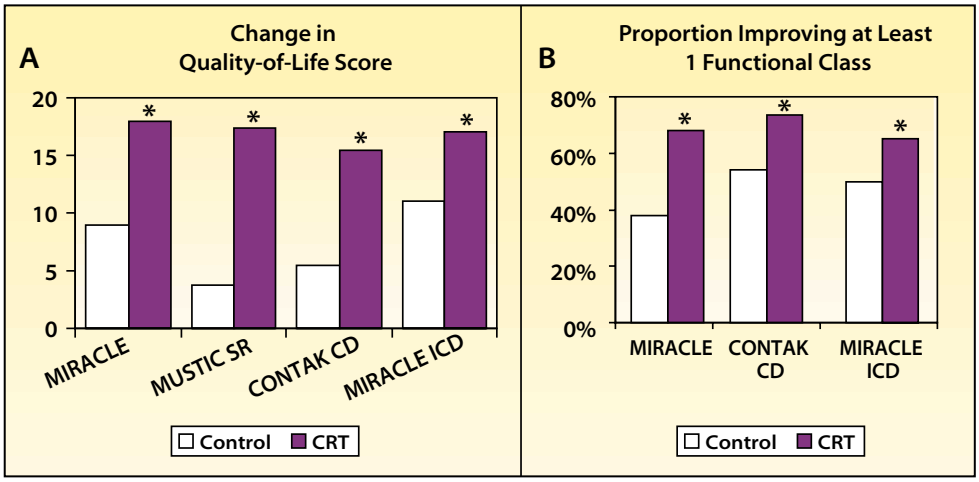


Figure 1. (A) *Effect of cardiac resynchronization therapy (CRT) on quality of life as measured by the Minnesota Living with Heart Failure questionnaire. *P < .05. All comparisons are between CRT and control during the randomization period of the trials. (6 months for MIRACLE, MIRACLE ICD, CONTAK CD; 3 months for MUSTIC SR).* **(B)** *Effect of cardiac resynchronization on New York Heart Association (NYHA) functional class during 6-month randomization period of trials shown. * P < .05.*

cacy and mechanisms of potential benefit of cardiac resynchronization therapy. Primary end points were changes in NYHA class, quality-of-life score using the Minnesota Living with Heart Failure questionnaire, and 6-minute corridor-walk distance. Secondary end points included assessments of a composite clinical heart failure response, metabolic exercise testing, neurohormone and cytokine levels, QRS duration, cardiac structure and function, a variety of measures of worsening heart failure, and combined measures of heart failure morbidity and all-cause mortality. The MIRACLE study was neither designed nor adequately powered to evaluate the effect of cardiac resynchronization on all-cause or cause-specific mortality alone; hence, mortality was collected primarily as a safety end point.

The MIRACLE trial began in October 1998 and was completed late in 2000. A total of 453 patients with moderate to severe symptoms of heart failure associated with LVEF ≤ 35% and a QRS duration ≥ 130 ms were randomized (double-blind) to cardiac resynchronization (n = 228) or to a control group (n = 225) for 6 months while conventional therapy for heart failure was maintained. At the end of 6 months, control patients were given the opportunity to cross over to active pacing, and all patients were followed at 3- to 6-month intervals until the InSync device was approved by the U.S. Food and Drug Administration (FDA) in August 2001.

Compared with the control group, patients randomized to cardiac resynchronization demonstrated a significant improvement in quality-of-life score (−18.0 vs −9.0 points; $P = .001$), 6-minute walk distance (+39 vs +10 m; $P = .005$), NYHA functional class ranking (–1 vs 0 class; $P < .001$), treadmill exercise time (+81 vs +19 seconds; $P = .001$), peak VO_2 (+1.1 vs +0.2 mL/kg/min; $P < .01$), and LVEF (+4.6% vs –0.2%; $P < .001$). Patients randomized to

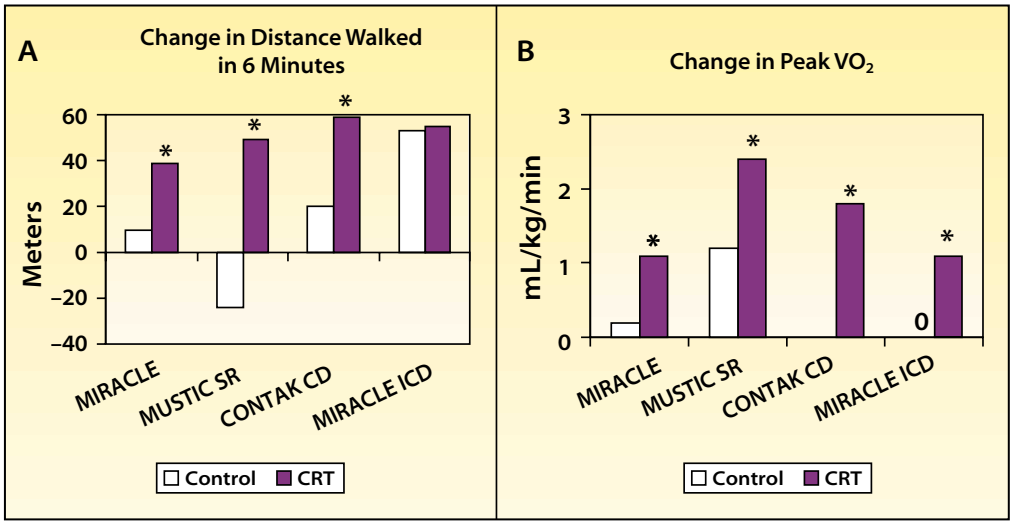


Figure 2. (A) *Effect of cardiac resynchronization therapy (CRT) on the distance walked in 6 minutes. All comparisons are between CRT and control groups during the randomization period. *P < .05.* **(B)** *Effect of cardiac resynchronization therapy on peak VO_2 during the randomization period. *P < .05.*

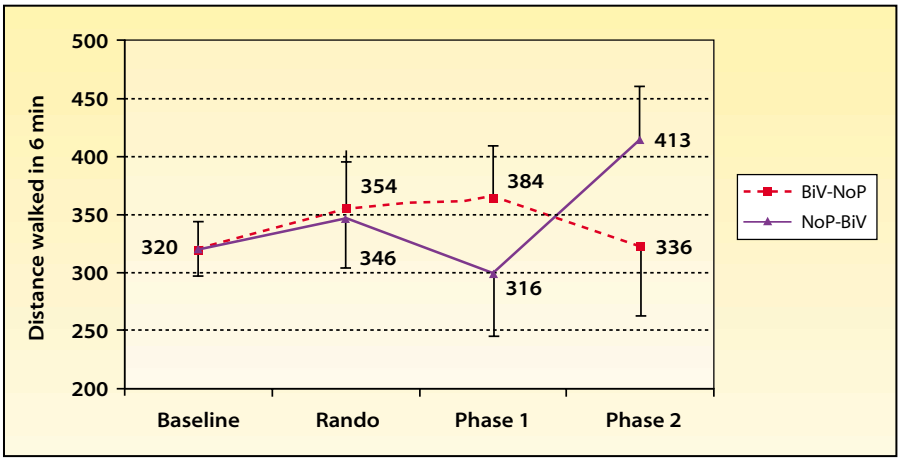


Figure 3. *Effect of cardiac resynchronization therapy on exercise capacity in the Multisite Stimulation in Cardiomyopathy (MUSTIC) trial. During periods of active pacing, there was a significant improvement in the distance walked in 6 minutes (a standard measure of exercise tolerance in heart failure patients). Taken together, the data demonstrate a 23% improvement in walk distance (P < .01). NoP, no pacing; BiV, biventricular pacing; Rando randomization. Reproduced with permission from Cazeau et al.*[16]

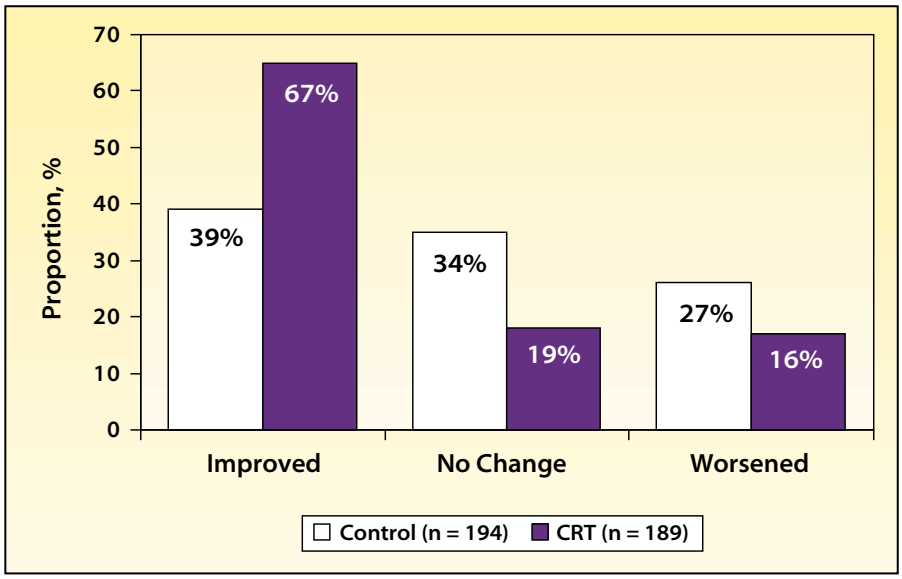
cardiac resynchronization therapy demonstrated a highly significant improvement in a composite clinical heart failure response end point compared with control subjects, suggesting an overall improvement in heart failure clinical status. Specifically, patients randomized to active therapy were much more likely to be improved and much less likely to have worsened or to have remained unchanged, according to the definitions set forth by the composite response instrument (Figure 4). In addition, when compared with the control group, fewer patients in the cardiac resynchronization group required hospitalization (8% vs 15%) or intravenous medications (7% vs 15%) for the treatment of worsening heart failure (both $P < .05$). In the cardiac resynchronization group, the 50% reduction in hospitalization was accompanied by a significant reduction in length of stay, resulting in a 77% decrease in total days hospitalized over 6 months compared with the control group. Implantation of the device was unsuccessful in 8% of patients.

Finally, 12-month data from the MIRACLE trial demonstrated persistence of these benefits in patients initially randomized to active therapy, as well as the expected beneficial treatment effect in those patients crossed over from no pacing to cardiac resynchronization therapy (unpublished observations). For example, in patients randomized to active therapy, the NYHA class remained improved by one full class at 12 months. In patients randomized to inactive therapy (initially demonstrating no improvement in NYHA class), the NYHA class was similarly improved after 6 months of active resynchronization therapy. Sustained improvement was also seen in quality-of-life score and 6-minute hall-walk distance.

MIRACLE ICD

The MIRACLE ICD trial[20] was designed to be similar to the MIRACLE study, with the notable additional prerequisite that eligible patients require an implantable cardioverter-defibrillator (ICD). MIRACLE ICD was a prospective, multicenter, randomized, double-blind, parallel-controlled clinical trial intended to assess the safety and clinical efficacy of a com-

Figure 4. *Effect of cardiac resynchronization therapy (CRT) on a composite clinical heart failure response end point in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial. Worsened: Patient dies; or is hospitalized due to or associated with worsening heart failure; or demonstrates worsening in New York Heart Association (NYHA) class at last observation carried forward (LOCF) or moderate–marked worsening of patient global assessment score at LOCF. Improved: Patient has not worsened (as defined above), and demonstrates improvement in NYHA class at LOCF and/or moderate–marked improvement in patient global assessment score at LOCF. Unchanged: Patient is neither improved nor worsened. P < .001 for × 2 analysis.*



bined ICD and cardiac resynchronization system in patients with chronic systolic heart failure (LVEF ≤ 35%), NYHA class III or IV heart failure (a cohort of class II patients was also enrolled but will be reported separately), QRS duration ≥ 130 ms, and an indication for an ICD. Primary and secondary efficacy measures were identical to those evaluated in the MIRACLE trial, but also included measures of ICD function, including the efficacy of antitachycardia therapy with biventricular pacing.

This study started in September 1999 and was completed in the summer of 2002. Of 369 patients receiving devices and randomized, 182 were controls (ICD activated, cardiac resynchronization OFF) and 187 were in the active resynchronization group (ICD activated, cardiac resynchronization ON). At 6 months, patients assigned to active resynchronization had a greater improvement in quality-of-life score (–18 vs –11 points; $P = .02$) and NYHA functional class (–1 vs 0 class; $P = 0.007$) than controls. Peak oxygen consumption increased by 1.1 mL/kg/min in the active resynchronization group versus 0.1 mL/kg/min in control subjects ($P = .04$), and treadmill exercise duration increased by 56 seconds in the active resynchronization group and decreased by 11 seconds in controls ($P = .0006$). No significant differences were observed in changes in left ventricular size or function, overall heart failure status, survival, and rates of hospitalization, although there were strong trends favoring active therapy for most of these end points. No pro-arrhythmia was observed, and arrhythmia termination capabilities were not impaired. In MIRACLE ICD, the magnitude of improvement in heart failure end points was comparable to that seen in the MIRACLE trial, suggesting that heart failure patients with an ICD indication benefit as much from cardiac resynchronization therapy as those patients without an indication for an ICD. Based on these data, the FDA approved the InSync ICD device in June 2002.

In MIRACLE ICD, the magnitude of improvement in heart failure end points was comparable to that seen in the MIRACLE trial, suggesting that heart failure patients with an indication for an implantable cardioverter defibrillator (ICD) benefit as much from cardiac resynchronization therapy as those patients without an indication for an ICD.

CONTAK CD

The CONTAK CD study[19] was also a randomized, controlled, double-blind trial comparing active cardiac resynchronization therapy with no pacing in heart failure patients requiring an ICD. The initial design was that of a 3-month crossover trial; however, this was later changed to a 6-month parallel control study design. Patients enrolled had NYHA functional class II–IV heart failure, LVEF ≤ 35%, QRS duration ≥ 120 ms, and an accepted indication for an ICD. The primary end point was a composite of mortality, hospitalizations for heart failure, and episodes of ventricular tachycardia or ventricular fibrillation.

A total of 581 patients were randomized in the CONTAK CD trial: 248 into the 3-month crossover study and 333 into the 6-month parallel controlled trial. For the primary composite end point, the study demonstrated an insignificant trend favoring the resynchronization group. However, peak VO_2, 6-minute hall-walk distance, quality of life, and NYHA class were significantly improved in the active pacing group compared with inactive control subjects, particularly in the NYHA Class III and IV subgroup of patients. The improvement seen in peak VO_2 was comparable to that observed in the MIRACLE trial. There was also a reduction in LV end-systolic and end-diastolic dimensions in patients randomized to active resynchronization therapy. As a result of this study, as well as confirmatory data evaluating the effect of the CONTAK CD device, the FDA approved this device in May 2002.

COMPANION and CARE-HF

Initiated in early 2000, COMPANION[23] was a multicenter, prospective, randomized, controlled clinical trial designed to compare drug therapy alone with drug therapy in combination with cardiac resynchronization with or without an ICD in patients with dilated cardiomyopathy, an intraventricular conduction delay, NYHA Class III or IV heart failure, and no indication for a device. The trial design called for randomization of 2200 patients into one of three treatment groups: group 1 (n = 440) received optimal medical care only, group II (n = 880) received optimal medical care and the CONTAK TR (biventricular pacing alone), and group III (n = 880) received optimal medical care and the CONTAK CD (combined heart failure/bradycardia/ tachycardia ICD device). The primary end point was the combination of all-cause mortality and all-cause hospitalization. Secondary end points included a variety of measures of cardiovascular morbidity.

The COMPANION trial was terminated prematurely in November

2002 at the recommendation of an independent data and safety monitoring board, following randomization of approximately 1500 patients. Preliminary reports suggest a significant reduction of nearly 20% in the primary end point in the combined cardiac resynchronization groups compared with patients randomized to medical therapy alone (Table 2).

Another randomized, controlled morbidity and mortality trial is CARE-HF.[24] This study is comparing optimal medical therapy alone with optimal medical therapy plus cardiac resynchronization (without an ICD) in 800 patients with NYHA Class III or IV systolic heart failure and ventricular dyssynchrony determined by either electrocardiographic (QRS duration > 150 ms) or echocardiographic (QRS duration 120–150 ms plus echocardiographic evidence of dyssynchrony) criteria. As of January 2003, more than 700 patients had been randomized in CARE-HF.

Cardiac resynchronization therapy offers a new approach for treating patients with ventricular dyssynchrony and moderate to severe heart failure.

Candidates for Cardiac Resynchronization Therapy

The criteria for selecting patients for cardiac resynchronization therapy is primarily determined by FDA labeling and the inclusion/exclusion criteria of the MIRACLE, MIRACLE ICD, and CONTAK CD trials. Patients with chronic, moderate to severe heart failure (NYHA Class III or IV) despite optimal standard medical therapy, LVEF < 35%, LV end-diastolic diameter > 55 mm, QRS duration > 120 ms, and with or without an indication for an ICD are considered appropriate candidates for cardiac resynchronization therapy. With the favorable conclusions of morbidity and mortality trials, the use of resynchronization therapy in these patients is mandated.

Summary

Cardiac resynchronization therapy offers a new approach for treating patients with ventricular dyssynchrony and moderate to severe heart failure. Clinical trials demonstrate that it is safe and effective and significantly improves both clinical symptoms as well as multiple measures of functional status and exercise capacity. Moreover, cardiac resynchronization therapy has reduced measures of morbidity and mortality in multiple studies and, thus, should be routinely offered to eligible heart failure patients. ■

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Main Points

- Early observational studies (eg, the InSync trial) supported the concept of cardiac resynchronization therapy (CRT) for the treatment of heart failure by demonstrating acute and chronic improvements in hemodynamics, echocardiographic measures of cardiac performance, and functional status.
- The MUSTIC trial evaluated the safety and clinical efficacy of CRT in patients with moderate heart failure associated with a dilated ischemic or non-ischemic cardiomyopathy and ventricular dyssynchrony. During the active pacing phase in the normal sinus rhythm arm of MUSTIC, the mean distance walked in 6 minutes was 23% greater than during the inactive pacing phase.
- In the MIRACLE trial, patients randomized to CRT demonstrated a significant improvement in quality-of-life score, 6-minute walk distance, NYHA functional class ranking, treadmill exercise time, peak VO_2, and left ventricular ejection fraction (LVEF), compared with the control group.
- In MIRACLE ICD, the magnitude of improvement in heart failure end points was comparable to that seen in the MIRACLE trial, suggesting that heart failure patients with an indication for an implantable cardioverter defibrillator (ICD) benefit as much from cardiac resynchronization therapy as those patients without an indication for an ICD.
- The CONTAK CD study compared active CRT with no pacing in heart failure patients requiring an ICD. Peak VO_2, 6-minute hall-walk distance, quality of life, and NYHA class were significantly improved in the active pacing group compared with inactive control subjects, particularly in the NYHA Class III and IV subgroup of patients.
- Patients with chronic, moderate to severe heart failure (NYHA Class III or IV) despite optimal standard medical therapy, LVEF < 35%, LV end-diastolic diameter > 55 mm, QRS duration > 120 ms, and with or without an indication for an ICD are considered appropriate candidates for CRT.

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