

# A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation in patients with systolic heart failure: Rationale, design, and baseline patient characteristics

William T. Abraham, MD,<sup>a</sup> Daniel Burkhoff, MD, PhD,<sup>b,c</sup> Koonlawee Nademane, MD,<sup>d</sup> Peter Carson, MD,<sup>e</sup> Robert Bourge, MD,<sup>f</sup> Kenneth A. Ellenbogen, MD,<sup>g</sup> Michael Parides, PhD,<sup>b</sup> and Alan Kadish, MD<sup>h</sup> On behalf of the FIX-HF-5 Investigators and Coordinators<sup>1</sup> Columbus, OH; New York, and Orangeburg, NY; Inglewood, CA; Washington, DC; Birmingham, AL; Richmond, VA; and Chicago, IL

Cardiac contractility modulation (CCM) signals are nonexcitatory electrical signals delivered during the cardiac absolute refractory period that enhance the strength of cardiac muscular contraction. Prior research in experimental and human heart failure has shown that CCM signals normalize phosphorylation of key proteins and expression of genes coding for proteins involved in regulation of calcium cycling and contraction. The results of prior clinical studies of CCM have supported its safety and efficacy. A large-scale clinical study, the FIX-HF-5 study, is currently underway to test the safety and efficacy of this treatment. In this article, we provide an overview of the system used to deliver CCM signals, the implant procedure, and the details and rationale of the FIX-HF-5 study design. Baseline characteristics for patients randomized in this trial are also presented. (Am Heart J 2008;156:641-648.e1.)

Cardiac resynchronization therapy (CRT) enhances pump function, improves quality of life, improves exercise tolerance, and reduces hospitalizations and mortality in the population of patients with chronic heart failure (CHF) for which it is indicated; namely, patients with ejection fraction (EF) <35%, New York Heart Association (NYHA), class III or IV symptoms with QRS duration >120-130 milliseconds.<sup>1-3</sup> Nevertheless, <50% of patients with CHF meet QRS duration criteria for CRT; approximately 30% of patients receiving CRT are considered nonresponders because their symptoms do not improve<sup>1</sup> and CRT does not improve clinical status in patients with normal QRS duration.<sup>4</sup> Moreover, despite major advances in drug and device therapies, heart failure

remains a cause of substantial disability, hospitalizations, and mortality. Thus, there is a crucial need for additional safe and effective heart failure therapies.

Cardiac contractility modulation (CCM) is a new electrical device-based approach developed for the treatment of CHF.<sup>5,6</sup> Cardiac contractility modulation signals are nonexcitatory electrical signals applied during the cardiac absolute refractory period that enhance the strength of cardiac muscular contraction.<sup>7</sup> Cardiac contractility modulation signals are delivered by a device (the OPTIMIZER, IMPULSE Dynamics, Orangeburg, NY) that looks like an implanted cardioverter-defibrillator (ICD) or pacemaker and attaches to the heart via standard pacing electrodes. Cardiac contractility modulation signal application has been associated with normalization of phosphorylation of key proteins and expression of genes coding for proteins involved in regulation of calcium cycling and contraction.<sup>5,8,9</sup> These findings, in both animals and humans, further suggest that the improvements in contractile strength are not associated with increases in myocardial oxygen consumption.<sup>8,10</sup>

The results of prior clinical studies of CCM have supported its safety and efficacy<sup>6</sup> including a recent double-blind, double crossover study in 164 patients.<sup>11</sup> This latter study showed that 3 months of CCM treatment improved quality of life and exercise tolerance as judged by peak VO<sub>2</sub>. A large-scale clinical study, called the FIX-HF-5 study, is currently underway to further test the safety and efficacy of this form of treatment. The purpose of this

From the <sup>a</sup>The Ohio State University Heart Center, Division of Cardiovascular Medicine, Columbus, OH, <sup>b</sup>Columbia University, New York, NY, <sup>c</sup>IMPULSE Dynamics, Orangeburg, NY, <sup>d</sup>Pacific Rim EP, Inglewood, CA, <sup>e</sup>Washington VA Hospital, Washington, DC, <sup>f</sup>University of Alabama, Birmingham, AL, <sup>g</sup>Virginia Commonwealth University School of Medicine, Richmond, VA, and <sup>h</sup>Northwestern University, Chicago, IL.

<sup>1</sup>FIX-F-investigators and Coordinators listed in Appendix A available online.

Registered randomized clinical trial no. NCT00112125.

The FIX-HF-5 study is supported by IMPULSE Dynamics. D. Burkhoff is an employee and shareholder in IMPULSE Dynamics.

Submitted February 19, 2008; accepted May 9, 2008.

Reprint requests: William T. Abraham, MD, The Ohio State University Heart Center, Division of Cardiovascular Medicine, 473 West 12th Avenue, Room 110P DHLRI, Columbus, Ohio 43210-1252.

E-mail: william.abraham@osumc.edu

0002-8703/\$ - see front matter

© 2008, Mosby, Inc. All rights reserved.

doi:10.1016/j.ahj.2008.05.019

**Figure 1**

The Optimizer III System consists of (A) an IPG with a rechargeable battery that delivers CCM signals and an atrial and 2 ventricular pacing leads ( $A_{\text{lead}}$ ,  $V_{\text{lead},1}$ , and  $V_{\text{lead},2}$ , respectively); (B) an IPG programmer; (C) a hemodynamic monitoring system; and (D) an IPG charger used by patients in their home.

article is to provide an overview of the OPTIMIZER System, the implant procedure, and the details and rationale of the FIX-HF-5 study design. Baseline characteristics for patients randomized in this trial are also presented.

### The OPTIMIZER System and implant procedure

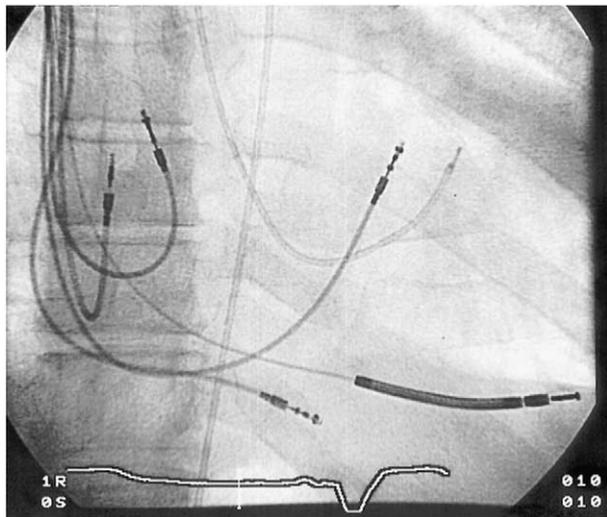
The Optimizer III System (Figure 1) consists of an implantable pulse generator (IPG) with a rechargeable battery that delivers CCM signals (described below), an atrial and 2 ventricular pacing leads, an IPG programmer (similar to a standard pacemaker/ICD programmer), a hemodynamic monitoring system that calculates the maximal rate of left ventricular pressure generation (LV  $dP/dt_{\text{max}}$ ) during the system implant, and an IPG charger used by patients at their home. The procedures for device implantation have been detailed previously.<sup>6</sup> In brief, the atrial lead is used only for sensing and is placed in the same manner as for other standard pacemaker or defibrillator implantations (Figure 2). The ventricular leads, used for both sensing local electrical activity and CCM signal delivery, are pacing leads placed on the right

ventricular (RV) septum. The goal is to ensure that electrodes are placed such that when CCM signals are applied they will impact on LV function. Therefore, CCM signals are applied and changes in  $dP/dt_{\text{max}}$  are measured (Figure 3). An acute increase of  $dP/dt_{\text{max}} \geq 5\%$  within approximately 10 minutes of signal application is considered adequate. If such a response is not elicited, the leads can be repositioned. If an increase in  $dP/dt_{\text{max}}$  is not measured after repositioning leads several times, the OPTIMIZER System is not implanted.

Cardiac contractility modulation signals used in this study consist of 2 biphasic square-wave pulses with peak-to-peak amplitude of  $\pm 7.73$  V that are applied 20 to 40 milliseconds after detection of electrical activation at the first ventricular lead.<sup>6</sup> Cardiac contractility modulation signal delivery is suspended upon detection of suspected ectopic beats (and during atrial fibrillation) and is reinitiated once the device senses 3 consecutive normal sinus beats. The device is programmed to deliver CCM signals for five 1-hour periods spaced equally throughout the 24 hours of the day.

Finally, the battery of the IPG is a rechargeable lithium-ion battery. Each patient receives a charging unit (Figure 1, D), and they are instructed to charge

**Figure 2**



Typical lead configuration for the OPTIMIZER System. See text details of lead placement.

the device once per week. When performed at this frequency, a charging session lasts approximately 90 minutes.

### **FIX-HF-5 study overview and objectives**

The FIX-HF-5 study is a prospective, randomized, parallel-controlled, trial of optimal medical therapy (OMT) alone (control group) versus OMT plus CCM (treatment group) (Figure 4). The objectives of the FIX-HF-5 study are to evaluate the safety (event-free survival) and efficacy (exercise tolerance and quality of life) of the OPTIMIZER System in subjects with moderate to severe heart failure despite OMT (including drug therapies and an ICD), ejection fraction  $\leq 35\%$ , and no indication for CRT.

### **Study population**

The trial design required randomization of 428 subjects to achieve its prespecified statistical power of 80% to test hypotheses for the safety and efficacy of CCM therapy (detailed below). Subjects were randomized at 50 sites in the United States. Recruitment began in March 2005 and was completed in June 2007.

The inclusion and exclusion criteria are summarized in Table I. In brief, the study recruited patients with EF  $\leq 35\%$  with NYHA class III or IV symptoms despite medical treatment with angiotensin converting enzyme inhibitor (ACE-I) and/or angiotensin receptor blocker (ARB) and  $\beta$ -blockers for at least 3 months who were in normal sinus rhythm and not indicated for a CRT device. Unless there were extenuating circumstances, patients were required to have an ICD.

The overall study flow is summarized in Figure 4 and Table II. After obtaining informed consent and passing baseline testing (as summarized in Table II), a device implant date was scheduled in the electrophysiology laboratory. Subjects were then randomized 1:1 to either the control group or to the treatment (CCM) group.

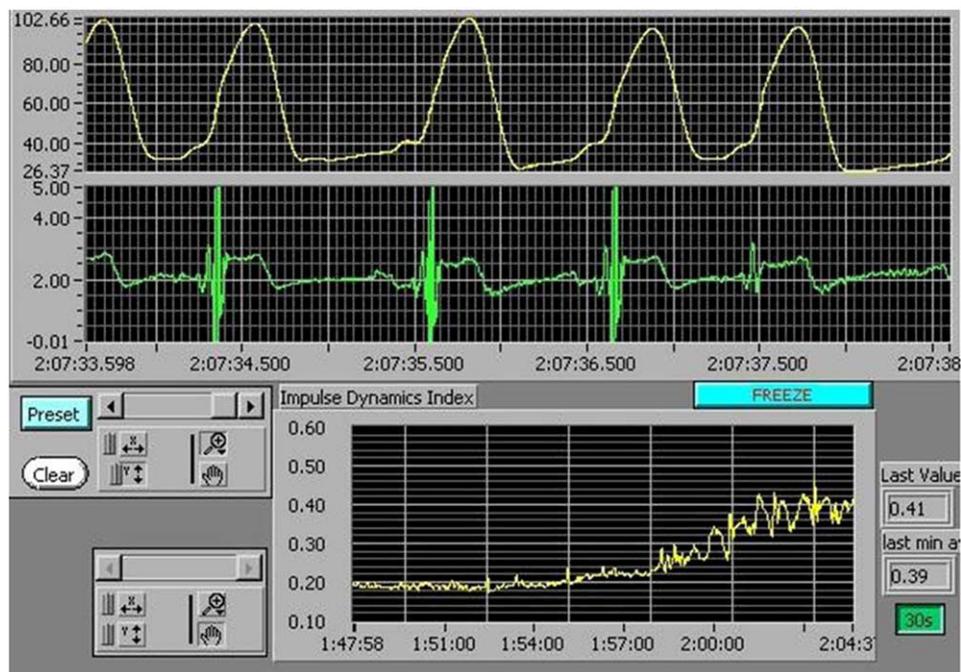
Subjects randomized to the treatment group underwent device implantation. For subjects not already having an ICD, one was implanted at the same time as the OPTIMIZER System implant. For determining the dates of follow-up visits, the implant date was used as the start date of study. Subjects randomized to the control group who required ICD implantation underwent that procedure within the same timeframe relative to baseline testing, as the treatment group. In these patients, the date of ICD implantation served as the study start date. Finally, for subjects randomized to the control group already having an ICD, an implant was not performed so the date of putative implant served as a study start date. Subjects in both groups were followed identically (except for interrogation of the investigational device) for 50 weeks as detailed in Table II. The first follow-up visit was at 2 weeks after the start of the study, at which time the OPTIMIZER System was interrogated and activated in those patients randomized to the treatment group.

Major follow-up visits were at weeks 12, 24, and 50, at which time cardiopulmonary stress test (CPX), Minnesota Living with Heart Failure Questionnaire (MLWHFQ), 6-minute walk test (6MW), NYHA class, echocardiograms, and Holter monitor tests were repeated. Additional follow-up visits occurred at weeks 4 and 36; these were for clinical follow-up and device interrogations. At the conclusion of the 50-week follow-up period, patients in the control group completed participation in the study. Patients in the treatment group continue to be followed at 3-month intervals for adverse events and device interrogations.

### **Approach to reducing placebo effect and bias**

Although a double-blind trial design using an implanted control as used in some implantable device trials (including the prior studies of the Optimizer<sup>11,12</sup>) was initially considered, a number of factors made this approach impractical for the present study. To obtain sufficient assurance of device safety, it was deemed necessary to acquire parallel-group controlled safety data over a 1-year period of follow-up. This extended period of follow-up created several challenges. First, the process of battery recharging created numerous opportunities for patient, study coordinator, and investigator unblinding. Second, ethical concerns were raised about subjecting control group patients to implantation of a device that would not be turned on for at least 1 year.

Figure 3



Method for optimizing ventricular lead placement. Computer screen showing the output of the Monita hemodynamic monitoring system used during system implant. Tracing at top is continuous LV pressure recording. Second tracing is ECG. The first three beats show CCM signal embedded in the QRS complex; the fourth beat is the first beat following suspension of CCM signal application showing the intrinsic electrogram. Changes in  $dp/dt_{max}$  (bottom part of screen) are measured to guide lead placement with the goal of acutely increasing  $dp/dt_{max} \geq 5\%$  within approximately 10 minutes of signal application.

Given the unblinded nature of the study, several measures were taken to minimize the placebo effect and investigator bias. First, as detailed below, the primary efficacy end point of the study is ventilatory anaerobic threshold (VAT). This parameter is measured during CPX testing and is an effort-independent parameter of exercise tolerance that is not known to be subject to the placebo effect. Importantly, neither the patient nor the test preceptor has knowledge of the value of the VAT during the conduct of the test, and its value cannot be manipulated. All CPX tests are sent to a single core laboratory for evaluation by 2 independent readers blinded to treatment group. Second, the primary safety end point of the study is the composite of all-cause mortality and all-cause hospitalization. This objective end point has been used in prior unblinded studies of heart failure treatment.<sup>13</sup> Moreover, an independent Events Adjudication Committee (EAC) evaluates original records of every hospitalization and death. Third, clinical assessments of NYHA are done by a blinded clinician interview. In addition, each patient completes a questionnaire that is specially designed and validated to allow a blinded core laboratory to assign an NYHA classification.<sup>14</sup> Finally, echocardiograms are read at a blinded

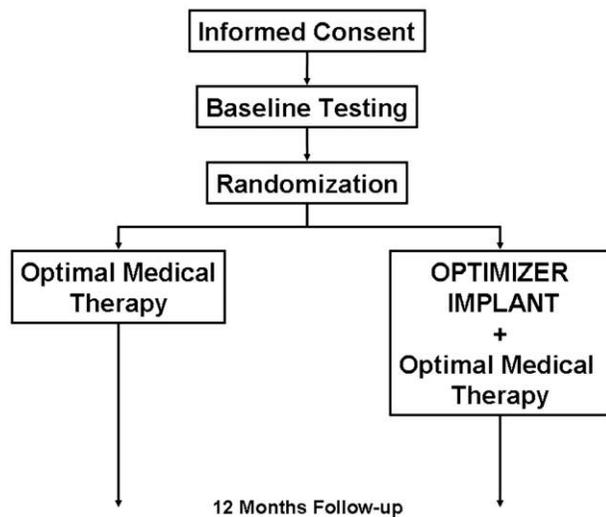
core laboratory. Core laboratory sites and directors are listed in Appendix C available online.

### Efforts to ensure cardiopulmonary stress test quality

Several measures were taken to optimize the quality CPX tests at all sites. These measures included the following: (1) on-site training on standardized procedures for conducting CPX tests and electronic transfer of data to the core laboratory; (2) site revalidation every 6 months; and (3) rapid feedback on test quality from the core laboratory (on the day they are performed).

Once obtained, metabolic data are sent to the blinded CPX core laboratory for analysis. Ventilatory anaerobic threshold, peak  $VO_2$ , and  $VE/VCO_2$  slope are determined from averaged 30-second gas exchange data from the start of exercise to the end of exercise. Ventilatory anaerobic threshold is determined using the V-slope method.<sup>15</sup> To avoid interobserver bias, the average of VAT determined by 2 independent readers of the core laboratory is reported. If, however, the 2 readings differ by  $>10\%$  or one or both of the readers is unable to identify the value of VAT, a third independent reading is obtained.

**Figure 4**



FIX-HF-5 study flow diagram. This was a prospective, randomized (with 1:1 randomization) study in which half of the patients received optimal medical treatment and half received an OPTIMIZER System implant and continued optimal medical treatment. Patients in both groups were followed for 12 months.

The average of the 2 values falling within 10% of each other is taken as the value to be used in analysis. If, however, all 3 readings disagree by >10%, VAT is considered indeterminate.<sup>16</sup>

### Events Adjudication Committee and Data Safety Monitoring Board

An EAC was established to review records of hospitalizations, deaths, and serious adverse events. This committee is composed of 3 independent cardiologists experienced in the adjudication process (Appendix B available online). The committee ensured consistent designation of events constituting a hospitalization. Specifically, protocol-specified hospitalizations include an admission that results in a calendar date change or is related to an adverse event that causes a prolongation of the index hospitalization for device implantation. The committee also adjudicates the cardiac and heart failure relatedness of deaths and hospitalizations.

An independent Data Safety Monitoring Board (DSMB) was established to review aggregate safety data and monitor for the emergence of any significant safety concerns. The DSMB is composed of 5 members with clinical trial experience in heart failure, electrophysiology, and statistics not otherwise participating in the study (Appendix B available online). The DSMB is unblinded to study group assignment.

**Table I.** Inclusion and exclusion criteria

#### Inclusion criteria

1. Age  $\geq 18$  y
2. Baseline EF  $\leq 35\%$  by echocardiography
3. Treated for heart failure for at least 90 d with appropriate, stable medical therapy during the 30 d before enrollment consisting of diuretics, ACE inhibitor, or angiotensin II receptor blocker and  $\beta$ -blocker unless intolerance; "stable" dosing is defined as not more than a 100% increase or 50% decrease in dose.
4. New York Heart Association class III or IV
5. Should have an ICD or agree to undergo implantation (unless there is a compelling reason to the contrary)
6. For female subjects of childbearing potential, must be using a medically approved method of birth control, must be surgically sterilized and should agree to continue to use birth control throughout the study
7. Willing and able to return for all follow-up visits
8. Provides informed consent to participate in the study

#### Exclusion criteria

1. Indicated for CRT (ie, QRS duration  $>130$  ms)
2. Potentially correctable cause of heart failure
3. Clinically significant angina pectoris
4. Hospitalized for heart failure which required the use of inotropic support within 30 d of enrollment
5. Clinically significant amount of ambient ectopy ( $>8900$  PVCs per 24 h)
6. PR interval  $>275$  ms
7. Chronic (permanent or persistent) atrial fibrillation or atrial flutter or cardioverted within 30 d of enrollment
8. Exercise tolerance limited by a condition other than heart failure or unable to participate in a 6-min walk or a cardiopulmonary stress test
9. Coronary bypass surgery within 90 d or PCI within 30 d
10. Myocardial infarction within 90 d
11. Mechanical tricuspid or aortic valves
12. Prior heart transplant
13. Participating in another experimental protocol
14. Unable to provide informed consent

PVC, Premature ventricular contractions; PCI, percutaneous coronary intervention.

### Statistical considerations and analysis plan

The trial's primary measure of effectiveness is the change from baseline in the VAT on CPX testing. The primary efficacy analysis is a superiority analysis comparing "responder" rates between the treatment and control groups at the 24-week follow-up visit. An individual subject will be considered a responder if VAT increases by  $\geq 20\%$  at 24 weeks compared to their respective baseline value. Responder rates between randomization arms is by a one-sided Fisher exact test with an  $\alpha$  of .025. Secondary efficacy end points are peak  $VO_2$  and quality of life assessed by MLWHFQ. Each of these parameters will also be assessed by a responder analysis, similar to VAT, with a 20% increase in peak  $VO_2$  and a 10-point reduction in MLWHFQ used to define a responder. The type I error rate is maintained across multiple tests of efficacy by employing a closed form hierarchical testing procedure.

The primary safety end point is the composite event rate of all-cause mortality and all-cause hospitalization

**Table II.** FIX-HF-5 schedule of events

Test	Follow-up schedule (relative to study start date)									
	Screening	Baseline	Implant*	Week 2 ± 2 d	+4 ± 1 wk	+12 ± 2 wk	+24 ± 2 wk	36 ± 2 wk	50 ± 2 wk	Every 3 mo*
Informed consent	X									
History	X			X	X	X	X	X	X	X
NYHA class (blinded site clinician assessment)	X					X	X		X	X
NYHA class (blinded core laboratory questionnaire)	X					X	X		X	
Medications	X			X	X	X	X	X	X	X
Physical examination	X			X	X	X	X	X	X	X
12-Lead electrocardiogram		X								
Echocardiogram		X				X	X		X	
MLWHFQ		X				X	X		X	
6-Minute Hall Walk Test		X				X	X		X	
Cardiopulmonary Stress Test		X				X	X		X	
24-h Holter Monitor		X				X	X			
Urine pregnancy test		X					X		X	
Eligibility determination		X								
Randomization		X								
OPTIMIZER System Implant*			X							
Chest x-ray*			X							
Optimizer Device Interrogation/Programming*			X	X	X	X	X	X	X	X
ICD Interrogation (episodes of VT/VF)				X	X	X	X	X	X	
Adverse events, hospitalizations, and procedures (as needed)		X	X	X	X	X	X	X	X	X

\*For subjects randomized to active treatment group, subjects are followed every 3 months ( $\pm 4$  weeks) after the 50-week interval.

through 50 weeks. The primary safety analysis is 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 noninferiority test<sup>17</sup> with a prespecified noninferiority margin of 0.125. In addition, the time to the first composite safety event (all-cause mortality and all-cause hospitalization) will be summarized in each group using Kaplan-Meier estimated survival curves, and the equality of the curves between groups will be assessed using the log-rank test.

#### Justification of sample size

The trial's sample size was calculated based on the primary safety end point and chosen to ensure adequate power (80%) to declare the safety of CCM therapy was not inferior to OMT. We assumed a conservative event rate (mortality or hospitalization for any cause) of 50%. The noninferiority margin was selected to be 12.5%, and  $\alpha$  was set at .05, which resulted in a sample size of 198 subjects per group. A small percentage of patients (5%-7%) were expected to be lost to follow-up, so that a total sample size of 428 patients (214 per group) was selected.

#### Additional analyses

A series of additional safety and efficacy analyses will be performed. These analyses, descriptive in nature, will

include comparisons between groups of changes from baseline in NYHA, 6MW distance, left ventricular ejection fraction, and left ventricular end-diastolic dimension. Additional safety analyses include all-cause mortality, cardiac mortality, heart failure mortality, all-cause hospitalizations, cardiac-related hospitalizations, heart failure-related hospitalizations, and overall incidence and seriousness of adverse events.

#### Methods of imputation of missing efficacy data

There are instances when study subjects perform a CPX test but for which a value of VAT cannot be ascertained by the core laboratory. In addition, a number of subjects will miss visits or will withdraw from the study. Preliminary experience in the early stage of this study and data taken from other trials using CPX testing<sup>11</sup> suggest that the rate of missing VAT values for all reasons could be 20% or more. To account for missing data, multiple imputation analyses will be used.<sup>18</sup> When a subject is missing VAT at either baseline or 24 weeks, but has a value of peak  $\text{VO}_2$  at the respective visit, a value of VAT can be imputed using stochastic regression based on peak  $\text{VO}_2$  and the respiratory exchange ratio. When a subject is missing VAT at both baseline and 24 weeks, the VAT difference can be imputed using stochastic regression based difference in peak  $\text{VO}_2$  and the respiratory exchange ratio. Finally, when a subject is missing both peak  $\text{VO}_2$  and VAT at 24 weeks, a

**Table III.** Phase II baseline characteristics

Characteristic	Control (n = 213)	Active (n = 215)
Age (y)	58.6 ± 12.2 (26-86; 59)	58.1 ± 12.8 (19-85; 57)
Male	151 (71)	158 (73)
Ethnicity		
White	142 (67)	154 (72)
Other	71 (33)	61 (28)
CHF etiology		
Ischemic cardiomyopathy	141 (66)	139 (65)
Nonischemic cardiomyopathy	72 (34)	76 (35)
History of diabetes	101 (47)	92 (43)
Resting HR (beat/min)	73.7 ± 12.2 (49-118; 72)	74.0 ± 13.1 (46-115; 72)
Systolic blood pressure (mm Hg)	115.6 ± 17.6 (78-174; 114)	116.5 ± 19.5 (78-195; 115)
QRS duration (ms)	101.7 ± 13.4 (60-160; 102)	101.7 ± 15.3 (70-160; 100)
LVEF (%)	26.1 ± 6.5 (10-35; 27)	25.8 ± 6.6 (10-40; 25)
LVEDD (mm)	63.0 ± 8.6 (46-88; 62)	62.5 ± 9.2 (30-89; 63)
Peak VO <sub>2</sub> (mL kg <sup>-1</sup> min <sup>-1</sup> )	14.7 ± 2.9 (9-21.4; 14.9)	14.8 ± 3.1 (9-22; 14.7)
6-Minute Hall Walk (m)	322.8 ± 94.2 (64-600; 321)	324.7 ± 83.3 (95-525; 330)
NYHA		
Class II	1	0
Class III	183 (86)	196 (91)
Class IV	29 (14)	19 (9)
MLWHFQ score	57.4 ± 22.6 (1-102; 59)	60.5 ± 23.0 (0-100; 64)

HR, Heart rate; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic dimension.  
All values are mean ± SD (min-max; median) or number (percentage) of subjects.

propensity matching and random selection method of imputation shall be used.

### 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 patients, 428 subjects passed baseline screening and were randomized to either the control group (n = 213) or the treatment group (n = 215). The baseline characteristics of these patients are summarized in [Table III](#). Overall, these characteristics are balanced between groups and are consistent with the study inclusion and exclusion criteria. Medication and ICD use at baseline are summarized in [Table IV](#) and [Table V](#), respectively. As shown, 91% of subjects were taking ACE-I and/or ARB and 93% were taking β-blockers; less than half were taking digoxin and aldosterone inhibitors. About 80% of subjects had an ICD prior to entry into the study. Another approximately 12% had an ICD placed at the start of the study. A few additional

**Table IV.** Phase II baseline medications

Medications	Control (n = 213)	Active (n = 215)
Angiotensin converting enzyme (ACEi)	148 (69)	153 (71)
ARB	50 (23)	52 (24)
ACEi or ARB	194 (91)	195 (91)
β-Blocker	198 (93)	202 (94)
Diuretic	195 (92)	198 (92)
Aldosterone inhibitor	102 (48)	95 (44)
Digoxin	97 (46)	84 (39)
Antiarrhythmic	30 (14)	37 (17)

Values are expressed as number (percentage).

**Table V.** Phase II ICD usage

Study Interval	Control (n = 213)	Optimizer (n = 215)	Total (n = 428)
ICD at baseline	171 (80)	179 (83)	350 (82)
ICD on SSD	21 (10)	26 (12)	47 (11)
Total ICD usage at baseline/SSD	192 (90)	205 (95)	397 (93)
ICD during follow-up	9 (4)	2 (1)	11 (3)
Total ICD usage	201 (94)	207 (96)	408 (95)

Values are expressed as number (percentage). SSD, Study Start Date.

devices were implanted during the follow-up period. Overall, therefore, 95% of study subjects have an ICD.

### Discussion

Despite major advances in drugs and devices to treat heart failure, many patients have persistent symptoms and exercise intolerance. A minority of patients are eligible for significant CRT, which is arguably, the most important advance in device-based treatment for heart failure over the past decade, and significant CRT nonresponder rates remain a limitation of this therapy. Preliminary studies with CCM suggest that this may be a viable treatment option for many of these patients. The FIX-HF-5 study is designed to provide additional evidence of safety and efficacy of CCM treatment delivered by the OPTIMIZER System. The cohort enrolled in the study is composed of patients with moderately advanced heart failure despite appropriate medical therapy not indicated for CRT.

There are 2 new and unique aspects of the present study design compared with prior studies of heart failure. First, is the use of VAT as the primary efficacy end point. Ventilatory anaerobic threshold is considered to be an unbiased measure of exercise tolerance not subject to placebo effect.<sup>19</sup> Although VAT offers these potential advantages, it must also be acknowledged that this parameter has not been measured systematically in any prior large-scale study, nor have changes in VAT been correlated directly with changes in functional class or

outcomes. Finally, there is limited information on the impact of proven therapies on VAT.

A second unique aspect of the present study is the use of a responder analysis. In contrast to a comparison of mean changes in VAT between randomized groups, the results of a responder analysis would permit a treating physician to tell a patient his or her odds of showing a clinically significant improvement in exercise tolerance. However, there are no prior studies in which a responder analysis, applied to a continuous variable has been used as the prospective approach in determining the effectiveness of a new heart failure treatment. Therefore, there are no historical data for comparison of response rates in this trial to other trials of effective therapies for heart failure. Because of these 2 untested features of the study, it was considered important to include other more traditional parameters, peak  $\text{VO}_2$  and MLWHFQ, as secondary end points.

With enrollment completed in June 2007, 50-week follow-up of the last enrolled patient is expected in June of 2008, with results to be available shortly thereafter. If proven safe and effective in this clinical trial, a new treatment option—CCM—will be available to a large group of patients that currently do not have other treatment options.

## References

1. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-53.
2. Bristow MR, Saxon LA, Boehmer J, Krueger, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-50.
3. Cleland JG, Daubert JC, Erdmann E, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CARDiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 2006;27:1928-32.
4. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007.
5. Burkhoff D, Ben Haim SA. Nonexcitatory electrical signals for enhancing ventricular contractility: rationale and initial investigations of an experimental treatment for heart failure. *Am J Physiol Heart Circ Physiol* 2005;288:H2550-6.
6. Lawo T, Borggreffe M, Butter C, et al. Electrical signals applied during the absolute refractory period: an investigational treatment for advanced heart failure in patients with normal QRS duration. *J Am Coll Cardiol* 2005;46:2229-36.
7. Bruckhorst CB, Shemer I, Mika Y, et al. Cardiac contractility modulation by non-excitatory currents: studies in isolated cardiac muscle. *Eur J Heart Fail* 2006;8:7-15.
8. Imai M, Rastogi S, Gupta RC, et al. Therapy with cardiac contractility modulation electrical signals improves left ventricular function and remodeling in dogs with chronic heart failure. *J Am Coll Cardiol* 2007;49:2120-8.
9. Butter C, Rastogi S, Minden HH, et al. Cardiac contractility modulation electrical signals improve myocardial gene expression in patients with heart failure. *J Am Coll Cardiol* 2008;51:1784-9.
10. Butter C, Wellenhofer E, Schlegel M, et al. Enhanced inotropic state of the failing left ventricle by cardiac contractility modulation electrical signals is not associated with increased myocardial oxygen consumption. *J Card Fail* 2007;13:137-42.
11. Borggreffe MM, Lawo T, Butter C, et al. Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure. *Eur Heart J* 2008;29:1019-28.
12. Neelagaru SB, Sanchez JE, Lau SK, et al. Nonexcitatory, cardiac contractility modulation electrical impulses: feasibility study for advanced heart failure in patients with normal QRS duration. *Heart Rhythm* 2006;3:1140-7.
13. Bristow MR, Feldman AM, Saxon LA. Heart failure management using implantable devices for ventricular resynchronization: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial. COMPANION Steering Committee and COMPANION Clinical Investigators [In Process Citation]. *J Card Fail* 2000;6:276-85.
14. Kubo SH, Schulman S, Starling RC, et al. Development and validation of a patient questionnaire to determine New York Heart Association classification. *J Card Fail* 2004;10:228-35.
15. Sue DY, Wasserman K, Moricca RB, et al. Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease. Use of the V-slope method for anaerobic threshold determination. *Chest* 1988;94:931-8.
16. Myers J. Essentials of cardiopulmonary exercise testing. Champaign (Ill): Human Kinetics; 1996.
17. Blackwelder WC. "Proving the null hypothesis" in clinical trials. *Control Clin Trials* 1982;3:345-53.
18. Little R, Rubin D. Statistical analysis with missing data. New York: John Wiley and Sons; 2002.
19. Milani RV, Lavie CJ, Mehra MR, et al. Understanding the basics of cardiopulmonary exercise testing. *Mayo Clin Proc* 2006;81:1603-11.

## Appendix A

Arizona Arrhythmia Research Center, Scottsdale, AZ: Thomas Mattioni, MD; Vijay Swarup, MD; Sara Scrivano; Claudia Williams, RN; Arrhythmia Center for Southern Wisconsin, Ltd/St. Luke's Medical Center, Milwaukee, WI: Imran Niazi, MD; Nguyen Phan, MD; Rebecca Dahme, RN; Jo Ann Kiemen; Aurora Denver Cardiology Associates, Aurora, CO: Andrew I. Cohen, MD; Susan M. Polizzi, MD; Karen Bickett; BryanLGH Heart Institute, Lincoln, NE: Andrew Merliss, MD; Steven K. Krueger, MD; June Christy, RN; California Pacific Medical Center, San Francisco, CA: Steven C. Hao, MD; Richard H. Hongo, MD; Eric J. Bernier, RN; Gina Im; Cardiovascular Associates, Kingsport, TN: Greg Jones, MD; Arun Rao, MD; Tammy Dicken; Cardiovascular Medical Group of Southern California, Beverly Hills, CA: Eli S. Gang, MD; Ronald P. Karlsberg, MD; Maria M. Thottam; Tracey S. Gerez; Center at St. Francis Hospital, Roslyn, NY: Steven M. Greenberg, MD; Rebecca Seeman, RN; Nedda Easterling; Center for Cardiac Arrhythmias, Houston, TX: Hue-Teh Shih, MD; Candace Pourciau; Comprehensive Cardiovascular Care, Milwaukee, WI: Masood Akhtar, MD; Anthony Chambers, RN; Deborah Heart & Lung Center, Trenton, NJ: Raffaele Corbisiero, MD; Linda Dewey, RN; Emory University Hospital, Atlanta GA: Jonathan Langberg, MD; Andrew Smith, MD; Sheila Heeke, RN; Jerilyn Steinberg, RN; Forsyth Medical Center, Winston-Salem, NC: David Smull, DO; Mark Mitchell, MD; Janice Dickson, RN; Harper University Hospital, Detroit, MI: Randy A. Lieberman, MD; Anne B. Mick; Heart & Vascular Institute of Texas, San Antonio, TX: Gregory A. Buser, MD; Armistead Lanford Wellford IV, MD; Edwin L. Whitney, MD; Steven W. Farris, RN; Henry Ford Hospital, Detroit, MI: Barbara Czerska, MD; Karen Leszczynski, RN; Inova Heart and Vascular Institute/Inova Fairfax Hospital: Mark Wish, MD; Ted Friebling, MD; Jessica Wolfe, RN; Marie Blake, RN; Lahey Clinic Medical Center, Burlington, MA: Roy M. John, MD; David T. Martin, MD; Bruce G. Hook, MD; Jean M. Byrne, RN; Lancaster Heart and Stroke Foundation, Lancaster, PA: Seth J. Worley, MD; Douglas C. Gohn, MD; Diane Noll, RN; Lone Star Arrhythmia and Heart Failure Center, Amarillo, TX: Suresh B. Neelaguru, MD; Tanya Welch, RN; Mayo Clinic, Rochester, MN: David L. Hayes, MD; Robert F. Rea, MD; Jane Trusty, RN; Mary (Libby) Hagen, RN; Midwest Heart Foundation, Lombard, IL: Maria Rosa Costanzo, MD; Lea Elder, RN; Moses Cone Hospital and Lebauer Cardiovascular Research Foundation, Greensboro, NC: Steve Klein, MD; Daniel Bensimhon, MD; Paul Chase; Mount Sinai Medical Center, Miami, FL: Gervasio A. Lamas, MD; Todd J. Florin, MD; Beatriz E. Restrepo, MD, MPH; Newark Beth Israel Medical Center, Newark, NJ: David A. Baran, MD; Laura Adams, RN; Northwestern University, Chicago, IL: Jeffrey Goldberger, MD; Dinita Galvez, RN; Katherine Small; NYU Medical Center, New York, NY: Jill Kalman, MD; Cristina Surach, RN; Ochsner Health Systems, New Orleans, LA: Freddy Abi-Samra, MD; Timothy Donahue, MD; Melanie Lunn; Cristine Hardy; Ohio State University,

Columbus, Ohio: Charles C. Love, MD; Philip E. Binkley, MD; Garrie J. Haas, MD; Leah Sanuk, RN; Laura Yamokoski, RN; Hope Heart Institute, Bellevue, WA: J. Alan Heywood, MD; Amy Payne, RN; Pacific Rim EP, Inglewood, CA: Koonlawee Nademanee, MD; Carla Drew; Penn Presbyterian Medical Center, Philadelphia, PA: Kent Volosin, MD; Janet Riggs, MSN, RN; Riverside Regional Medical Center, Newport, VA: Allan L. Murphy, MD; Virginia M. Oehmann, RN; Southern California Heart Centers: Stanley K. Lau, MD; Nita Cheng, RN; Peter Yiu; Spokane Cardiology/Deaconess Medical Center, Spokane, WA: Harold R. Goldberg, MD; Vickie Shumaker, RN; Stern Cardiovascular Center, Germantown, TN: Frank McGrew III, MD; Barbara Hamilton, RN; St. Joseph's Research Institute, Atlanta, GA: Nirav Raval, MD; Nicolas Chronos, MD; Stephen P. Prater, MD; Sarah Conley; St. Lukes-Roosevelt Hospital Center, New York, NY: Jonathan S. Steinberg, MD; Marrick L. Kukin, MD; Robin Knox, RN; Cathleen B. Varley, RN; St. Paul Heart Clinic, St. Paul, MN: Alan Bank, MD; Stuart Adler, MD; R. Dent Underwood, MD; Lisa Tindell, RN; Texas Cardiac Arrhythmia Research, Austin, TX: Javier E. Sanchez, MD; G. Joseph Gallinghouse, MD; Deb S. Cardinal, RN; Chantel M. Scallon, RN; Tyler Cardiovascular Consultants, Tyler, TX: Stan Weiner, MD; Linda Holt; University of Alabama at Birmingham, Birmingham, AL: Jose Tallaj, MD; Tom McElderry Jr, MD; Karen Rohrer, RN; University of South Florida Heart Health, Tampa, FL: Bengt Herweg, MD; Robyn Aydelott-Nuce, RN; Mary Ann K. Yarborough, RN; University of Texas Southwestern Medical Center, Dallas, TX: Jose Joglar, MD; Owen Obel, MD; Carol Nguyen, RN; Dana Red, RN; University of Wisconsin, Madison, WI: Nancy Sweitzer, MD; Vanderbilt Heart and Vascular Institute, Nashville, TN: Mark Wathen, MD; Darwood Darber, MD; Nancy M. McDonough, RN; Lindee D. Dye, RN; Virginia Commonwealth University Health System/MCV Hospitals, Richmond, VA: Mark Wood, MD; Kenneth Ellenbogen, MD; Michael Hess, MD; Kim Hall, RN.

## Appendix B. Committees

Steering Committee: William T. Abraham (Cochairman), Alan Kadish (Cochairman), Koonlawee Nademanee, Peter Carson, Robert Bourge, Kenneth A. Ellenbogen, and Michael Parides.

EAC: Peter Carson (Chairman), Christopher O'Conner, Inder Anand.

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

## Appendix C. Core laboratories

Cardiopulmonary Stress Test: Rochelle Goldsmith, Columbia University, New York, NY.

Echocardiography: Marco DiTullio, Columbia University  
NYHA Blinded Core Laboratory: Steven P. Schulman, The Johns Hopkins University, Baltimore, MD.