A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure

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Background Cardiac contractility modulation (CCM) delivers nonexcitatory electrical signals to the heart during the absolute refractory period intended to improve contraction.

Methods We tested CCM in 428 New York Heart Association class III or IV, narrow QRS heart failure patients with ejection fraction (EF) ≤35% randomized to optimal medical therapy (OMT) plus CCM (n = 215) versus OMT alone (n = 213). Efficacy was assessed by ventilatory anaerobic threshold (VAT), primary end point, peak VO_2 (pVO_2), and Minnesota Living with Heart Failure Questionnaire (MLWFQ) at 6 months. The primary safety end point was a test of noninferiority between groups at 12 months for the composite of all-cause mortality and hospitalizations (12.5% allowable delta).

Results The groups were comparable for age (58 ± 13 vs 59 ± 12 years), EF (26% ± 7% vs 26% ± 7%), pVO_2 (14.7 ± 2.9 vs 14.8 ± 3.2 mL kg^{-1} min^{-1}), and other characteristics. While VAT did not improve at 6 months, CCM significantly improved pVO_2 and MLWHFQ (by 0.65 mL kg^{-1} min^{-1} [*P* = .024] and –9.7 points [*P* < .0001], respectively) over OMT. Forty-eight percent of OMT and 52% of CCM patients experienced a safety end point, which satisfied the noniferiority criterion (*P* = .03). Post hoc, hypothesis-generating analysis identified a subgroup (characterized by baseline EF ≥25% and New York Heart Association class III symptoms) in which all parameters were improved by CCM.

Conclusions In the overall target population, CCM did not improve VAT (the primary end point) but did improve pVO_2 and MLWHFQ. Cardiac contractility modulation did not have an adverse affect on hospitalizations or mortality within the prespecified boundaries. Further study is required to clarify the role of CCM as a treatment for medically refractory heart failure. (Am Heart J 2011;161:329-337.e2.)

Cardiac resynchronization therapy (CRT) enhances pump function, improves quality of life, improves exercise tolerance, and reduces hospitalizations and mortality in the population of chronic heart failure (CHF) patients with ejection fraction (EF) ≤35% and New York Heart Association (NYHA) class III or IV symptoms with QRS duration >120 to 130 milliseconds.[1-3] Nevertheless, <50% of CHF patients with decreased EF meet QRS duration criteria for CRT and approximately 30% of patients receiving CRT are considered nonresponders because their symptoms do not improve.[1] Thus, there is a large unmet need for new therapies that can improve CHF symptoms, especially for medically refractory patients with normal QRS duration.

Cardiac contractility modulation (CCM) is an electrical device–based approach developed for the treatment of CHF.[4,5] Cardiac contractility modulation signals are nonexcitatory electrical signals applied during the cardiac

absolute ventricular refractory period that enhance the strength of cardiac muscular contraction.[6] Cardiac contractility modulation signal application is associated with normalization of phosphorylation of key proteins and expression of genes coding for proteins involved in regulation of calcium cycling and contraction.[4,7,8]

The results of prior clinical studies of CCM (delivered by the OPTIMIZER, Impulse Dynamics, Orangeburg, NY) have supported its safety and efficacy[5] including a recent double-blind, double crossover study in 164 subjects.[9] This latter study showed that 3 months of CCM treatment improved quality of life and exercise tolerance as judged by peak VO_2 in patients with NYHA class II and III symptoms. The purpose of the present study was to test the longer-term safety and efficacy of CCM treatment.

Methods

The FIX-HF-5 study was a prospective, randomized, parallel-group, controlled trial of optimal medical therapy (OMT group) versus OMT plus CCM (CCM group) conducted at 50 centers in the United States. The details of the protocol, device implantation procedure, primary and secondary end points, and statistical analysis plan have been provided previously.[10] In brief, the study included subjects ≥18 years old with EF ≤35%, with NYHA class III or IV symptoms despite medical treatment with angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker and β-blockers for at least 3 months with a baseline peak VO_2 on cardiopulmonary stress testing (CPX) ≥9 mL O_2 kg^{-1} min^{-1} who were in normal sinus rhythm and not indicated for a CRT device (ie, QRS duration <130 milliseconds). Unless there were extenuating circumstances, subjects were required to have an implantable cardioverter defibrillator (ICD). Subjects were excluded if they were hospitalized within 30 days of enrollment, were inotrope dependent, had >8,900 premature ventricular contractions per 24 hours on a baseline Holter monitor, had permanent atrial fibrillation, had a myocardial infarction within 90 days, had percutaneous coronary intervention within 30 days, or had coronary artery bypass surgery within 90 days of enrollment.

After informed consent, all subjects underwent baseline evaluation that included CPX, Minnesota Living with Heart Failure Questionnaire (MLWHFQ), 6-minute hall walk test, NYHA class determination by a clinician blinded to therapy assessment, an echocardiogram, and a 24-hour Holter monitor. After meeting inclusion criteria, a device implant date was scheduled. This scheduled implant date served as the study start date (SSD) for all subjects. Subjects were then randomized (1:1) to either the OMT group or to the CCM group. Subjects randomized to the CCM group underwent OPTIMIZER device implantation on the SSD. The implant procedure and electrical characteristics of CCM signals have been detailed previously.[10] Major follow-up visits were at 3 and 6 months.

Statistical considerations and analysis plan

The primary effectiveness end point, as required by the US Food and Drug Administration (FDA), was the change from baseline in the ventilatory anaerobic threshold (VAT) measured on CPX. The primary analysis is based on a comparison of "responder" rates between the CCM and OMT groups at the 24-week follow-up visit. An individual subject is considered a responder if VAT increases by ≥20% at 24 weeks compared to their respective baseline value. Comparison of responder rates between groups was by a 1-sided Fisher exact test with an α of .025. The primary analysis was based on the intent to treat population; imputation was used to account for missing data as detailed previously.[10] Ten different imputations were performed and the data combined to arrive at an overall test of significance according to the methods of Rubin.[11] Secondary efficacy end points were peak VO_2 and quality of life assessed by MLWHFQ. Each of these parameters was also assessed by a responder analysis with a 20% increase in peak VO_2 and a 10-point reduction in MLWHFQ used to define responders. The type I error rate was maintained across multiple tests of efficacy by using a closed-form hierarchical testing procedure. Additional end points included changes in NYHA functional class (with a one-class change considered a response) and 6-minute walk (6MW) test (with a 40-m increase considered a response). In addition to the responders analyses, treatment effects were also assessed by applying traditional methods using comparison of mean changes from baseline in each parameter. These comparisons were made using 1-sided Student t tests (with equal or unequal variances as appropriate). Baseline characteristics were compared with 2-sided Wilcoxon rank sum test, Fisher exact test, Pearson χ^2 test and 2-sample t tests as appropriate and as specified in the text. P values ≤.025 for 1-sided tests and ≤.05 for 2-sided tests were considered to be statistically significant. All statistical tests were performed using SAS Version 9.13 (SAS Institute, Cary, NC).

The primary safety end point was the composite event rate of all-cause mortality and all-cause hospitalization through 50 weeks. The primary safety analysis was a test of the noninferiority of CCM therapy compared to OMT with respect to the proportion of subjects experiencing death or hospitalization within 50 weeks using the Blackwelder non-inferiority test[12] with a prespecified noninferiority margin of 0.125. The noninferiority margin was selected to be 12.5% and α was set at .05, which resulted in a sample size of 198 subjects per group. A percentage of subjects (∼7%) were expected to be lost to follow-up, so that a total sample size of 428 subjects (214 per group) was selected. While the basis for sample size was the safety end point, power was computed for the expected difference between the control and test populations. It was anticipated that the control success rate in the responder analysis would be about 20% and that the rate in the test group would be >40%. Thus, the power of this difference is in excess of 95% with a sample size of >198 in each group.

Core laboratories and oversight committees

Because of the upfront known difficulties in assessing VAT, significant measures were taken to optimize CPX quality.[10] All CPX tests were sent to a single core laboratory where a detailed procedure was followed for objective determination of VAT (using the V-slope method[13]) by 2 independent readers blinded to treatment group. Ventilatory anaerobic threshold could not be assigned in tests without clear changes in slopes; these were classified as indeterminate. When discrepancies (amounting to >10% differences) arose between the 2 readers, a third reader was used and the final VAT was determined by the 2 closest values. When concordance could not be achieved,

Table I. Baseline characteristics

Variable	OMT group (n = 213) Mean (SD) or n (%)	CCM group (n = 215) Mean (SD) or n (%)	P
Age (y)	58.55 (12.23)	58.09 (12.79)	.5109[*]
Male	151 (70.9%)	158 (73.5%)	.5901[†]
Ethnicity			
White	142 (66.7%)	154 (71.6%)	.5026[‡]
Black	45 (21.1%)	36 (16.7%)	
Other	26 (12.2%)	25 (11.7%)	
Weight (kg)	93.30 (22.16)	91.17 (23.27)	.1632[*]
BMI (kg/m^2)	30.95 (6.53)	30.44 (7.04)	.2179[*]
Resting HR (beat/min)	73.74 (12.19)	73.98 (13.13)	.9681[*]
SBP (mm Hg)	115.61 (17.61)	116.65 (19.48)	.8695[*]
CHF etiology			
Ischemic	142 (66.7%)	139 (64.7%)	.6465[‡]
Idiopathic	48 (22.5%)	58 (27.0%)	
Other	23 (10.8%)	18 (8.3%)	
NYHA			
Class I	0 (0%)	0 (0%)	.1720[‡]
Class II	1 (0.47%)	0 (0%)	
Class III	183 (85.92%)	196 (91.16%)	
Class IV	29 (13.62%)	19 (8.84%)	
Prior MI	126 (59.15%)	125 (58.14%)	.8449[†]
Prior CABG	86 (40.38%)	82 (38.14%)	.6923[†]
Prior PCI	83 (38.97%)	86 (40%)	.8437[†]
Diabetes	102 (47.89%)	91 (42.33%)	.2853[†]
QRS duration (ms)	101.51 (12.81)	101.63 (15.30)	.5968[§]
PVCs/24 h (Holter)	1365 (2001) 457 (1499)[‖]	1323 (1931) 339 (2136)[‖]	.5113[*]
LVEF (%)	26.09 (6.54)	25.74 (6.60)	.5641[*]
LVEDD (mm)	63.01 (8.56)	62.41 (9.22)	.7715[*]
MLWHFQ	57.38 (22.62)	60.49 (23.00)	.1109[*]
6MW (m)	323.99 (92.44)	326.38 (82.10)	.5971[*]
CPX (core laboratory)			
Duration (min)	11.50 (3.46)	11.34 (3.20)	.4814[*]
Peak SBP (mm Hg)	138.8 (24.6)	139.7 (27.1)	.9714[*]
Peak HR (beat/min)	121.2 (20.5)	122.1 (20.2)	.5223[*]
Peak RER	1.13 (0.09)	1.14 (0.10)	.5189[*]
Peak VO$_2$ (mL kg^{-1} min^{-1})	14.71 (2.92)	14.74 (3.06)	.8575[*]
VAT (mL kg^{-1} min^{-1})	10.97 (2.18)	10.95 (2.24)	.9719[§]

HR, Heart rate; RER, respiratory exchange ratio; OMT, optimal medical therapy; CCM, cardiac contractility modulation; BMI, body mass index; SBP, systolic blood pressure; CHF, chronic heart failure; NYHA, New York Heart Association symptom class; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; PVC, premature ventricular contractions; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic dimension; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; 6MW, 6-minute walk test; CPX, cardiopulmonary stress testing; VAT, ventilatory anaerobic threshold.

[*] Two-sided Wilcoxon rank sum test.
[†] Two-sided Fisher exact test.
[‡] Two-sided Pearson χ^2 test.
[§] Two-sided unequal variance 2-sample t test.
[‖] PVCs/24 h is nonnormally distributed; values provided are both mean (SD) and median (interquartile range).

tests were also classified as indeterminate. The core laboratory procedures have been detailed previously.[10] Despite these efforts, it was anticipated that some tests would be classified as indeterminate because of poor test quality, inability of subjects to reach VAT, or because of subject noncompliance with scheduled follow-up visits.

In an exploratory analysis, the impact of specific baseline characteristics (heart failure etiology, NYHA, and EF) on treatment effectiveness was evaluated using regression analysis. Prespecified cut points for the subgroup analysis included NYHA class III vs IV symptoms and LVEF dichotomized at 25%, which was the median value for the overall population. After an exploratory analysis revealed that CCM tended to be more effective in patients with less severe heart failure, a post hoc analysis was performed on patients with LVEF >25% and NYHA class III heart failure.

To ensure accuracy of the primary safety end point, an independent Events Adjudication Committee evaluated original records of every hospitalization and death. Protocol-specified hospitalizations included any admission that results in a calendar date change or was related to an adverse event that caused a prolongation of the index hospitalization for device implantation. An independent Data and Safety Monitoring Board was established to review aggregate safety data and monitor for the emergence of any significant safety concerns.

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Figure 1
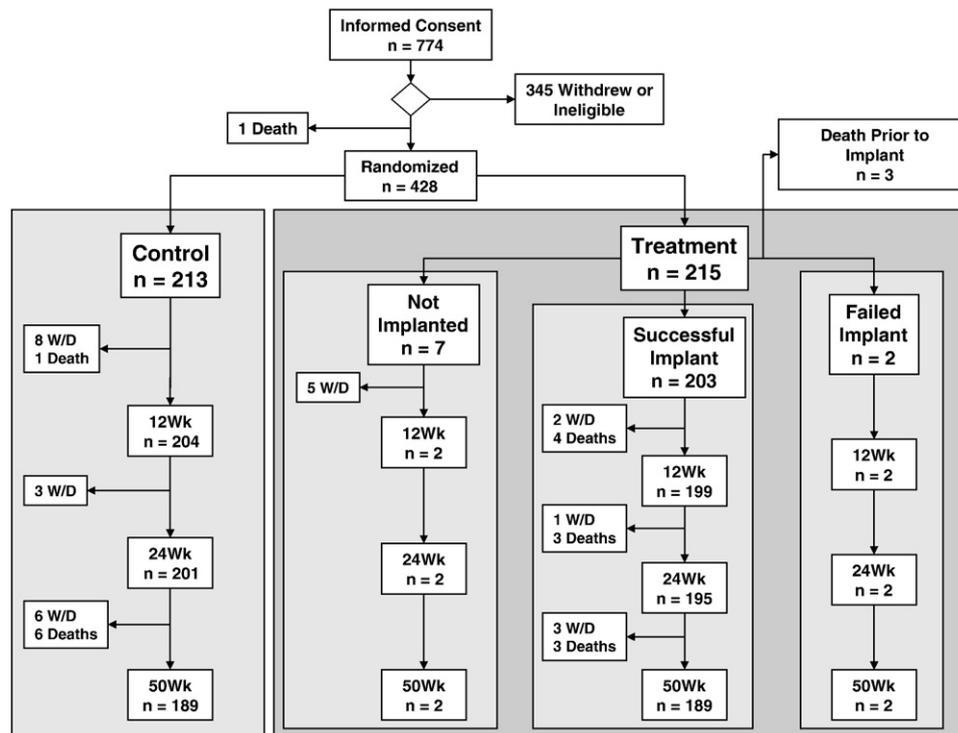
Flow of patients through the study. *W/D*, Withdrawn.

all study analyses, the drafting and editing of the paper and its final contents.

Results
Baseline characteristics of enrolled study subjects

Between March 2005 and June 2007, 773 potential study subjects provided informed consent to participate in this study. From among these subjects, 428 subjects passed baseline screening and were randomized to either the OMT group (n = 213) or the CCM group (n = 215). The baseline characteristics of these subjects are summarized in Table I. These characteristics are similar between groups and are consistent with the study inclusion and exclusion criteria. Eighty-two percent of subjects had an ICD before entry into the study. Another 11% had an ICD placed at the start of the study. Another 2% of patients had devices implanted during the follow-up period so that overall, 95% of study subjects had an ICD. Implantable cardioverter defibrillator use was balanced between groups (202/213, 95% of the OMT group; 207/215, 96% of the CCM group). The reason why some patients did not have an ICD was because of patient refusal for a device. Patients in both groups were well medicated with angiotensin-converting enzyme inhibi-

tors or angiotensin receptor blockers (91%) and β-blockers (93%) as detailed previously.[10]

Screening and randomization

The flow of subjects through the course of the study is summarized in Figure 1. Of 774 subjects who signed informed consent, 429 subjects passed initial baseline testing and agreed to participate. One subject died before randomization. Four hundred twenty-eight subjects were randomized, 213 to the OMT group and 215 to the CCM group. As detailed in the figure, 17 subjects withdrew and 7 subjects died in the OMT group, so that a total of 189 (88.7%) subjects completed the 50-week follow-up period. In the CCM group, 3 subjects died before the implant and 7 subjects elected not to undergo device implantation. In 2 subjects, the implant was aborted; one because of right ventricular perforation that led to cardiac tamponade and one because of a substantially prolonged PR interval (~300 milliseconds) that precluded CCM signal delivery for technical reasons. (After this experience, subjects with PR interval >275 milliseconds were excluded). Of the 203 subjects with a successful implant, 5 withdrew and 10 died so that 188 (92.6%) completed the 50 follow-up period.

The implant procedure took 180 ± 91 minutes (median 165 minutes) and involved 2.4 ± 2.2 (median 1.5,

Table II. Serious adverse events

	Randomization to SSD		SSD to 1 y	
AE category	OMT (n = 213)	CCM (n = 215)	OMT (n = 212)	CCM (n = 210)
General cardiopulmonary event	2 (2)	2 (2)	58 (46)	60 (42)
Arrhythmias	2 (2)	5 (4)	30 (25)	40 (29)
Worsening heart failure	3 (3)	5 (5)	85 (50)	72 (50)
ICD/pacemaker system related	0	1	7 (6)	13 (11)
Bleeding	0	1	8 (8)	8 (6)
Localized infection	0	2 (2)	36 (29)	33 (27)
Sepsis	0	1	2 (2)	11 (10)
Neurologic dysfunction	0	0	14 (12)	3 (3)
Thromboembolism (nonneurologic)	0	0	5 (5)	3 (3)
General medical	2 (2)	5 (5)	81 (54)	98 (63)
Total	9 (8)	22 (13)	326 (115)	341 (129)

interquartile range 2.0) different electrode positions to reach an 8.1% ± 3.7% (median 7%) increase in dP/dt_{max} in response to acute CCM application.

Safety end points and adverse events

For the composite safety end point of all-cause hospitalizations and all-cause mortality, 4 subjects in the CCM group and 14 subjects in the OMT group were withdrawn from the study before experiencing a safety end point and therefore lost to follow-up. Based on best efforts to confirm vital status (including a search of the death registries), none of these subjects died within the 50-week follow-up period. For the intent-to-treat population (assuming subjects lost to follow-up did not have any events), there were 103 events in the 213 subjects randomized to the OMT group (48.4%) and 112 events in the 215 subjects randomized to the CCM group (52.1%). Based on the Blackwelder test, the difference of 3.7% had an upper 1-sided 95% confidence limit of 11.7%, which was below the prespecified allowable 12.5% (P = .035). Thus, the primary safety end point of the study was met.

As noted above, 7 (3.3%) of the 213 OMT subjects and 10 (4.9%) of the 203 subjects who received and OPTIMIZER system died during the 50-week follow-up period (P = .47, Fisher exact test). With an intent-to-treat analysis, 13 (6.0%) of the 215 subjects randomized to the CCM group died during the 50-week follow-up period (P = .25 vs OMT by Fisher exact test).

A summary of serious adverse events (defined as any event that was considered life-threatening, required a hospitalization, or required invasive treatment) is provided in Table II. Several events were reported between the time of randomization and the SSD, slightly more in the CCM group (22 events in 13 patients) than in the OMT group (9 events in 8 patients, P = .027, Fisher exact test). Overall, serious adverse events were balanced between the groups, with 326 events reported

Table III. Device-related serious adverse events

OPTIMIZER system related	30 (27)
OPTIMIZER lead fracture	3 (3)
OPTIMIZER RV lead dislodgement	6 (6)
IPG problem/change	2 (1)
OPTIMIZER RA lead dislodgement	6 (5)
OPTIMIZER pocket dehiscence/erosion	3 (3)
OPTIMIZER pocket infection	2 (2)
OPTIMIZER pocket stimulation	2 (2)
Lead perforation	2 (2)
OPTIMIZER pocket bleeding	1
Sensation due to CCM	2 (2)
Extracardiac stimulation	1

Number of events (number of patients).
RV, Right ventricular; RA, right atrium; IPG, implanted pulse generator.

in 115 OMT patients versus 341 events in 129 CCM subjects (P = .66).

Device-related serious adverse events are summarized in Table III. The most common adverse events were lead fracture or displacement. The total incidence of lead complications was 14 (7%).

Efficacy end points

Results of primary and secondary efficacy variables and analyses are summarized in Figure 2. For each variable, the figure indicates the number of completed cases for each group, the mean changes from baseline, and the difference (and P value) between the changes. Results of the responders analysis are summarized in Table IV. Ventilatory anaerobic threshold (the primary efficacy parameter) decreased by 0.14 mL kg^{-1} min^{-1} in both groups at 24 weeks. For 17.6% of subjects in the CCM group and 11.7% of subjects in the OMT group, VAT increased by $\geq$20%; the difference in responder rates at 24 weeks (5.9%) was not statistically significant (P = .093). Data were missing for VAT from 59 subjects (27.7%) in the

Figure 2
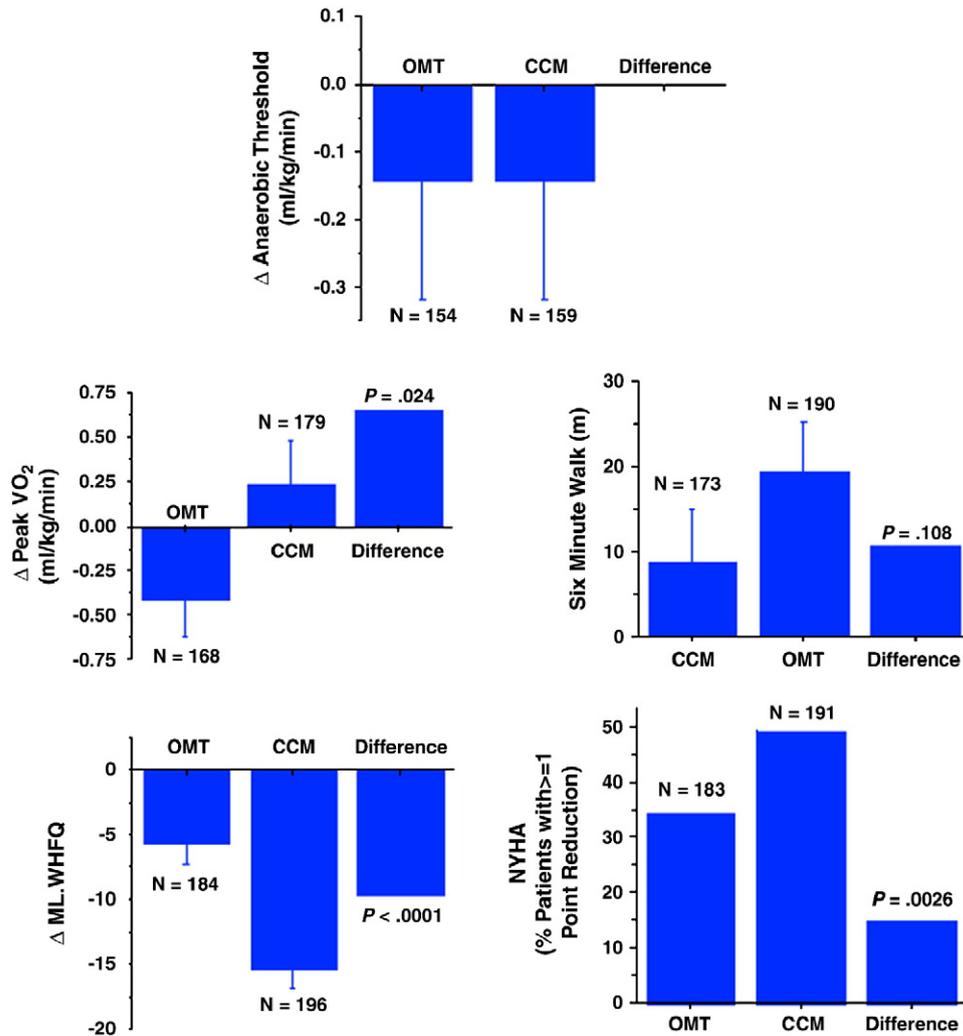
Efficacy results in the completed cases population. *OMT*, Optimal medical therapy; *CCM*, group receiving CCM signals.

OMT group and 56 subjects (26.0%) in the CCM group. For the responders analysis of the intent-to-treat population (which was the primary efficacy end point), an overall *P* value was obtained by combining information from 10 separate imputations[11] with a final *P* value of .31. At 50 weeks, 14.4% of patients in the OMT group versus 23.7% of patients in the CCM group were responders, a difference of 9.3% (*P* = .027, completers analysis).

Peak Vo_2 increased in the CCM group and decreased in the OMT group; the difference (0.65 mL kg^{-1} min^{-1}) was statistically significant (*P* = .024). The responders analysis, however, did not show a difference in the percent of patients in which peak Vo_2 improved by ≥20%.

The MLWHFQ and NYHA improved significantly more in the CCM group when analyzed either as differences in changes of mean values from baseline or with a responders analysis. There were also nonsignificant (~10 m) increases in 6MW distances. There was no significant difference between groups in ejection fraction or left ventricular end-diastolic dimensions.

Subgroup analyses

The etiology of heart failure (ischemic versus non-ischemic) was not associated with improvement. A multivariate model of the continuous variables done with Proc Mixed detected a statistically significant interaction between the treatment and composite variable of ejection fraction and NYHA class with a *P* value of .0219. Patients with an EF ≥25% in the CCM group had a 12.2% greater responder rate than those in the OMT group. Patients with NYHA class III in the CCM

Table IV. Results of responders analyses for primary and secondary study end points at 24-week follow-up in the entire study cohort

Parameter	OMT group (n = 213) n/N (%) LCL, UCL	CCM group (n = 215) n/N (%) LCL, UCL	CCM-OMT LCL, UCL (%)	P
VAT (mL kg^{-1} min^{-1})	18/154 (11.7) 7.1, 17.8	28/159 (17.6) 12.0, 24.4	5.9 −2.0, 13.9	.093
VAT (mL kg^{-1} min^{-1}) (ITT*)	28/213 (13.2%) 8.9, 18.4	38/215 (17.7%) 12.8, 23.4	4.5 −2.4, 11.5	.314
Peak VO$_2$ (mL kg^{-1} min^{-1})	23/168 (13.7) 8.9, 19.8	31/179 (17.3) 12.1, 23.7	3.6 −4.1, 11.3	.233
MLWHFQ	77/184 (41.8) 34.6, 49.3	110/196 (56.1) 48.9, 63.1	14.3 4.2, 24.1	.0037
NYHA class	63/183 (34.4) 27.6, 41.8	94/191 (49.2) 41.9, 56.5	14.8 4.8, 24.5	.0026
6MW (m)	51/173 (29.5) 22.8, 36.9	65/190 (34.2) 27.5, 41.4	4.7 −4.9, 14.2	.197

All data are based on completed cases population except for VAT, for which both completed cases and intent-to-treat populations are included. *P* values by 1-sided Fisher exact test.
LCL, Lower confidence limit; *UCL*, upper confidence limit; *ITT*, intention to treat.
*ITT population based on imputation of missing data.

group had a response rate that was 6.9% greater than those in the OMT group. Patients with NYHA class IV who were in the CCM group had a 7.3% lower response rate. Thus, an additional analysis was performed in those patients with LVEF ≥25% and NYHA class III. This subgroup was composed of 97 OMT and 109 CCM subjects, 48% of the overall population. In this subgroup, there were statistically and clinically significantly greater improvements in VAT (0.64 mL kg^{-1} min^{-1}, P = .03 for the completed cases; P = .024 for the intention-to-treat population with imputed missing data), increased peak VO$_2$ (1.31 mL kg^{-1} min^{-1}, P = .001), improved MLWHFQ (10.8 points, P = .003), and improved NYHA (−0.29, P = .001) at 24 weeks. With regard to the primary safety end point, there were 42 events in the 97 OMT subjects (43.3%) compared to 52 events in the 109 CCM subjects (47.7%, Blackwelder test P = .12). From among these subjects, there were 2 deaths in the OMT group (0.9%) and 4 deaths in the CCM group from the SSD to 1 year (2.0%, P = .69, Fisher exact test).

Discussion

Prior studies have provided evidence of safety and efficacy of 3 months CCM treatment in subjects with symptomatic heart failure with EF ≤35% and normal QRS duration.[9] The FIX-HF-4 study[9] enrolled 168 patients in a randomized, double-blind, double crossover study of patients with NYHA II or III symptoms and EF ≤35% showed an average increase of peak VO$_2$ of ~0.6 mL kg^{-1} min^{-1} and a reduction in MLWHFQ of ~3 points with just 3 months of treatment. The present study was designed to test the longer-term effects of CCM treatment. The study demonstrated that CCM was safe within prespecified boundaries but did not meet the primary end point of an improvement in VAT.

The primary safety end point of the study, which was a noninferiority assessment of the composite of all-cause mortality and all-cause hospitalizations, was satisfied. The primary efficacy end point of the study, that is, the proportion of subjects whose VAT increased by >20% at 24 weeks, was not different between groups; nor was there any difference in the mean change of VAT from baseline. However, mean peak VO$_2$ increased more in the CCM than OMT group at 24 weeks. We found that subjects in the CCM group exercised for longer durations, but there was no difference in respiratory exchange ratio at peak exercise between groups, indicating equal degrees of subject effort during exercise. In addition, there was no difference between groups at the earlier 12-week follow-up (data not shown), a time point at which the placebo effect was expected to be greatest. Thus, these supporting data argue against, although do not exclude, a placebo effect on peak VO$_2$ as a cause for the difference between the groups at 24 weeks.

The MLWHFQ improved by an average of 10 points more in the CCM group and 20% more subjects experienced a 10-point or greater reduction in the CCM group. However, this parameter is subject to placebo effect in the context of the present unblinded study. Nevertheless, the magnitude of this point reduction is similar to what has been reported previously for CRT.[1] Similar effects were noted in NYHA, although the magnitudes were slightly less than reported for CRT.[1]

Limitations

The results of the present study need to be interpreted within the context of several important and, in some respects, unique aspects of the study design that were less than ideal. It is important to note that the study design was developed under restrictions imposed by the

FDA and study details were arrived at largely on the need to obtain safety data through 1 year of treatment. Because of difficulties ensuring blinding with a device that has a weekly recharging requirement, prior blinded study designs used in the evaluation of CRT devices were not applicable. It was also felt that implanting a device and leaving it "off" for 12 months was not ethical or practical. Thus, an unblinded design was used. Because most measures of quality of life and exercise tolerance used in heart failure studies are subjective, FDA required that VAT be the primary end point of the study because it is considered to be objective and not subject to placebo effect.[14,15] However, VAT, although appealing from a theoretical perspective, has not been validated as an end point in heart failure trials and, when evaluated in a real-life application, there were extensive missing data due to inability to designate a value even when the test was conducted properly. Another unique aspect of the study is that the primary end point was analyzed through a responders analysis.[16] The goal of using this approach, in contrast to the traditional comparison of mean changes, is to be able to more clearly define the population of subjects who exhibit a clinically meaningful benefit from the therapy. This may have certain advantages from a regulatory perspective. However, such an approach has not been used for primary and secondary end point analyses in prior heart failure studies. A dilemma in interpretation of the results is created by the fact that peak Vo_2 increased by a statistically significant amount (just slightly less than in prior studies of CRT) but failed to show an increase in the rate of "responders" (when defined as a 20% improvement from baseline). These unusual aspects of study design complicate interpretation of the results of the present study.

Other study limitations should be considered. As is the case with most multicenter randomized studies of device therapies, study recruitment practices may differ among centers so that study subjects may not be consecutive that could result in selection bias compared to the overall population of eligible patients. Issues related to the relatively large number of imputations required for primary intent-to-treat efficacy analysis of anaerobic threshold parameter have been discussed.

Although the primary effectiveness end point was not achieved in the overall study population, signs of efficacy were noted in the less severely ill subgroup in subjects with baseline ejection fraction ≥25% and NYHA class III symptoms. The explanation for this finding cannot be determined with certainty. One possible explanation is that the effects of CCM delivered only to the right ventricular septum are not substantial enough to overcome severe contractile dysfunction with severely reduced EF, which also correlates with a more severely enlarged heart. It could be that in such cases, CCM delivered to multiple sites (although less practical to implement) could be more effective. Another possibility

is that the molecular effects of CCM identified in prior studies[8] are not as effective when the degree of dysfunction is too severe. Independent of the underlying reason, because this subgroup was identified based on a post hoc analysis, we consider these findings to be hypothesis generating.

Patients enrolled in the present study were required to have an ICD. There was no increase in reports of ventricular arrhythmias, ICD shocks, or antitachycardia pacing. It is important to note that the risk of potential interference between the ICD and the OPTIMIZER device is eliminated at the time of implantation and by specifically designed testing procedure and recommendations for ICD device programming. There have been no reports of either inappropriate ICD firings or failure to detect an arrhythmia and deliver therapy when this testing and programming are performed.

Cardiac resynchronization therapy is approved by the US FDA for subjects with QRS duration >120 to 130 milliseconds, EF ≤35%, and NYHA class III or IV symptoms despite appropriate medical therapy. However, NYHA functional class does not improve in approximately 30% of subjects receiving a CRT device.[17,18] In addition, CRT has only been shown to be effective in patients with a prolonged QRS duration.[19,20] Cardiac contractility modulation was developed several years ago to treat underserved populations.[4,5] Prior short-term (3-month), double-blind studies showed CCM to be safe and effective.[10] The results of the present study show that over a 1-year follow up period, CCM was safe within the prespecified boundaries. However, based on the prespecified primary end point, CCM efficacy was not demonstrated. Further studies will be required to determine the role of CCM in the treatment of patients with medically refractory heart failure.

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Disclosures

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Appendix A

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Appendix B

Committees

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Events Adjudication Committee: Peter Carson (Chairman), Christopher O'Connor, Inder Anand.

Data Safety and Monitoring Board: Sidney Goldstein (Chairman), Stephen Gottlieb, Andrea Natale, David Naftel, David Callans.

Appendix C

Core Laboratories

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Echocardiography: Marco DiTullio, Columbia University.

NYHA Blinded Core Lab: Steven P. Schulman, The Johns Hopkins University.