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CARDIAC RESYNCHRONIZATION IN CHRONIC HEART FAILURE

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ABSTRACT

Background Previous studies have suggested that cardiac resynchronization achieved through atrial-synchronized biventricular pacing produces clinical benefits in patients with heart failure who have an intraventricular conduction delay. We conducted a double-blind trial to evaluate this therapeutic approach.

Methods Four hundred fifty-three patients with moderate-to-severe symptoms of heart failure associated with an ejection fraction of 35 percent or less and a QRS interval of 130 msec or more were randomly assigned to a cardiac-resynchronization group (228 patients) or to a control group (225 patients) for six months, while conventional therapy for heart failure was maintained. The primary end points were the New York Heart Association functional class, quality of life, and the distance walked in six minutes.

Results As compared with the control group, patients assigned to cardiac resynchronization experienced an improvement in the distance walked in six minutes (+39 vs. +10 m, $P=0.005$), functional class ($P<0.001$), quality of life (-18.0 vs. -9.0 points, $P=0.001$), time on the treadmill during exercise testing (+81 vs. +19 sec, $P=0.001$), and ejection fraction (+4.6 percent vs. -0.2 percent, $P<0.001$). In addition, fewer patients in the group assigned to cardiac resynchronization than control patients required hospitalization (8 percent vs. 15 percent) or intravenous medications (7 percent vs. 15 percent) for the treatment of heart failure ($P<0.05$ for both comparisons). Implantation of the device was unsuccessful in 8 percent of patients and was complicated by refractory hypotension, bradycardia, or asystole in four patients (two of whom died) and by perforation of the coronary sinus requiring pericardiocentesis in two others.

Conclusions Cardiac resynchronization results in significant clinical improvement in patients who have moderate-to-severe heart failure and an intraventricular conduction delay. (N Engl J Med 2002;346:1845-53.)

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IN approximately 30 percent of patients with chronic heart failure, the disease process not only depresses cardiac contractility but also affects the conduction pathways by causing a delay in the onset of right or left ventricular systole.^{1,2} Such dyssynchrony is apparent on the electrocardiogram as a QRS interval lasting more than 120 msec. Some have proposed that this intraventricular conduction delay may further impair the ability of the failing heart to eject blood and may thus enhance the severity of regurgitant flow through the mitral valve.³⁻⁶ The finding of an intraventricular conduction delay has been associated with clinical instability and an increased risk of death in patients with heart failure.⁷⁻¹⁰

Devices that make use of atrial-synchronized biventricular pacing to coordinate right and left ventricular contraction have been developed, and early studies have suggested that short- and long-term cardiac resynchronization can improve cardiac function and enhance functional capacity and the quality of life.¹¹⁻¹⁹ However, previous studies evaluated only small numbers of patients and either were uncontrolled or were not carried out in a double-blind manner.

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We report the results of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE), a double-blind study of cardiac resynchronization in patients with moderate-to-severe heart failure and a prolonged QRS interval.

METHODS

Patients

Patients were eligible for the study if they had moderate or severe (New York Heart Association functional class III or IV) chronic heart failure due to either ischemic or nonischemic cardiomyopathy. All patients had a left ventricular ejection fraction of 35 percent or less, a left ventricular end-diastolic dimension of 55 mm or more, a QRS interval of 130 msec or more, and a six-minute walking distance of 450 m or less. Patients received all appropriate treatments for heart failure, which included a diuretic, an angiotensin-converting-enzyme inhibitor or an angiotensin-receptor blocker, and (usually) digitalis and a beta-blocker. The doses of these background medications were stable for at least one month, except for doses of the beta-blocker (which were stable for three months).

Patients were excluded if they had a pacemaker or cardioverter-defibrillator or had an indication for or a contraindication to cardiac pacing, if they had had a cardiac or cerebral ischemic event within the previous three months, or if they had had an atrial arrhythmia within the previous month. In addition, patients were not allowed to participate if they had a systolic blood pressure of more than 170 or less than 80 mm Hg, a heart rate of more than 140 beats per minute, a serum creatinine level of more than 3.0 mg per deciliter (265 μ mol per liter), or serum aminotransferase levels more than three times the upper limit of normal. Other reasons for exclusion have been described previously.²⁰ The institutional review board of each center approved the study protocol, and all patients gave written informed consent.

Study Design

Patients meeting the criteria for entry underwent the following evaluations at base line: New York Heart Association class,²¹ six-minute walking test,²² maximal treadmill exercise test (with the use of the modified Naughton protocol²³), quality-of-life evaluation (with the use of the Minnesota Living with Heart Failure Questionnaire²⁴), two-dimensional Doppler-flow echocardiography (to assess the left ventricular ejection fraction, the internal diastolic dimensions, and the degree of mitral regurgitation), and QRS interval (from a 12-lead electrocardiogram).

After this initial evaluation, patients underwent implantation of a cardiac-resynchronization device (InSync model 8040, Medtronic) along with three pacing leads: a standard right atrial lead, a standard right ventricular lead, and a specialized left ventricular lead,²⁵ which was placed into a distal cardiac vein by way of the coronary sinus through a guiding catheter. Patients who had undergone successful implantation were randomly assigned to atrial-synchronized biventricular pacing (the resynchronization group) or to a control group (no pacing) for six months, during which time medications for heart failure were to be kept constant. Randomization occurred in permuted blocks to ensure a balance between groups within centers. Base-line variables were reevaluated one, three, and six months after randomization. Crossover from the control mode to the cardiac-resynchronization mode before the six-month assessment was prohibited, except for patients in whom a bradyarrhythmia that required cardiac pacing developed. Neither the patients nor the physicians treating them for heart failure and performing the study evaluations were aware of the treatment assignment. At each site, an electrophysiologist, who was otherwise uninvolved with clinical care, opened a sealed envelope at the time of randomization, programmed the device, and performed all tests that could reveal the identity of the assigned pacing mode.

Statistical Analysis

The study had three primary end points (the New York Heart Association class, the quality-of-life score, and the distance walked in six minutes) and several secondary end points (peak oxygen consumption, time on a treadmill, left ventricular ejection fraction and end-diastolic dimension, severity of mitral regurgitation, duration of QRS interval, and a clinical composite response, which assigns patients to one of three response groups — improved, worsened, or unchanged — as previously defined^{20,26}) as the major efficacy variables for the study. In addition, the protocol specified an analysis of death or worsening heart failure (as safety variables), as well as the number of days spent in the hospital (as part of the assessment of utilization of health care resources).

All end points were analyzed according to the intention-to-treat principle; patients who crossed over were analyzed according to their original treatment assignment. For continuous variables, comparisons of changes from base line to the six-month visit between the control group and the resynchronization group were evaluated for significance with the use of the Wilcoxon rank-sum test. For categorical end points, differences in the distribution of responses to treatment at six months in the two groups were compared with the use of a chi-square test. Only patients for whom data were available at base line and at six months were included in these analyses, but the results were similar if patients with incomplete data were also included and had their last available double-blind value carried forward. Cumulative survival curves for the risk of a major clinical event were constructed according to the Kaplan-Meier method,²⁷ and differences between the curves were tested for significance by the log-rank statistic.²⁸ Cox proportional-hazards regression models²⁹ were used to estimate hazard ratios.

For the primary efficacy variables, the study would achieve its prespecified objective if the difference between the groups in all three end points had a P value less than or equal to 0.05, if two had a P value less than or equal to 0.025, or if one had a P value less than or equal to 0.0167. The sample size (224 patients per treatment group) was estimated on the basis of the assumption that the study would have 80 percent power (two-sided alpha, 0.0167) to detect a difference in New York Heart Association class of 0.75, quality of life of 13 points, or distance walked in six minutes of 50 m. For secondary end points, a P value of less than 0.05 was used to assess statistical significance.

Investigators had full access to all data and performed analyses without restrictions or limitations from the sponsor. Data are presented as median changes from base line to six months (with 95 percent confidence intervals). All P values are two-sided.

RESULTS

Between November 1998 and December 2000, 571 patients at 45 centers agreed to participate in the study. Of these, 47 patients were not enrolled because the device was not successfully implanted (43 patients), the patient required cardiac pacing (2 patients), or the patient's condition became clinically unstable (2 patients). Seventy-one patients underwent randomization but agreed to be enrolled in an initial pilot phase of the study, which followed patients for only three months. The remaining 453 patients (who made up the patients described in this report) were enrolled in the main six-month study; 225 patients were randomly assigned to the control group, and 228 patients were randomly assigned to the cardiac-resynchronization group. The two groups were similar with respect to all base-line characteristics (Table 1).

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.*

CHARACTERISTIC	CONTROL GROUP (N=225)	CARDIAC- RESYNCHRONIZATION GROUP (N=228)
Age (yr)	64.7±11.2	63.9±10.7
Male sex (%)	68	68
White race (%)	91	90
Ischemia (%)	58	50
New York Heart Association functional class III (%)	91	90
Duration of the QRS interval (msec)	165±20	167±21
Left ventricular ejection fraction (%)	21.6±6.2	21.8±6.3
Left ventricular end-diastolic dimension (mm)	69±10	70±10
Area of the mitral regurgitant jet (cm ²)	7.2±4.9	7.6±6.4
Distance walked in six minutes (m)	291±101	305±85
Score on the Minnesota Living with Heart Failure Questionnaire†	59±21	59±20
Total exercise time (sec)	462±217	484±209
Peak oxygen consumption (ml/kg of body weight/min)	13.7±3.8	14.0±3.5
Systolic blood pressure (mm Hg)	115±18	114±18
Diastolic blood pressure (mm Hg)	68±10	69±10
Heart rate (beats/min)	75±13	73±13
Receiving digitalis (%)	79	78
Receiving diuretic agents (%)	93	94
Receiving angiotensin-converting–enzyme inhibitors or angiotensin-receptor antagonists (%)	90	93
Receiving beta-blockers (%)	55	62

*Plus–minus values are means ±SD. Percentages are based on the number of patients who underwent randomization.

† Scores range from 0 to 105, with higher scores indicating more severe impairment.

Follow-up and Disposition of Patients

Of the 225 patients assigned to the control group, 24 did not complete six months of follow-up — 16 died, 2 received a heart transplant, 1 had complications related to the device, and 5 missed the six-month visit. Of the 228 patients assigned to cardiac resynchronization, 13 did not complete six months of follow-up — 12 died and 1 had complications related to the device. No patient was lost to follow-up for the analysis of death or worsening heart failure.

All patients continued to receive the assigned treatment for the intended duration of the study, except for 10 patients in the control group who had their device reprogrammed to the cardiac-resynchronization mode, 7 because of worsening heart failure and 3 because of bradycardia.

Effect on Primary End Points

As compared with the control group, patients assigned to cardiac resynchronization had improvements in the distance walked in six minutes, the quality-of-life score, and the New York Heart Association functional class ($P=0.005$, $P=0.001$, and $P<0.001$, respectively) (Table 2). Differences in favor of cardiac

resynchronization were apparent as early as after one month of treatment, and the magnitude of improvement was maintained without attenuation for the entire study period (Fig. 1). The magnitude of the effect on the three primary end points was not influenced by the use of a beta-blocker, the cause of heart failure (ischemic or nonischemic), the configuration of the QRS complex (left or right bundle-branch block), or the base-line duration of the QRS interval (analyzed as a continuous variable, $P>0.10$ for all interactions).

Effect on Secondary End Points

As compared with the control group, patients in the resynchronization group had an improvement in the two measures of maximal exercise performance: peak oxygen consumption ($P=0.009$) and total exercise time ($P=0.001$) (Table 2). Furthermore, the left ventricular ejection fraction increased and the end-diastolic dimension, the area of the mitral regurgitant jet, and the duration of the QRS interval all decreased in the resynchronization group (all $P<0.001$ for the comparison with the control group) (Table 2). Finally, cardiac resynchronization had a

TABLE 2. EFFECT OF CARDIAC RESYNCHRONIZATION ON EFFICACY END POINTS.

END POINT*	CONTROL GROUP	CARDIAC-RESYNCHRONIZATION GROUP	P VALUE
Change in the distance walked in six minutes — m			
Median	+10	+39	0.005
95 percent confidence interval	0 to +25	+26 to +54	
No. of patients	198	214	
Change in the Minnesota Living with Heart Failure score			
Median	-9	-18	0.001
95 percent confidence interval	-12 to -5	-22 to -12	
No. of patients	193	213	
Change in the New York Heart Association functional class — no. (%)			<0.001
Improved by two or more classes	12 (6)	34 (16)	
Improved by one class	62 (32)	109 (52)	
No change	115 (59)	64 (30)	
Worsened	7 (4)	4 (2)	
Change in peak oxygen consumption — ml/kg/min			
Median	+0.2	+1.1	0.009
95 percent confidence interval	-0.2 to +0.8	+0.6 to +1.7	
No. of patients	145	158	
Change in total exercise time — sec			
Median	+19	+81	0.001
95 percent confidence interval	-1 to +47	+62 to +119	
No. of patients	146	159	
Change in patient's view of progress — no. (%)			<0.001
Markedly improved	24 (12)	80 (38)	
Moderately improved	42 (22)	46 (22)	
Slightly improved	44 (23)	40 (19)	
No change	51 (26)	26 (12)	
Slightly worse	20 (10)	11 (5)	
Moderately worse	10 (5)	5 (2)	
Markedly worse	4 (2)	3 (1)	
Absolute change in left ventricular ejection fraction — %			
Median	-0.2	+4.6	<0.001
95 percent confidence interval	-1.0 to +1.5	+3.2 to +6.4	
No. of patients	146	155	
Change in left ventricular end-diastolic dimension — mm			
Median	0.0	-3.5	<0.001
95 percent confidence interval	-1 to +2	-6 to -1	
No. of patients	98	90	
Change in area of the mitral regurgitant jet — cm ²			
Median	-0.5	-2.7	<0.001
95 percent confidence interval	-1.1 to 0.0	-4.0 to -2.1	
No. of patients	118	116	
Change in QRS duration — msec			
Median	0	-20	<0.001
95 percent confidence interval	-10 to 0	-20 to -12	
No. of patients	192	206	

*The numbers of patients with data available for each variable are listed.

highly favorable effect on the clinical composite heart-failure score. At the end of six months, the condition of more patients in the group assigned to cardiac resynchronization was considered to have improved (67 percent, vs. 39 percent in the control group) and that of fewer was considered to have worsened (16 percent vs. 27 percent) ($P < 0.001$).

Effect on Death and on Worsening Heart Failure

In the intention-to-treat analysis, there were 16 deaths in the control group and 12 deaths in the resynchronization group. During the six-month follow-up period, there were 50 hospitalizations for heart failure in 34 control patients, for a total of 363 hospital days for heart failure, but there were only 25

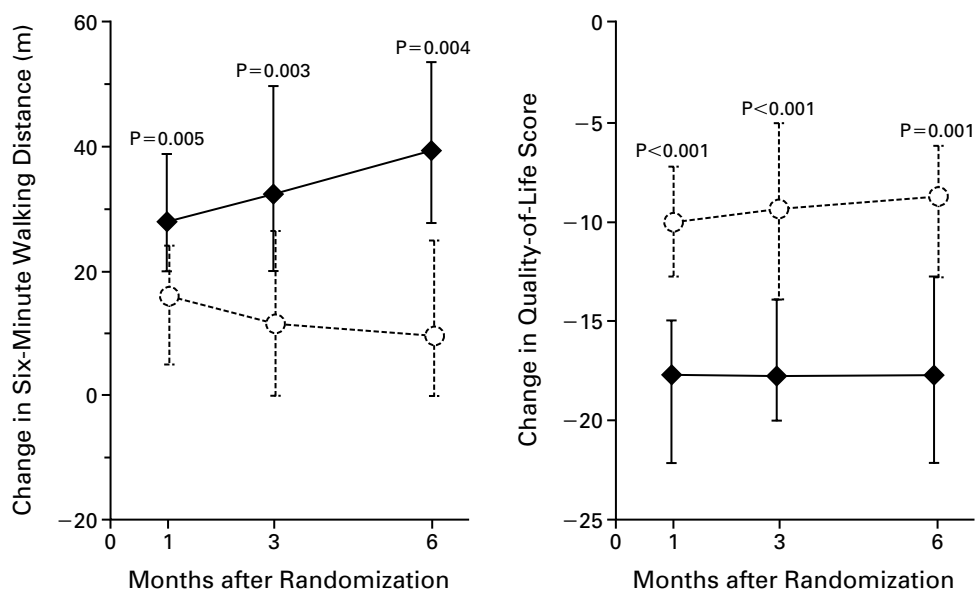


Figure 1. Change in the Distance Walked in Six Minutes and the Quality-of-Life Score.

Shown are median changes (with 95 percent confidence intervals) one, three, and six months after randomization in the control group (circles) and the cardiac-resynchronization group (diamonds). P values are for the comparison between groups. For each variable, data are shown for patients who had values at all three time points (for the six-minute walk, 196 patients in the control group and 212 patients in the resynchronization group; for the quality-of-life score, 192 patients and 211 patients, respectively).

hospitalizations for heart failure in 18 patients in the resynchronization group, for a total of 83 hospital days for heart failure. Differences between the groups in the frequency of hospitalization or the use of an intravenous medication for worsening heart failure were significant ($P=0.02$ and $P=0.004$, respectively) (Table 3).

In an analysis of time to a first event, 44 patients (20 percent) in the control group but only 28 patients (12 percent) in the resynchronization group died or were hospitalized for worsening heart failure (Fig. 2). The risk of a major clinical event was 40 percent lower in the resynchronization group (95 percent confidence interval, 4 to 63 percent; $P=0.03$). Favorable effects of cardiac resynchronization were also seen when episodes of worsening heart failure requiring the use of intravenous drugs were included in the analysis ($P=0.02$) (Table 3).

As compared with the control group, patients in the resynchronization group were more likely to be hospitalized for repositioning or replacement of the left ventricular lead (11 and 3 patients in the resynchronization and control groups, respectively). However, the two treatment groups were similar with respect to hospitalizations not related to heart failure or to the function of the left ventricular lead (37 and

33 hospitalizations in the resynchronization and control groups, respectively).

Adverse Events

Of the 571 participating patients, 4 did not undergo randomization because of adverse clinical events during the implantation procedure. Complete heart block that required permanent cardiac pacing developed in two patients; progressive hypotension developed in one patient, who died later the same day; and one patient had asystole and required cardiopulmonary resuscitation, did not recover neurologically, and died one month later. In addition, during the procedure, 23 patients (4 percent) had a coronary-sinus dissection, and 12 patients (2 percent) had a cardiac-vein or coronary-sinus perforation. Of these, three required intravenous catecholamines, pericardiocentesis, or both for a presumed or confirmed diagnosis of hemopericardium but recovered without sequelae and continued in the study.

Of the 528 patients who underwent successful implantation, the median duration of the procedure was 2.7 hours (range, 0.9 to 7.3). After implantation, 20 patients required repositioning of the left ventricular lead and 10 required its replacement; 7 patients reported a pacemaker-related infection that required

TABLE 3. CLINICAL EVENTS DURING THE DOUBLE-BLIND TREATMENT PERIOD.*

EVENT	CONTROL GROUP (N=225)	CARDIAC-RESYNCHRONIZATION GROUP (N=228)	HAZARD RATIO (95% CI)	P VALUE
	no. of patients			
Death from any cause	16	12	0.73 (0.34–1.54)	0.40
Death or worsening heart failure requiring hospitalization	44	28	0.60 (0.37–0.96)	0.03
Death or worsening heart failure requiring hospitalization or intravenous treatment	55	36	0.61 (0.40–0.93)	0.02
Hospitalization for worsening heart failure	34	18	0.50 (0.28–0.88)	0.02
Worsening heart failure leading to the use of intravenous diuretic agents	24	13	0.51 (0.26–1.00)	0.05
Worsening heart failure leading to the use of intravenous vasodilators or positive inotropic agents	14	6	0.41 (0.16–1.08)	0.06
Worsening heart failure leading to the use of intravenous medication for heart failure	35	16	0.43 (0.24–0.77)	0.004

*Events are not mutually exclusive. Hazard ratios are based on Cox proportional-hazards regression models applied to an analysis of the time to the first event. CI denotes confidence interval.

explantation, 4 of whom had the device reimplemented uneventfully. The rate of device-related events was substantially lower than the rates described in the prespecified criteria established in the original study protocol.²⁰ The frequency of adverse events unrelated to the device or to heart failure did not differ significantly between the two treatment groups.

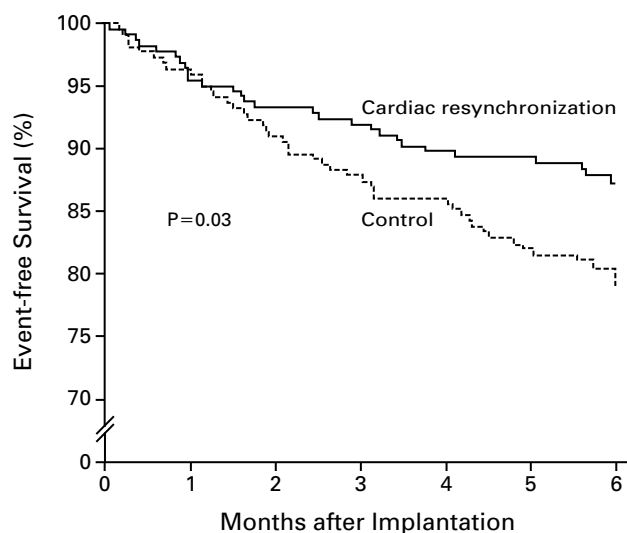
DISCUSSION

The results of the present study indicate that cardiac resynchronization improves a broad range of measures of cardiac function and clinical status in patients with moderate-to-severe heart failure and a prolonged QRS interval. Cardiac resynchronization reduced the degree of ventricular dyssynchrony (as evidenced by a shortened duration of the QRS interval), and this effect was accompanied by both an increase in the left ventricular ejection fraction and a decrease in the left ventricular end-diastolic dimension and in the magnitude of mitral regurgitation. As a result, as compared with the control group, patients in the cardiac-resynchronization group had significant improvements in functional capacity, clinical status, and quality of life. Resynchronization also enhanced both maximal and submaximal exercise capacity (assessed by a treadmill test and the distance walked in six minutes, respectively). The magnitude of these hemodynamic and clinical benefits was similar to (if not greater than) that reported with effec-

tive pharmacologic interventions for heart failure,³⁰⁻³³ and yet they were seen in patients already receiving these drugs.

Cardiac resynchronization not only increased the likelihood of clinical improvement, but also reduced the risk of clinical deterioration during the course of follow-up. Patients in the resynchronization group were less likely than those in the control group to require treatment with an intravenous medication for worsening heart failure. Furthermore, cardiac resynchronization was associated with fewer admissions to the hospital and with fewer days in the hospital for the treatment of heart failure. The combined risk of a major clinical event (death or hospitalization for heart failure) was 40 percent lower in the resynchronization group than in the control group (Fig. 2). Yet, even though background therapy was intensified more frequently in the control group, these patients had fewer hemodynamic and clinical benefits at the end of double-blind treatment than those in the resynchronization group.

Implantation and maintenance of a resynchronization device were associated with risks that were greater than those of a conventional pacing device. During implantation, a resynchronization device — unlike conventional pacemakers — requires the insertion of an additional pacing lead into the coronary sinus, which is advanced into a cardiac vein to allow pacing of the left ventricle.²⁵ In some patients, efforts to im-



No. AT RISK	0	1	2	3	4	5	6
Control	225	214	204	197	191	179	70
Cardiac resynchronization	228	218	213	209	204	201	99

Figure 2. Kaplan–Meier Estimates of the Time to Death or Hospitalization for Worsening Heart Failure in the Control and Resynchronization Groups. The risk of an event was 40 percent lower in the resynchronization group (95 percent confidence interval, 4 to 63 percent; $P=0.03$).

plant the lead were unsuccessful (about 8 percent) or were accompanied by dissection or perforation of the coronary sinus or cardiac vein (about 6 percent). Although these events are generally asymptomatic, attempts to implant the lead or the device may have serious complications, including complete heart block, hemopericardium, and cardiac arrest (which together occurred in about 1.2 percent of patients). The left ventricular lead may also become dislodged during long-term pacing (which occurred in about 6 percent) and may require repositioning or replacement,³⁴ but this did not result in the discontinuation of treatment in any patient. When all possible reasons for technical failure were considered, about 8 percent of the 571 participating patients were unable to receive and be maintained on resynchronization therapy for the planned duration of treatment.

Our findings are consistent with the results of earlier studies that reported both hemodynamic and symptomatic improvement after cardiac resynchronization.¹¹⁻¹⁹ These reports were difficult to interpret, however, because the studies evaluated only small numbers of patients, had a high proportion of patients who did not complete the study, and failed to ensure that patients or investigators were unaware of

the identity of the treatment assignment. Our study did not suffer from these limitations. However, we evaluated the effects of cardiac resynchronization in a double-blind manner for only six months. Although the duration was longer than that of earlier controlled studies of resynchronization and similar to that of many trials of pharmacologic treatments, the outcomes, both beneficial and adverse, reported in a study of 500 patients evaluated for six months may not reflect the effects seen in thousands of patients treated for years.³⁵⁻³⁸ Nevertheless, the effects of resynchronization on the combined risk of death and worsening heart failure seen in this study are encouraging. Large-scale, controlled trials to evaluate the effects of cardiac resynchronization on the natural history of heart failure are now in progress.^{39,40}

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APPENDIX

The following investigators and study centers participated in MIRACLE: **Clinical Events Review Committee:** W. Abraham (chair), A. Curtis, D. Hayes, E. Loh, J. Sackner-Bernstein, A. Tang; **Safety Monitoring Board:** G. Francis (chair), G. Crossley, S. Norsted, J. Young; **Operations Team (Medtronic):** V. Manda, S. Petersen-Stejskal, J. Johnson, L. Ford, K.

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