JACC: HEART FAILURE VOL. ■, NO. ■, 2018

A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation

William T. Abraham, MD,[a] Karl-Heinz Kuck, MD,[b] Rochelle L. Goldsmith, PhD,[c] JoAnn Lindenfeld, MD,[d] Vivek Y. Reddy, MD,[e] Peter E. Carson, MD,[f] Douglas L. Mann, MD,[g] Benjamin Saville, PhD,[h] Helen Parise, ScD,[i] Rodrigo Chan, MD,[j] Phi Wiegn, MD,[k] Jeffrey L. Hastings, MD,[k] Andrew J. Kaplan, MD,[l] Frank Edelmann, MD,[m] Lars Luthje, MD,[m] Rami Kahwash, MD,[n] Gery F. Tomassoni, MD,[o] David D. Gutterman, MD,[p] Angela Stagg, BS,[q] Daniel Burkhoff, MD, PhD,[r] Gerd Hasenfuß, MD[s]

ABSTRACT

OBJECTIVES The authors sought to confirm a subgroup analysis of the prior FIX-HF-5 (Evaluate Safety and Efficacy of the OPTIMIZER System in Subjects With Moderate-to-Severe Heart Failure) study showing that cardiac contractility modulation (CCM) improved exercise tolerance (ET) and quality of life in patients with ejection fractions between 25% and 45%.

BACKGROUND CCM therapy for New York Heart Association (NYHA) functional class III and IV heart failure (HF) patients consists of nonexcitatory electrical signals delivered to the heart during the absolute refractory period.

METHODS A total of 160 patients with NYHA functional class III or IV symptoms, QRS duration $<$130 ms, and ejection fraction $\geq$25% and $\leq$45% were randomized to continued medical therapy (control, $n = 86$) or CCM (treatment, $n = 74$, unblinded) for 24 weeks. Peak VO_2 (primary endpoint), Minnesota Living With Heart Failure questionnaire, NYHA functional class, and 6-min hall walk were measured at baseline and at 12 and 24 weeks. Bayesian repeated measures linear modeling was used for the primary endpoint analysis with 30% borrowing from the FIX-HF-5 subgroup. Safety was assessed by the percentage of patients free of device-related adverse events with a pre-specified lower bound of 70%.

RESULTS The difference in peak VO_2 between groups was 0.84 (95% Bayesian credible interval: 0.123 to 1.552) ml O_2/kg/min, satisfying the primary endpoint. Minnesota Living With Heart Failure questionnaire ($p < 0.001$), NYHA functional class ($p < 0.001$), and 6-min hall walk ($p = 0.02$) were all better in the treatment versus control group. There were 7 device-related events, yielding a lower bound of 80% of patients free of events, satisfying the primary safety endpoint. The composite of cardiovascular death and HF hospitalizations was reduced from 10.8% to 2.9% ($p = 0.048$).

CONCLUSIONS CCM is safe, improves exercise tolerance and quality of life in the specified group of HF patients, and leads to fewer HF hospitalizations. (Evaluate Safety and Efficacy of the OPTIMIZER System in Subjects With Moderate-to-Severe Heart Failure; NCT01381172) (J Am Coll Cardiol HF 2018;■:■–■) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Division of Cardiovascular Medicine, The Ohio State University, Columbus, Ohio; [b]Department of Cardiology, ASKLEPIOS Klinik St. Georg, Hamburg, Germany; [c]Exercise Physiology Laboratory, Columbia University Medical Center, New York, New York; [d]Department of Heart Failure and Transplant, Vanderbilt Heart, Nashville, Tennessee; [e]Department of Cardiac Arrhythmia Services, The Mount Sinai Hospital, New York, New York; [f]Medical Intensive Care Unit, Washington VA Medical Center, Washington, DC; [g]Division of Cardiovascular, Washington University School of Medicine, St. Louis, Missouri; [h]Berry Consultants, Austin, Texas; [i]Biostatistics and Clinical Trials Consultant, Las Vegas, Nevada; [j]Chan Heart Rhythm Institute, Mesa, Arizona; [k]Department of Clinical Cardiac Electrophysiology, Dallas VA Medical Center, Dallas, Texas; [l]Department of Clinical Cardiac Electrophysiology, Cardiovascular Associates of Mesa, Mesa, Arizona; [m]Department of Cardiology and Pneumology, Universität Göttingen, Göttingen, Germany; [n]Department of Heart Failure & Transplantation, The Ohio State University Heart and Vascular Center, Columbus, Ohio; [o]Department of Clinical Cardiac Electrophysiology, Baptist Health Lexington, Lexington, Kentucky; [p]Cardiovascular Center, Medical College of Wisconsin, Milwaukee, Wisconsin; [q]Clinical Trials, Impulse Dynamics, Orangeburg, New York; [r]Cardiovascular Research Foundation, New York, New York; and the [s]Heart Center of Göttingen, University Medical Center Göttingen, Göttingen, Germany. This study was supported by research grants from Impulse Dynamics. Ms. Stagg is an employee of Impulse Dynamics. Drs. Abraham, Parise, Gutterman, Burkhoff, and Hasenfuß have served as consultants to Impulse Dynamics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 13, 2018; revised manuscript received April 24, 2018, accepted April 24, 2018.

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2018.04.010

ABBREVIATIONS AND ACRONYMS

6MHW = 6-min hall walk test

CCM = cardiac contractility modulation

CI = confidence interval

CPX = cardiopulmonary exercise stress test

DSMB = data and safety monitoring board

EF = ejection fraction

FDA = Food and Drug Administration

ICD = implantable cardiac-defibrillator

MLWHFQ = Minnesota Living With Heart Failure Questionnaire

NYHA = New York Heart Association

OMT = optimal medical therapy

pVO_2 = peak rate of oxygen consumption

QoL = quality of life

Cardiac contractility modulation (CCM) is an electrical device-based approach developed for the treatment of chronic heart failure with reduced and midrange ejection fractions (EFs) (**Figure 1**) (1,2). CCM signals are nonexcitatory electrical signals applied during the cardiac absolute refractory period that enhance the strength of cardiac muscular contraction (3).

After completion of a successful double-blind, double-crossover study in Europe (FIX-HF-4 [Evaluate Safety and Efficacy of the OPTIMIZER System in Subjects With Moderate-to-Severe Heart Failure] study) (4) and a pilot study in the United States (5), the randomized FIX-HF-5 trial was performed to study the safety and efficacy of CCM in patients with New York Heart Association (NYHA) functional class III or IV symptoms and reduced EF (6). That 428-patient study met its primary safety endpoint (a noninferiority assessment of the composite of all-cause mortality and all-cause hospitalizations). However, the primary efficacy endpoint, responders' analysis of changes in ventilatory anaerobic threshold on cardiopulmonary exercise stress testing (CPX), was not met (6). An exploratory, hypothesis-generating subgroup analysis showed significant treatment effects on primary and secondary endpoints in patients with EFs ranging from 25% to 45% (7).

We therefore designed the FIX-HF-5 *confirmatory* study (FIX-HF-5C study) to prospectively test the efficacy and safety of CCM in patients with EF ranging from 25% to 45% (8). A Bayesian statistical analysis plan was employed to take advantage of data available from the original study.

METHODS

STUDY DESIGN. This was a prospective, randomized study of optimal medical therapy (OMT) alone (control group) versus OMT plus CCM (CCM treatment group) in patients with medically refractory, but ambulatory heart failure (NYHA functional class III or IV) with EF ranging from 25% to 45%. The details of the study design have been provided previously (8). As will be discussed in the following text, the final design was influenced by the fact that the Optimizer system (Impulse Dynamics, Orangeburg, New York) was designated as eligible for the Expedited Access Pathway of the U.S. Food and Drug Administration (FDA) (9) because it potentially provides a treatment for an underserved population. The study was registered on ClinicalTrials.gov (NCT01381172).

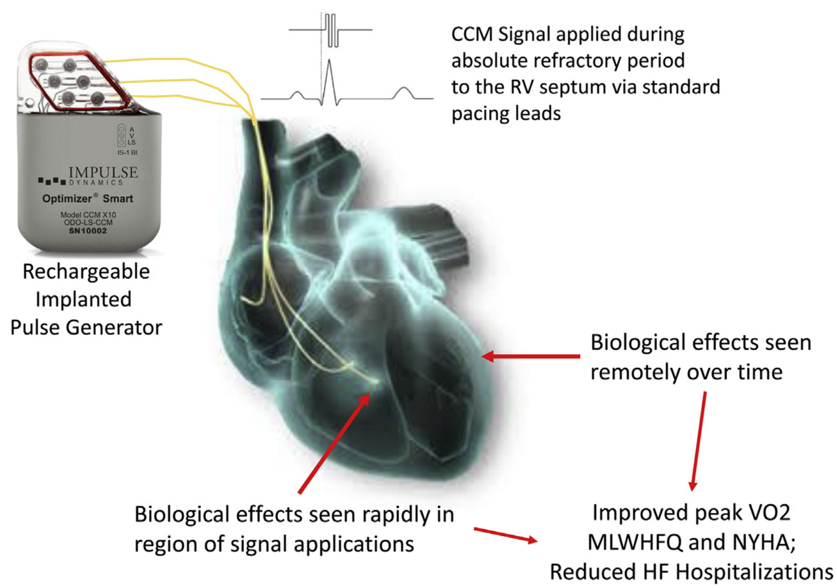
STUDY POPULATION. The inclusion and exclusion criteria are summarized in Online Table 1 (8). Patients with NYHA functional class III or ambulatory class IV heart failure despite OMT, an EF ranging from 25% to 45% as determined by an echocardiographic core laboratory, and normal sinus rhythm with QRS duration <130 ms were eligible for the study. Unless there were extenuating circumstances, patients with EF ≤35% were required to have an implantable cardiac-defibrillator (ICD) according to published guidelines.

The overall study flow is summarized in Online Figure 2, and the detailed schedule of events is summarized in Online Table 2. In brief, after signing informed consent, patients underwent baseline testing, which included peak oxygen consumption (pVO_2) assessed on CPX, determination of quality of life (QoL) score using the Minnesota Living with Heart Failure Questionnaire (MLWHFQ), 6-min hall walk test (6MHW), and NYHA functional class assessment. If patients passed baseline testing, a device implant date was scheduled in the electrophysiology laboratory; this scheduled implant date served as the study start date from which the timing of all future follow-up visits were determined. After passing baseline testing and meeting all entry criteria, patients were randomized in a 1:1 manner into either the control group or the CCM treatment group. Subjects randomized to the treatment group underwent device implantation. For subjects randomized to the control group, the implantation procedure was canceled, but the putative implant date served as the study start date. Major follow-up visits were at weeks 12 and 24, at which time CPX, MLWHFQ, 6MHW, and NYHA functional class assessments were performed.

DEVICE AND IMPLANTATION PROCEDURE. The Optimizer system consists of an implantable pulse generator with a rechargeable battery, 1 atrial and 2 ventricular pacing screw-in leads, an implantable pulse generator programmer, and a battery charger. The device and implantation procedure have been detailed previously (2,5,10). In brief, an atrial lead is used for sensing and is placed in the same manner as for standard pacemakers and defibrillators. Two ventricular leads, used for both sensing local electrical activity and CCM signal delivery, are placed on the right ventricular septum. The device was programmed to deliver CCM signals for 5 1-h periods spaced equally throughout the 24 h of the day.

EXERCISE TESTING AND CORE LABORATORY. Rigorous procedures applied by a core laboratory served to optimize test quality and achieve maximal effort from each patient. These measures included:

FIGURE 1 Clinical Implementation of CCM Treatment



CCM signals are delivered from an implanted pulse generator connected to the heart via one atrial lead (for p-wave sensing) and two ventricular leads (for sensing timing of local electrical activation and for delivering CCM signals). CCM signal are biphasic pulses delivered during the absolute refractory period. CCM signals impact the biology of the failing muscle local and, over time, distal to the site of signal delivery. These myocardial effects ultimately contribute to favorable clinical effects. CCM = cardiac contractility modulation; MLWHFQ = Minnesota Living With Heart Failure questionnaire; NYHA = New York Heart Association.

1) on-site training on standardized procedures for conducting CPX testing; 2) normal subject validation testing and revalidation every 6 months; 3) providing the patient with instructions on how to prepare for the CPX test; 4) rapid feedback on the quality of every test from the core laboratory and retest requests for inadequate tests; and 5) 2 tests performed at each time point (detailed in the following text). Criteria for declaring a test inadequate are summarized in the Online Appendix. The pVO_2 and respiratory exchange ratio (RER) were determined by the blinded core laboratory from averaged 20-s gas exchange data from the start of exercise to the end of exercise. Tests were deemed to be of maximal effort if the respiratory exchange ratio reached ≥1.05.

As noted, 2 CPX tests were performed for each patient at baseline and at the 12- and 24-week follow-up visits. If both tests were deemed adequate, the average of the 2 tests was used for the value at that time point. If only 1 test was deemed adequate, then only that 1 value was used for the analysis.

EVENTS ADJUDICATION COMMITTEE AND DATA AND SAFETY MONITORING BOARD. An events adjudication committee was established to review records of adverse events, hospitalizations, and deaths. This committee was composed of 3 independent cardiologists experienced in the adjudication process. The committee provided definitions for protocol-specified hospitalizations, which included a hospital admission that resulted in a calendar date change or was related to an adverse event that caused a prolongation of the index hospitalization for device implantation. The committee also adjudicated the cardiac and heart failure relatedness of deaths and hospitalizations.

An independent data and safety monitoring board (DSMB) reviewed aggregate safety data and monitored for the emergence of any significant safety concerns. The DSMB was composed of 5 members with clinical trial experience in heart failure, electrophysiology, and statistics who were not otherwise participating in the study. The DSMB was unblinded to study group assignment. Details of members of the events adjudication committee, DSMB, and other oversight committees are provided in the Online Appendix along with a complete list of investigators and sites.

STATISTICAL ANALYSIS PLAN. The primary measure of efficacy was defined as the change in pVO_2 as evaluated by the blinded core laboratory. The primary analysis employed a Bayesian repeated measures linear model to estimate group differences in mean pVO_2 at 24 weeks from baseline, with 30% borrowing of information (70% down-weighting) from the corresponding treatment group difference observed in the FIX-5 study subgroup.

More specifically, the Bayesian linear model incorporated pVO_2 data from baseline, 12 weeks, and 24 weeks for each patient, in which a mean treatment difference was estimated at 12 and 24 weeks, and set equal to 0 (no treatment difference) at baseline on the premise of randomization. A random intercept was used to account for repeated observations within the same individual. An informative prior distribution was used for the treatment effect at 12 and 24 weeks based on FIX-HF-5 data, using the power prior methodology of Ibrahim and Chen (11), with a 30% weight or 70% down-weighting of the FIX-HF-5 subgroup treatment group difference. Non-informative prior distributions were specified for all other model parameters. The pre-specified primary analysis would conclude superiority of the CCM treatment group versus control group if the Bayesian posterior probability of a positive treatment difference in favor of CCM treatment exceeded 0.975. In addition, a 95% Bayesian credible interval was provided based on the 2.5th and 97.5th percentiles of the Bayesian posterior distribution of the treatment difference. For summary purposes, a similar (non-Bayesian) repeated measures model was also fitted to the FIX-HF-5 and -5C studies (without borrowing) to summarize the treatment differences of each trial independently.

SECONDARY AND OTHER EFFICACY ANALYSES. Secondary efficacy parameters include change in QoL as assessed by the MLWHFQ and NYHA functional class. The assessment of treatment differences at 24 weeks for MLWHFQ and pVO_2 were conducted with linear mixed models (non-Bayesian) with a similar structure as the primary analysis but without borrowing from the FIX-HF-5 study. The analysis of changes in NYHA functional class tested the hypothesis that the subjects treated with the device have a greater proportion of subjects who improve by at least 1 NYHA category at 24 weeks compared with the control group. The NYHA hypothesis was evaluated via a stratified Cochran Mantel-Haenszel test, with strata defined by etiology of heart failure.

Among the additional pre-specified analyses (8) were assessments of the CCM treatment effects in patients with EF $<35\%$ and with patients with EF $\geq35\%$. Because of the smaller number of patients, these analyses were performed on the per-protocol population of data pooled from the FIX-HF-5 subgroup and the FIX-HF-5C cohorts.

PRIMARY SAFETY ANALYSIS. The safety of the Optimizer system was assessed by evaluating the incidence of Optimizer device- or procedure-related complications. The primary safety endpoint was defined as the proportion of subjects who did not experience either an Optimizer device-related complication or a procedure-related complication by 24 weeks. The criterion for satisfying the safety analysis was that the proportion of complication-free subjects was significantly larger than 70% (1-sided significance level of 0.025), a criterion set by the FDA. Satisfying the primary safety endpoint required rejecting the null hypothesis at a 1-sided significance level of 0.025 using an exact binomial test. It is noteworthy that the point estimate of freedom from this composite endpoint at 24 weeks among subjects in the subgroup EF $\geq25\%$ in the original FIX-HF-5 study was 88%.

Secondary safety analyses included 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. The survival analyses were performed using Kaplan-Meier analysis and the adverse events were tabulated by seriousness and treatment group using the Fisher exact test.

RESULTS

ENROLLMENT, BASELINE CHARACTERISTICS AND COMPARISON WITH FIX-HF-5. The overall study flow is summarized in Online Figure 1, which also accounts for the patients from the original FIX-HF-5 study. In FIX-HF-5C, 488 patients signed informed consent and underwent baseline testing. A total of 160 patients passed baseline testing, of whom 86 were randomized to the control group and 74 were randomized to the CCM treatment group. A total of 68 of the 74 subjects assigned to the CCM treatment group underwent device implantation. Reasons why patients did not receive an implant included: 1 patient died before device implant, 1 was lost to follow-up, 1 was deemed ineligible (NYHA functional class II) and withdrawn after being randomized, 1 was discovered to have an additional abandoned ICD lead and the implant was canceled, and 2 decided not to undergo the implant.

Baseline characteristics of subjects in the current study and in the designated subgroup of subjects of the prior FIX-HF-5 study with EF $\geq25\%$ are summarized in Table 1. Among the 21 baseline characteristics examined, a few differences existed within treatment groups between patients of the current (FIX-HF-5C) and original (FIX-HF-5) studies. Although statistically

TABLE 1 Baseline Characteristics: Comparisons Between FIX-HF-5C and FIX-HF-5 Subgroup (With EF ≥25%) Cohorts by Group and Pooled

	Control Group			CCM Group					
	FIX-HF-5 Subgroup* (n = 112)	FIX-HF-5C* (n = 86)	p Value	FIX-HF-5 Subgroup* (n = 117)	FIX-HF-5C* (n = 74)	p Value	Control Merged (n = 198)	CCM Merged (n = 191)	p Value* (Control vs. CCM, Combined)
Age, yrs	60 ± 12	63 ± 11	0.08	59 ± 12	63 ± 11	**0.011**	61 ± 12	60 ± 12	0.51
Male	83/112 (74.1)	68/86 (79.1)	0.50	83/117 (71.0)	54/74 (73.0)	0.869	151/198 (76.3)	137/191 (71.3)	0.34
White ethnicity	81/112 (72.3)	61/74 (70.9)	0.87	88/117 (75.2)	55/74 (74.3)	1.0000	142/198 (71.72)	143/191 (74.87)	0.49
Ischemic CHF etiology	77/112 (68.8)	51/86 (59.3)	0.18	84/117 (71.8)	46/74 (62.2)	0.2026	128/198 (64.65)	130/191 (68.06)	0.52
Prior MI	66/112 (58.9)	51/86 (59.3)	1.00	78/117 (66.7)	36/74 (48.7)	**0.0157**	117/198 (59.09)	114/191 (59.69)	0.92
Prior PT/ICD	88/112 (78.6)	73/86 (84.9)	0.28	93/117 (79.5)	65/74 (87.8)	0.1702	161/198 (81.31)	158/191 (82.72)	0.79
Diabetes	58/112 (51.8)	42/86 (48.8)	0.77	57/117 (48.7)	38/74 (51.4)	0.7675	100/198 (50.51)	95/191 (49.74)	0.92
NYHA functional class IV	15/112 (13.4)	8/86 (9.3)	0.50	8/117 (6.8)	10/74 (13.50)	0.1350	23/198 (11.62)	18/191 (9.42)	0.51
QRS duration, ms	101.1 ± 13.8	103.6 ± 12.1	0.18	99 ± 14	103 ± 13	0.13	102 ± 13	101 ± 14	0.24
LVEF, % (core laboratory)	32 ± 4	33 ± 5	0.13	31 ± 4	33 ± 6	**0.012**	32 ± 5	32 ± 5	0.89
LVEDD, mm (core laboratory)	56 ± 11	60 ± 7	**0.003**	57 ± 10	58 ± 7	0.25	58 ± 9	58 ± 10	0.76
MLWHFQ	56 ± 24	57 ± 23	0.72	60 ± 23	56 ± 23	0.25	57 ± 23	59 ± 23	0.36
6MHW, m	324 ± 91	324 ± 90	0.97	326 ± 84	317 ± 88	0.48	324 ± 91	322 ± 86	0.08
CPX (core laboratory)									
Peak VO_2, ml/kg/min	14.8 ± 3.2	15.4 ± 2.8	0.20	14.6 ± 3.0	15.5 ± 2.6	**0.036**	15.0 ± 3.0	15.0 ± 2.9	0.73
Exercise time, min	11.7 ± 3.5	10.6 ± 3.1	**0.025**	11.3 ± 3.2	11.4 ± 3.1	0.77	11.2 ± 3.3	11.3 ± 3.1	0.74
Physical examination									
Weight, kg	96 ± 23	100 ± 23	0.23	92 ± 22	100 ± 21	**0.027**	98 ± 23	95 ± 22	0.20
Height, cm	173 ± 10	174 ± 9	0.44	173 ± 9	175 ± 102	0.24	174 ± 10	174 ± 9	0.98
BMI, kg/m^2	32 ± 7	33 ± 7	0.36	31 ± 7	32 ± 6	0.05	32 ± 7	31 ± 7	0.15
Resting HR, beats/min	73 ± 12	76 ± 14	0.09	71 ± 12	74 ± 11	**0.039**	75 ± 13	72 ± 12	0.07
Blood pressure									
Systolic	117 ± 18	126 ± 19	**0.0007**	119 ± 18	123 ± 18	0.12	121 ± 19	120 ± 18	0.71
Diastolic	71 ± 11	74 ± 11	**0.023**	70 ± 11	74 ± 11	0.058	72 ± 11	72 ± 11	0.65

Values are mean ± SD or n/N (%). **Bold** values indicate statistical significance. *p value from 2-sample Student's *t*-test or Fisher exact test as appropriate.

6MHW = 6-min hall walk test; BMI = body mass index; CHF = chronic heart failure; CPX = cardiopulmonary exercise stress test; HR = heart rate; ICD = implanted cardiac-defibrillator; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MLWHFQ = Minnesota Living With Heart Failure Questionnaire; NYHA = New York Heart Association; PT = pacing therapy.

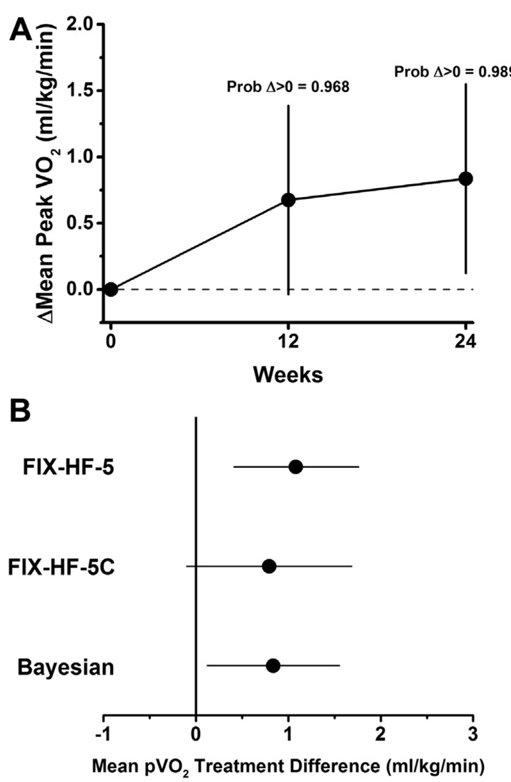
different, the quantitative differences were generally small and were not considered clinically significant. Overall, patients' average age was approximately 60 years, approximately 75% were male, 50% had prior myocardial infarction, 50% had diabetes, EF averaged 32%, pVO_2 was ~15 ml O_2/kg/min, MLWHFQ was 57 points, 6MHW distance was 325 m, and 90% were in NYHA functional class III. Patients were well medicated, as detailed in Online Table 3.

PRIMARY EFFICACY RESULT. A total of 160 patients contributed 442 pVO_2 observations across baseline and 12- and 24-week follow-up visits; follow-up values were available from 74 control and 68 CCM patients. The model-based estimated mean difference in pVO_2 at 24 weeks between CCM treatment and control groups was 0.836 ml O_2/kg/min (15.042 ml O_2/kg/min vs. 14.206 ml O_2/kg/min, respectively), with a 95% Bayesian credible interval of 0.123 to 1.552 ml O_2/kg/min, as summarized in **Figure 2A and** Online Table 4. The probability that CCM treatment is superior to control is 0.989, which exceeds the 0.975 criteria required for statistical significance of the primary endpoint.

Summarizing each trial separately (**Figure 2B**), the model-based estimated treatment differences at 24 weeks in the FIX-HF-5 and FIX-HF-5C studies are 1.08 ml O_2/kg/min (95% confidence interval [CI]: 0.41 to 1.76 ml O_2/kg/min) and 0.79 ml O_2/kg/min (95% CI: −0.10 to 1.68 ml O_2/kg/min), respectively.

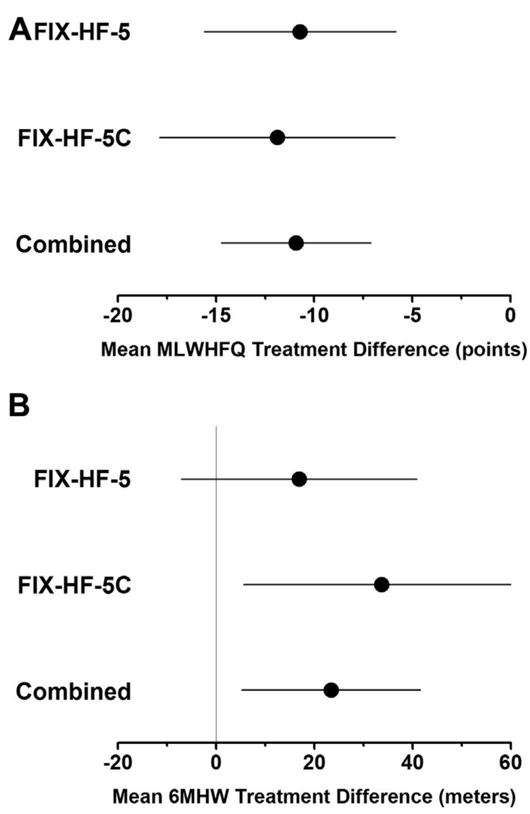
SENSITIVITY ANALYSES FOR PRIMARY EFFICACY ANALYSIS. Several sensitivity analyses were conducted to evaluate the robustness of the primary efficacy results. These included various methods of imputation for missing data (missing data due to death imputed as 0, imputed as the lowest pVO_2 at any visit, or no imputation), as well as an assessment of site-to-site heterogeneity of the treatment effect. The conclusion of CCM superiority with respect to mean pVO_2 was consistent across all sensitivity analyses (details not shown). In addition, it was noted that the primary analysis would achieve statistical significance with any borrowing weight of 0.11 or

FIGURE 2 Primary Efficacy Results



(A) Between group-differences in peak VO_2 over time. **(B)** 24-week between-group treatment effects in FIX-HF-5 subgroup alone, FIX-HF-5C alone, and Bayesian result.

FIGURE 3 Secondary Efficacy Results



Treatment effects at 24 weeks in FIX-HF-5, FIX-HF-5C separately and pooled for **(A)** Minnesota Living With Heart Failure questionnaire (MLWHFQ) and **(B)** 6-min hall walk (6MHW) test.

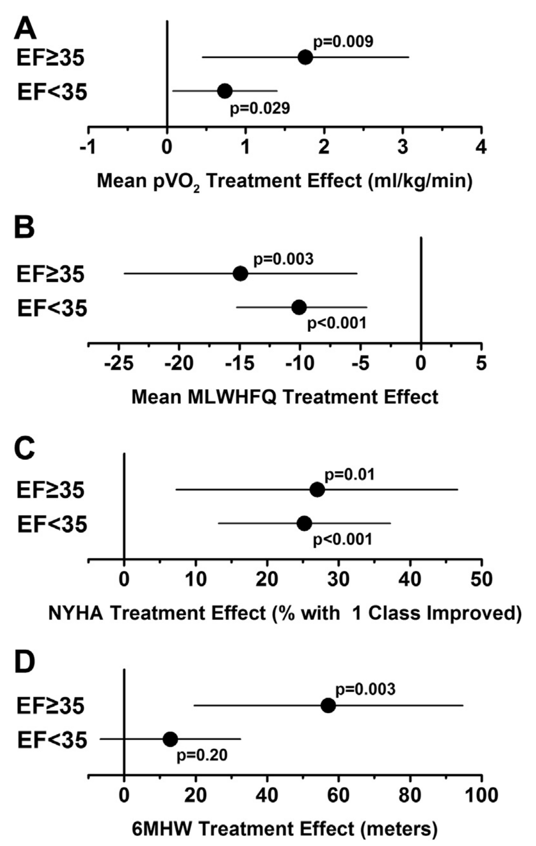
larger (as noted in the previous text, 0.30 was prespecified in the analysis plan).

SECONDARY EFFICACY RESULTS. MLWHFQ (Figure 3A): The model-based mean difference in MLWHFQ at 24 weeks between CCM treatment and control groups for the FIX-HF-5C cohort alone was −11.7 points (95% CI: −17.6 to −5.9 points), with a 1-sided p value <0.001, where a negative number indicates improvement according to this QoL instrument. Additional quantitative details are provided in Online Table 5.

NYHA functional class: At 24 weeks, 57 patients (81%) in the CCM treatment group experienced at least a 1-class NYHA improvement compared with 32 patients (42%) in the control group. The odds of improving by at least 1 NYHA functional class was 5.97 times the odds of improving among control patients (1-sided p value <0.001). Comparison of average changes in NYHA functional classes in the FIX-HF-5C, FIX-HF-5, and pooled data are summarized in Online Table 6.

TREATMENT EFFECTS IN LEFT VENTRICULAR EF <35% AND ≥35%. An original analysis of a small subgroup of the FIX-HF-5 study suggested particularly strong effects of CCM in patients with left ventricular EF ≥35% (12). From among the FIX-HF-5 and -5C studies, there were a total of 96 patients with EF ≥35%: 49 in the control group and 47 in the treatment group. By comparison, a total of 275 patients had EF <35%: 145 in the control group and 130 in the treatment group. A comparison of baseline characteristics broken down by EF group and treatment group is provided in Online Table 7; aside from EF, there were no significant differences between groups or between treatment groups. Treatment effects (i.e., the mean differences and 95% CIs of control and treatment groups) on the primary endpoint (pVO_2) and 2 secondary endpoints (MLWHFQ and NYHA functional class) in the 2 EF subgroups are summarized in Figure 4. As seen, better efficacy results were obtained in the CCM group in all cases.

FIGURE 4 Efficacy Results by EF Groups

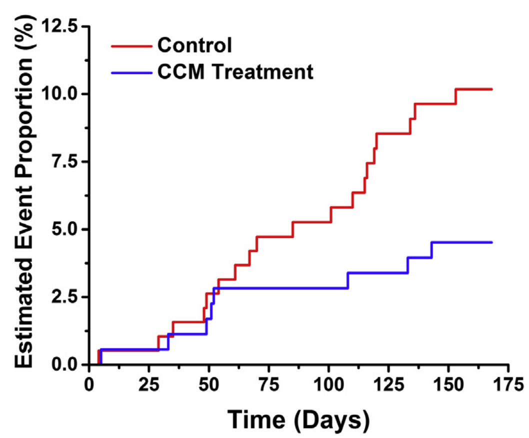


CCM treatment effects (difference between control and CCM groups and 95% confidence intervals) for patients with ejection fraction (EF) <35% versus EF ≥35% for **(A)** Peak VO_2, **(B)** Minnesota Living With Heart Failure questionnaire (MLWHFQ), **(C)** New York Heart Association (NYHA) functional class, and **(D)** 6-min hall walk test. CCM = cardiac contractility modulation; EF = ejection fraction.

Treatment effects in the EF ≥35% subgroup were 1.76 ml/kg/min (95% CI: 0.45 to 3.07 ml/kg/min) for pVO_2 ($p = 0.009$ vs. control) and −15 units (95% CI: −23 to −8 units) for MLWHFQ ($p = 0.003$ vs. control), and NYHA improved by ≥1 functional class in 71% (95% CI: 55% to 83%) of treatment patients compared with only 57% in the control group ($p = 0.012$ between groups). Thus, in all cases, improvements in each efficacy parameter were better in patients with EF ≥35%.

6-MIN HALL WALK TEST. In the FIX-HF-5C cohort, 6MHW in the control group increased by 9.3 ± 87.4 m compared with a 43.0 ± 80.7 m improvement in the treatment group ($p = 0.0093$). Treatment effects in the FIX-HF-5 subgroup cohort and for data pooled from the 2 studies are summarized in Figure 3B. 6MHW improved more in patients with EF ≥35% (Figure 4D). Additional quantitative details are provided in Online Table 8.

FIGURE 5 Heart Failure and Mortality Events



Comparison of estimated event proportions of the composite of cardiac death and heart failure hospitalizations between Control and Treatment; $p = 0.042$ by log-rank test and $p = 0.036$ when comparing 24 weeks using Greenwood's formula for the variance. Further details in Online Table 6. CCM = cardiac contractility modulation.

PRIMARY SAFETY RESULT. There were 7 Optimizer device-related or procedure-related safety endpoints among the 68 patients who underwent Optimizer device implantation. This corresponded to an 89.7% complication-free rate (95% CI: 79.9% to 95.8%), which achieved the primary safety endpoint. The safety/adverse events included 5 events of lead dislodgements, 1 deep vein thrombosis, and 1 generator erosion resulting in pocket stimulation that required pocket revision and replacement of pacemaker leads.

SECONDARY SAFETY RESULTS. There were 6 deaths during the study period: 4 in the Control group and 2 in the CCM group. One CCM patient death occurred 2 days before the scheduled implantation date (patient never received an implant), and the other occurred at 164 days after implantation and was due to sepsis following a cholecystectomy. The 4 deaths in the control group included 2 deaths due to cardiac pump failure (on days 4 and 36), 1 death following a VT ablation procedure (on day 70), and pulmonary complications of a noncardiac procedure (on day 117).

Overall survival in the FIX-HF-5C cohort through 24 weeks was high in both groups (98% in treatment and

95% in control; p = NS), and survival free of any hospitalization was the same (78% in both groups). However, despite the short follow-up and small sample size, there was a significant improvement in survival free of cardiac death and heart failure hospitalization (97.1% in treatment vs. 89.2% in control; p = 0.07 by log-rank test and p = 0.048 when comparing Kaplan-Meier estimates at exactly 24 weeks using Greenwood's formula for the variance), representing a 73% reduction in event rates (from 10.8% in the control to 2.9% in the treatment group). Furthermore, when data from FIX-HF-5 and -5C were pooled, freedom from cardiac death and heart failure hospitalization was similarly improved from 89.8% in the control and 95.5% in the treatment group (p = 0.042 by log-rank test and p = 0.036 when comparing Kaplan-Meier estimates at exactly 24 weeks using Greenwood's formula for the variance). Graphs showing the estimated event proportions are shown in **Figure 5** (additional details provided in Online Table 9). Finally, subgroup analysis showed that this improvement was mainly driven by a significant reduction in events for the EF 25% to 35% cohort (p = 0.009).

ADJUDICATED SERIOUS ADVERSE EVENTS. Serious adverse events as adjudicated by the Clinical Events Committee are summarized in Online Table 10. Overall, 19 control patients (22%) and 20 CCM-treatment patients (27%) experienced a serious adverse event. Seven control subjects (13%) versus 3 CCM treatment subjects (4%) had a worsening heart failure serious adverse event (p = 0.34). There were no significant differences in any category between the treatment groups.

DISCUSSION

The results of the present unblinded study confirm that CCM is safe and significantly improves exercise tolerance (pVO_2), quality of life (MLWHFQ score), and functional status (NYHA functional class) in patients with heart failure and EF ranging from 25% to 45%, QRS during <130 ms, normal sinus rhythm, and persistent NYHA functional class III or ambulatory IV symptoms despite guideline-recommended therapies. These observations are further supported by a between-group difference (improvement) in 6MHW distance in excess of 30 m favoring CCM treatment over control. The analysis of the primary efficacy endpoint employed a Bayesian approach to take advantage of results of a prior study (6) to show superiority of pVO_2 in the CCM group compared with the control group. Additional sensitivity analyses further confirmed the robustness of the findings, independent of other assumptions concerning the methods of Bayesian borrowing and imputation for deaths and missing data. Finally, a significant reduction in the composite of cardiac deaths and heart failure hospitalizations was observed.

An analysis of a small subset of the FIX-HF-5 study population (n = 38) suggested that CCM treatment effects were particularly large in patients with EF ≥35% (12). That finding was also further corroborated when data from an additional 59 patients from the FIX-HF-5C study were included in the analysis. This cohort is of interest because these patients do not have an indication for an ICD, so a standalone CCM device could be applicable.

In addition to the data of the present study, the safety of CCM has been consistently demonstrated in prior studies (4-6). In particular, the FIX-HF-5 study demonstrated that 1-year event-free survival was noninferior in the CCM group compared with the control group (6). Consistent across studies has been the finding that the rate and severity of overall adverse events is not significantly different than in the respective control group, despite the fact that the control group does not receive a device implant.

The magnitude of the treatment effect of CCM on pVO_2 is comparable to those identified in patients studied in prior studies of cardiac resynchronization therapy (CRT). These include MIRACLE (Multicenter InSync Randomized Clinical Evaluation) (0.9 ml/kg/min) (13), MIRACLE-ICD (Multicenter InSync ICD Randomized Clinical Evaluation) (1.0 ml/kg/min) (14), and CONTAC-CD study (0.8 ml/kg/min) (15). Although these studies have different entry criteria, they do provide a basis for comparing the effects of CCM to CRT.

The current study also identified a significant reduction of the composite of cardiovascular death and heart failure hospitalizations, which are important therapeutic targets for this therapy. Although the current study was too short in duration and included too few patients to fully address survival benefit, prior studies have provided evidence of beneficial effects on survival and hospitalization (16-20). In addition, an ongoing multicenter registry study is underway in Europe (CCM-REG) to further address this issue.

SERVING AN UNMET NEED. CRT has long been available for patients with EF ≤35%, normal sinus rhythm, QRS duration ≥130 ms, and persistent NYHA functional class III or ambulatory class IV symptoms despite guideline-directed medical therapies. However, HF patients who do not qualify for CRT represent a large group that experiences poor quality of life and poor exercise tolerance despite optimal medical therapies. Although ICDs are applicable to the broad population of patients with EF ≤35%, they do not deliver a therapy for improving exercise tolerance or quality of life. It is noteworthy that for patients with EF <35%, a device that combines CCM and ICD functions is under development. Similarly, indwelling pulmonary artery pressure sensors are also applicable and help optimize medical therapies but do not, on their own, provide a heart failure therapy. Thus, there is a relatively large cohort of heart failure patients who are failing medical therapy but do not have the benefit of a simply implanted device-based therapy. It is these patients that CCM is currently aiming to serve.

Thus, as noted in the preceding text, the Optimizer system was designated as an Expedited Access Pathway device by the FDA because the device potentially provides a treatment for an underserved population (9). In this case, the underserved population includes patients with heart failure who remain significantly symptomatic despite guideline-recommended treatment for heart failure, are not eligible for CRT, and are not symptomatic enough to justify implantation of a left ventricular assist device. The implication of this designation is that multiple efficacy endpoints, including pVO_2, exercise tolerance, quality of life, and other factors, are considered in their totality for approval. Safety data, such as mortality and hospitalizations, acquired in previously conducted trials (inside and outside of the United States) combined with data to be acquired in a post-approval registry study are used to fully establish the safety profile of the device.

STUDY LIMITATIONS. First, the limited follow-up duration of the current study limits the ability to evaluate the long-term effects of CCM on mortality and hospitalizations. Yet, even with the small sample size and short follow-up duration, the composite of cardiovascular death and heart failure hospitalizations was decreased.

Second, although a double-blinded trial design employing an implanted, nonactivated control group as used in some device trials (including the prior feasibility study of the Optimizer [5]) was initially considered, this was deemed unfeasible as detailed in the description of the original FIX-HF-5 study (10). Accordingly, given the unblinded nature of the study, several measures were taken to minimize placebo effect and investigator bias. Cardiopulmonary exercise tests were performed according to rigorous protocols with significant oversight of a core laboratory. Test results were read blinded, with specific criteria applied to exclude tests that were not performed properly and resulted in inadequate tests. Patients were required to perform 2 tests on separate days at each time point to ensure that maximal efforts were achieved.

CONCLUSIONS

The results of the present study supplement and confirm results of prior studies in showing that CCM is safe and improves exercise tolerance and quality of life in patients with EF ranging from 25% to 45%, QRS duration <130 ms, normal sinus rhythm, and persistent NYHA functional class III or ambulatory class IV symptoms despite guideline-recommended therapies, including medications and ICDs when indicated. The composite of cardiovascular death and heart failure hospitalizations was reduced. The clinical effects were observed across the range of EFs studied, and clinical effectiveness was even greater in patients with EFs between 35% and 45%.

ADDRESS FOR CORRESPONDENCE: Dr. William Abraham, Division of Cardiovascular Medicine, The Ohio State University, 473 West 12th Avenue, Room 110P DHLRI, Columbus, Ohio 43210-1252. E-mail: William.Abraham@osumc.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CCM delivered by the Optimizer system improves exercise tolerance and quality of life in heart failure patients with QRS duration <130 ms and left ventricular EF between 25% and 45%. The Optimizer device is available in countries that recognize the CE Mark and in China, India, Brazil, and Australia. The present results will be submitted to the FDA to support a pre-market approval submission. If approved, this would provide a therapy for a large group of patients in the United States. In the patients with EF <35%, CCM can be integrated into a device with an ICD; for patients with EF ≥35%, CCM can be used without an ICD.

TRANSLATIONAL OUTLOOK: Future research is needed to explore the impact of CCM on mortality in the current target population. In addition, because CCM works via a mechanism completely different than cardiac resynchronization (CRT), future research can explore the impact of CCM in patients with prolonged QRS duration in addition to CRT, in particular in CRT nonresponders.

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KEY WORDS heart failure, exercise tolerance, peak VO_2, QRS duration, quality of life

APPENDIX For additional study information as well as a supplemental figure and tables, please see the online version of this paper.