Circulation: Heart Failure

ORIGINAL ARTICLE

Safety, Performance, and Efficacy of Cardiac Contractility Modulation Delivered by the 2-Lead Optimizer Smart System

The FIX-HF-5C2 Study

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BACKGROUND: Prior studies of cardiac contractility modulation (CCM) employed a 3-lead Optimizer system. A new 2-lead system eliminated the need for an atrial lead. This study tested the safety and effectiveness of this 2-lead system compared with the 3-lead system.

METHODS: Patients with New York Heart Association III/IVa symptoms despite medical therapy, left ventricular ejection fraction 25% to 45%, and not eligible for cardiac resynchronization therapy could participate. All subjects received an Optimizer 2-lead implant. The primary end point was the estimated difference in the change of peak VO_2 from baseline to 24 weeks between FIX-HF-5C2 (2-lead system) subjects relative to control subjects from the prior FIX-HF-5C (3-lead system) study. Changes in New York Heart Association were a secondary end point. The primary safety end point was a comparison of device-related adverse events between FIX-HF-5C2 and FIX-HF-5C subjects.

RESULTS: Sixty subjects, 88% male, 66±9 years old with left ventricular ejection fraction 34±6% were included. Baseline characteristics were similar between FIX-HF-5C and FIX-HF-5C2 subjects except that 15% of FIX-HF-5C2 subjects had permanent atrial fibrillation versus 0% in FIX-HF-5C. CCM delivery did not differ significantly between 2- and 3-lead systems (19 892±3472 versus 19 583±4998 CCM signals/day, CI of difference [−1228 to 1847]). The change of peak VO_2 from baseline to 24 weeks was 1.72 (95% Bayesian credible interval, 1.02–2.42) mL/kg per minute greater in the 2-lead device group versus controls. 83.1% of 2-lead subjects compared with 42.7% of controls experienced ≥1 class New York Heart Association improvement ($P<0.001$). There were decreased Optimizer-related adverse events with the 2-lead system compared with the 3-lead system (0% versus 8%; $P=0.03$).

CONCLUSIONS: The 2-lead system effectively delivers comparable amount of CCM signals (including in subjects with atrial fibrillation) as the 3-lead system, is equally safe and improves peak VO_2 and New York Heart Association. Device-related adverse effects are less with the 2-lead system.

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Key Words: atrial fibrillation ■ cardiomyopathies ■ genotype ■ heart failure ■ quality of life

Cardiac contractility modulation (CCM) is an electrical device–based therapy developed for the treatment of chronic heart failure.[1,2] CCM signals are nonexcitatory electrical signals applied during the cardiac absolute refractory period. Although the fundamental mechanisms of action remain to be clarified, these signals have been shown to have myocardial effects within minutes to hours in the region near the simulation electrodes; these effects include phosphorylation of key proteins involved with calcium cycling and contractile proteins and shifts of myocardial gene expression from a fetal genotype typical of chronic heart failure to a more normal adult genotype. Over time (weeks to months), these effects are evident in regions remote from the stimulation site.

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WHAT IS NEW?

- Cardiac contractility modulation (also known as CCM), a therapy that was recently approved by the US FDA, was previously delivered by an implanted pulse generator that employed 3 standard leads: 1 placed in the right atrium (RA) and 2 placed in the right ventricular (RV) septum.
- A new-generation, 2-lead system eliminated the RA lead. The results of the current study show that the new system performed as expected (ie, delivered the desired number of CCM pulses) and that patients experienced the same or even greater clinical effects than were noted in the prior FIX-HF-5C study while the number of device-related complications was reduced.

WHAT ARE THE CLINICAL IMPLICATIONS?

- There are 2 important clinical implications of reducing the number of leads required to deliver CCM from 3 to 2: first, lead-related adverse events were observed to be significantly decreased; second, the original 3-lead system relied on detection of a *P*-wave for proper timing of CCM signal delivery; this requirement was eliminated in the 2-lead system.
- Accordingly, the 2-lead system allows for CCM therapy to be delivered in patients with atrial fibrillation.

Nonstandard Abbreviations and Acronyms

BCI	Bayesian credible interval
CPX	Cardiopulmonary stress testing
NT-proBNP	N-terminal-pro hormone B-type natriuretic peptide
NYHA	New York Heart Association

CCM has been studied in several randomized studies, including a double blind, double crossover study in Europe (the FIX-HF-4 study),[3] a blinded randomized pilot study in the United States,[4] a prospective randomized study in the United States including 428 subjects (the FIX-HF-5 trial),[5,6] and a second prospective randomized study in the United States and EU that included 160 subjects (the FIX-HF-5C study).[7] Collectively, the results of these prior randomized studies indicated that CCM improves functional class, quality of life, and exercise tolerance, particularly in patients with left ventricular ejection fraction (LVEF) between 25% and 45%, New York Heart Association (NYHA) III symptoms despite guideline-directed medical therapy (and an implantable cardioverter defibrillator if indicated), normal QRS duration (ie, not indicated for cardiac resynchronization therapy), and sinus rhythm. Based on these findings, the Optimizer system received approval for use in this patient population by the US Food and Drug Administration. Additional information from registry studies have suggested that LVEF is improved by ≈5 percentage points[8–10] that clinical effects are sustained through 2 years of follow-up[10,11] and that CCM therapy is associated with reduced rates of heart failure hospitalizations compared with the number of hospitalizations observed the year before Optimizer system implant.[10–12]

All of the aforementioned studies were performed with an Optimizer device that employs 3 leads placed in the heart: 1 to the right atrium and 2 to the right ventricular septum. While the right ventricular septal leads are used for both sensing and CCM signal delivery, the atrial lead is used only for sensing the timing of atrial depolarization. That information was used as input to an algorithm that ensured proper timing of CCM signal delivery during the myocardial absolute refractory period, including suppression of CCM delivery on premature ventricular contractions. This requirement imposed a technical limitation for the use of CCM in patients with atrial fibrillation or flutter which is overcome in the 2-lead system. The CCM signals delivered by the 2- and 3-lead Optimizer systems are identical. In addition, as with cardiac rhythm devices in general, device-related adverse events have mainly been related to the leads (see for example[13]) so that reduction of the number of leads has the potential to reduce adverse events.

In view of these considerations, a new CCM delivery algorithm has been developed that eliminates the need for an atrial sensing lead, which has led to the development of a 2-lead Optimizer device. The FIX-HF-5C2 study was a prospective, multicenter, single-arm study designed to test the performance, safety, and clinical effects of this 2-lead Optimizer Smart System.

METHODS

The methods used in this study are described in full herein, and the materials used (ie, Optimizer systems) are available for use on a clinical basis in the United States, in countries which accept the Conformité Européene mark, in India, Australia, China, Brazil, Russia, and Saudi Arabia. The raw data used in the analysis of this research will not be made available. The FIX-HF-5C2 study was approved by the IRB or ethics committee at each participating center and all subjects gave informed consent to participate.

Sixty subjects were enrolled from 7 medical centers in the United States and 1 medical center in Germany. Subjects were evaluated at baseline and again at 12 and 24 weeks after implant. The inclusion and exclusion criteria are summarized in Table 1. Major criteria included: adult subjects with LVEF ≥25% and ≤45% by echocardiography (assessed by core laboratory); NYHA III or ambulatory IV symptoms despite 90 days of guideline-directed heart failure medical therapy (including implantable cardioverter defibrillator when indicated) that was stable for 30 days before enrollment; and, not indicated for cardiac resynchronization therapy. Patients were excluded if they were hospitalized for heart

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
Age 18 y or older.
Male or a nonpregnant female.
Baseline ejection fraction ≥25% and ≤45% by echocardiography core laboratory.
NYHA III or IV despite guideline-directed medical therapy for heart failure for at least 90 d (including treatment with a β-blocker for at least 90 d unless intolerant).
Medical therapy is stable defined as no more than a 100% increase or 50% decrease in dose during the 30 d before enrollment.
ICD if indicated
Willing and able to return for all follow-up visits.
Exclusion criteria
Peak VO_2 <9 or >20 mL O_2/min per kg. The qualifying CPX test must be deemed adequate.
Subjects who have a potentially correctible cause of heart failure (eg, valvular or congenital heart disease).
Clinically significant angina pectoris, an episode of unstable angina within 30 d, or angina and/or ECG changes during exercise testing performed during baseline evaluation.
Hospitalized for heart failure requiring acute treatment with intravenous loop diuretics, IV inotropes, or hemofiltration within 30 d, or receiving any form of positive inotropic support within 30 d before enrollment, including continuous IV inotrope therapy.
Exercise tolerance is limited by a condition other than heart failure or unable to perform baseline stress testing.
Scheduled for CABG or PCI or has undergone a CABG within 90 d or PCI within 30 d.
Biventricular pacing system, an accepted indication for such a device, or a QRS width of 130 ms or greater.
Myocardial infarction within 90 d.
Mechanical tricuspid valve.
Prior heart transplant.
Chronic hemodialysis.
Participating in another experimental protocol.
Unable to provide informed consent.

CABG, indicates coronary artery bypass grafting; CPX, cardiopulmonary stress testing; ICD, implantable cardioverter defibrillator; and NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and QRS, QRS duration on electrocardiogram.

failure requiring intravenous loop diuretics, inotropes, or hemofiltration within 30 days; if they were receiving any form of positive inotropic support within 30 days before enrollment; if peak VO_2 on cardiopulmonary stress testing (CPX) was <9 or >20 mL O_2/minute per kg (assessed by core laboratory); if they had a potentially correctible cause of heart failure (eg, valvular or congenital heart disease); if exercise tolerance was limited by a condition other than heart failure; or if they were schedule for or had recent CABG, PCI, or MI. Notably, in comparison to all prior studies in the United States, patients with atrial fibrillation could be enrolled.

The schedule of events is summarized in Table 2. Following eligibility determination, subjects underwent implantation of a 2-lead Optimizer Smart System. After device programming, subjects were generally discharged from the hospital the same day or the day following implantation. Subjects returned for routine wound and device checks (when CCM signal parameters were checked and optimized) after ≈2 weeks. Study follow-up visits for clinical assessments were conducted at 12 and 24 weeks (±2 weeks) following device implantation. In addition to an interim safety assessment, NYHA was determined by a site clinician and CPX tests were repeated at these visits.

The design of the FIX-HF-5C2 trial, including end points and statistical methods, was developed in collaboration with the US Food and Drug Administration. This study was registered on www.clinicaltrials.gov (unique identifier: NCT03339310).

Study End Points

The primary effectiveness end point was an assessment of improvement from baseline in exercise tolerance at 24 weeks as measured by peak VO_2 obtained on CPX. CPX data were evaluated by an independent core laboratory. Changes in peak VO_2 from baseline to 24-week follow-up in subjects implanted with the 2-lead system were compared (using Bayesian statistics as detailed below) to the changes observed in control group subjects of the prior FIX-HF-5C study.

Performance of the 2-lead Optimizer system was based on an assessment of the average daily amount of CCM signals delivered between the 2-week visit (for device check and parameter optimization) to the end of the 24-week study period. The device has an internal counter which, among other things, keeps track of the total number of CCM signals delivered, and this information is readily available from device interrogation using the system programmer. The performance was specifically assessed through a comparison between the number of CCM signals delivered by the 2-lead device and the number of signals delivered in subjects implanted with the 3-lead system over a 24-week period in the prior FIX-HF-5C study. Additional efficacy end points included assessment of New York Heart Association functional class and NT-proBNP (N-terminal-pro hormone B-type natriuretic peptide).

The primary safety end point was the percentage of subjects experiencing an Optimizer device- or procedure-related complication through the 24-week follow-up period. Complications were adjudicated by an independent events adjudication committee. The Events Adjudication Committee reviewed, adjudicated, classified, and validated all reported serious adverse events that occurred over the 24-week course of study. The classifications included whether the event was related to either the device or to the implant procedure, and whether such an event constituted a complication as defined by the Events Adjudication Committee charter. The committee also adjudicated the cardiac and heart failure relatedness of deaths and hospitalizations.

All-cause mortality and the composite of cardiovascular mortality and heart failure hospitalizations constituted additional safety end points.

Cardiopulmonary Stress Testing Procedures

As in the prior FIX-HF-5C study, rigorous quality measures and procedures were used during the conduct of CPX tests to optimize test quality and assure maximal effort was attained by each subject. All tests were reviewed by the same core laboratory employed in the prior FIX-HF-5 and FIX-HF-5C studies. Specific quality measures included the following: (1) on-site training on standardized procedures for conducting CPX testing; (2) normal subject validation testing and revalidation every 6 months; (3) providing the subject with instructions on how to

Table 2. Study Schedule of Events

Tests and Assessments	Screening/Baseline	Optimizer Implant	Week 2±7 d	12±2 wk	24±2 wk	1 y±1 mo	Every 6 mo*
Informed consent	X						
Interim history	X		X	X	X	X	X
NYHA class (site clinician assessment)	X			X	X		
Medications	X			X	X		
Physical examination	X			X	X		
12-lead EKG†	X						
NT-proBNP	X			X	X		
Echocardiogram†	X						
Cardiopulmonary stress test	X			X	X		
Pregnancy test	X						
Eligibility determination	X						
Optimizer Smart System Implant		X					
Chest X-ray (before hospital discharge)		X					
Optimizer Device Interrogation		X	X	X	X	X	X
Safety reporting		X	X	X	X	X	X

NT-proBNP indicates N-terminal-pro hormone B-type natriuretic peptide; and NYHA, New York Heart Association.

*Visits shall continue every 6 mo until the premarket approval order has been issued by the Food and Drug Administration, for device interrogation and reporting of Optimizer device–related serious adverse events, if any.

†12-lead EKG and echocardiogram test results (from the study-qualified laboratory) obtained within 30 d before informed consent and performed in accordance with the protocol, testing, and data collection requirements may be used for eligibility determination and baseline testing.

prepare for the CPX test; and (4) rapid feedback on quality of every test from the core laboratory and retest requests for inadequate tests. Tests were deemed inadequate if: (1) the subject had an erratic or oscillatory breathing pattern; (2) the data were nonphysiological; (3) an issue was identified with the testing equipment; or (4) the test was submaximal, meaning it was terminated by either the subject or the supervising clinician/technician before the subject reaching volitional exhaustion. Reasons for early termination could include nonheart failure symptoms (eg, angina, heart rhythm disturbance, or leg, foot, or back pain) or the subject was technically challenged to perform the test.

Metabolic data were collected for 2 minutes before the start of exercise to confirm respiratory exchange ratio, VO_2, and the subject's ventilation volume were at normal, physiological, and stable resting values before beginning the test. Metabolic data were then collected for the duration of the test and for an additional 2-minute recovery period following termination of the test. Peak VO_2 and peak respiratory exchange ratio were determined by the core laboratory from 20 second averaged gas exchange data from the start of exercise to the end of exercise. Tests were deemed to be of maximal effort if respiratory exchange ratio reached 1.05 or greater.

Statistics

The main purpose of the present study was to determine, relative to the 3-lead Optimizer system that recently received approval by the US Food and Drug Administration, whether the 2-lead Optimizer Smart system performs similarly with regard to the amount of CCM delivered, whether the device is equally safe in terms of device- and procedure-related complications (primary safety end point), and whether the device provides similar clinical benefits in terms of improvements in exercise tolerance (primary efficacy end point) and functional class (secondary efficacy end point). The current study is a single arm, treatment only study. Accordingly, results from the present study were compared with data from the prior FIX-HF-5C control and treatment patients in which the 3-lead Optimizer system was used.

Baseline demographic data were summarized using descriptive statistics. Demographic data from the prior FIX-HF-5C study are also summarized here and compared with those of patients enrolled in the present study. Continuous data were compared using the 2-sample *t*-test, and categorical data were compared using Fisher Exact test.

Efficacy: Peak VO_2

Analogous to the FIX-HF-5C primary efficacy analysis plan (and with US Food and Drug Administration collaboration), the FIX-HF-5C2 primary efficacy analysis plan used a Bayesian repeated measures model to estimate group differences in the change in mean peak VO_2 at 24 weeks from baseline in FIX-HF-5C2 2-lead Optimizer subjects compared with FIX-HF-5C control subjects, with 30% borrowing of information (70% down-weighting) from the corresponding treatment group difference observed in the FIX-HF-5 subgroup data. The 30% borrowing was based on power-prior methodology of Ibrahim and Chen.[14]

Efficacy: NYHA

Changes from baseline of at least one category in NYHA class were assessed and compared between groups via Fisher Exact test. Shift tables for NYHA class in the FIX-HF-5C2 study were analyzed using the extended McNemar test for paired data and >2 groups and were compared between groups via the Cochran-Mantel-Haenszel test.

Device Performance

Device performance was assessed via an evaluation of the average daily number of CCM signals delivered through the 24-week study follow-up period. The device was considered to perform as intended if the number of CCM signals delivered did not differ significantly from the number of CCM signals delivered by the 3-lead system during the 24-week period of the FIX-HF-5C study. Bioequivalence was assessed by the 2-sided $100(1-2\alpha)\%$ CI, for the difference in the anticipated mean values of the FIX-HF-5C2 and FIX-HF-5C total CCM delivery, $\mu_{5C2}-\mu_{5C}$. The lower and upper bounds of bioequivalence were established by θ_L and θ_U, where $\theta_L<0<\theta_U$ and defined as $\theta_L=-0.125\mu_{5C}$ and $\theta_U=0.125\mu_{5C}$. According to Schuirmann,[15] bioequivalence could be conceded if the 2-sided $100(1-2\alpha)\%$ CI, for the difference $\mu_{5C2}-\mu_{5C}$, was completely contained within the interval (θ_L, θ_U). Based on the estimated mean in the FIX-HF-5C study, the lower and upper bounds for bioequivalence was (−2448, 2448) CCM signals/day, which was calculated from the estimated mean daily rate of CCM delivery observed in the 5C study (19 583) as −125× the estimated mean and +125× the estimated mean (ie, 19 583×0.125=±2448).

Safety

The primary safety analysis evaluated the procedure- or device-related complication rates through 24 weeks of follow-up. An exact binomial 95% CI for the complication free proportion was generated. These rates were compared with those observed in the FIX-HF-5C study via Fisher Exact test.

Assessment of all-cause mortality and the composite of cardiovascular mortality and heart failure hospitalizations were explored via Kaplan-Meier analyses. Results were compared with those of the FIX-HF-5C control group via the log-rank test.

Sample Size Justification

Sixty subjects were enrolled in the FIX-HF-5C2 study. Simulations were used to quantify power and Type I error of the primary efficacy analysis under a variety of assumptions and magnitude of treatment effects, in which data were prospectively simulated for both FIX-HF-5C control and FIX-HF-5C2 device patients. For instance, assuming the variance of change in peak VO_2 in the FIX-HF-5C2 and FIX-HF-5C populations was equivalent to the estimated variance in the FIX-HF-5 trial, the study had ≈80% power to detect a mean difference in peak VO_2 of 0.65 mL/kg per minute. The type I error was estimated to be ≈0.10 or less, which was deemed acceptable for the FIX-HF-5C2 trial by the US regulatory authorities.

RESULTS

Subject disposition is summarized in Table 3. One hundred fifty-three subjects were screened at 8 sites. Of these, 60 subjects qualified, were enrolled, and were implanted with the 2-lead Optimizer system. One subject withdrew from the study before 24 weeks due to incarceration. There were no deaths during the 24-week study period and all remaining 59 subjects completed the final follow-up visits, including assessments of CCM delivery and NYHA functional class. Of these, 55 subjects (91.7%) completed the 24-week CPX test. Reasons for the 4 missing tests were intervening knee replacement, knee injury, lung tumor, and pulmonary embolism (one each). In addition, four 24-week CPX tests were deemed inadequate by the core laboratory for which the patients declined requests to repeat testing, resulting in 52 tests for the primary end point analysis. However, to ensure robustness of findings, an additional analysis was performed that included these inadequate tests.

Table 3. Subject Disposition

Variable	FIX-HF-5C2 Optimizer
Screened	153
Enrolled/implanted	60 (39.2%)
Died*	0 (0.0%)
Withdrawn*	1 (1.7%)
12-wk visit completed	59 (98.3%)
12-wk exercise tolerance test completed	53 (88.3%)
12-wk exercise tolerance test evaluable†	52 (86.7%)
24-wk visit completed	59 (98.3%)
24-wk exercise tolerance test completed	55 (91.7%)
24-wk exercise tolerance test evaluable†	52 (86.7%)

*Before 24-wk visit.

†Includes only subjects with valid peak VO_2, as determined by the core laboratory, at the indicated visit.

Baseline Characteristics

Baseline characteristics of FIX-HF-5C2 subjects are summarized in Table 4 along with baseline characteristics of the FIX-HF-5C study groups. As detailed above, results from the prior FIX-HF-5C study are used as basis for assessment of the 2-lead Optimizer system performance (compared with FIX-HF-5C Optimizer group) and clinical effects (compared with FIX-HF-5C control group). Consistent with one goal of implementing the 2-lead system, 15% of FIX-HF-5C2 subjects had permanent atrial fibrillation compared with 0% in the prior study ($P<0.0005$). In addition, FIX-HF-5C2 subjects tended to be older (66.3±8.9 versus 62.8±11.4; $P=0.049$), had a lower prevalence of diabetes mellitus (30% versus 48.8%; $P=0.027$), and had a lower LV end-diastolic dimension (57.7±6.8 versus 60.2±7.0; $P=0.040$) than subjects in the FIX-HF-5C control group; left ventricular ejection fraction, however, did not differ between groups (34.1±6.1% versus 32.5±5.2%). Baseline peak VO_2 was similar between the 2 groups, but the FIX-HF-5C2 subjects exercised longer than the FIX-HF-5C control group subjects (11.6±2.9 versus 10.6±3.1 minutes; $P=0.044$). All other baseline characteristics were similar between the groups. NT-proBNP (N-terminal-pro hormone B-type natriuretic peptide; which was not recorded in the prior FIX-HF-5C study) was only minimally elevated at baseline (median [IQR]: 511 [219–867] pg/mL) and did not change significantly during the study period (median [IQR] value at 24 weeks: 524 [245–1182] pg/mL). Comparison of baseline characteristics between

Table 4. Baseline Characteristics of the FIX-HF-5C2 Population vs Those of the FIX-HF-5C Study

	FIX-HF-5C2	FIX-HF-5C			
Variable	Optimizer	Optimizer	*P* Value*	Control	*P* Value*
Age, y	66.3±8.9 (60)	63.1±10.9 (74)	0.071	62.8±11.4 (86)	0.049
Male	53 (88.3%)	54 (73.0%)	0.032	68 (79.1%)	0.182
Ethnicity (white)	40 (66.7%)	55 (74.3%)	0.346	61 (70.9%)	0.590
BMI, kg/m^2	31.4±6.1 (60)	32.5±5.6 (74)	0.267	32.9±6.9 (86)	0.167
Resting HR, bpm	72.9±14.4 (60)	72.1±10.9 (74)	0.720	74.3±13.4 (86)	0.525
Systolic blood pressure, mm Hg	121.8±14.6 (60)	122.7±17.7 (74)	0.767	126.0±18.8 (86)	0.147
Diastolic blood pressure, mm Hg	74.0±9.2 (60)	73.5±11.4 (74)	0.781	74.2±10.8 (86)	0.940
CHF etiology, ischemic	41 (68.3%)	46 (62.2%)	0.473	51 (59.3%)	0.299
Prior MI	36 (60.0%)	36 (48.6%)	0.224	51 (59.3%)	1.000
Prior CABG	13 (21.7%)	18 (24.3%)	0.837	23 (26.7%)	0.560
Prior ICD or PM system	55 (91.7%)	67 (94.4%)	0.731	73 (85.9%)	0.432
Prior ICD (ICD, CRT-D, S-ICD)	53 (88.3%)	66 (93.0%)	0.382	73 (85.9%)	0.804
Prior PM	2 (3.3%)	1 (1.4%)	0.593	0 (0.0%)	0.170
Diabetes mellitus	18 (30.0%)	38 (51.4%)	0.014	42 (48.8%)	0.027
Permanent atrial fibrillation	9 (15.0%)	0 (0%)	0.0005	0 (0%)	0.0002
NYHA					
Class III	59 (98.3%)	64 (86.5%)	0.023	78 (90.7%)	0.082
Class IV	1 (1.7%)	10 (13.5%)	0.023	8 (9.3%)	0.082
QRS duration, ms	101.2±12.3 (60)	102.5±12.6 (74)	0.555	103.6±12.1 (86)	0.244
LVEF (%; core laboratory)	34.1±6.1 (60)	33.1±5.5 (74)	0.329	32.5±5.2 (86)	0.107
LVEDD, mm (core laboratory)	57.7±6.8 (57)	58.5±7.2 (74)	0.543	60.2±7.0 (82)	0.040
Baseline peak VO_2, mL/kg per min	15.0±2.9 (60)	15.5±2.6 (73)	0.317	15.4±2.8 (86)	0.462
Baseline RER	1.15±0.06 (60)	1.15±0.06 (73)	0.891	1.14±0.07 (86)	0.500
Baseline exercise time, min	11.6±2.9 (60)	11.4±3.1 (73)	0.662	10.6±3.1 (86)	0.044

BMI indicates body mass index; CABG, coronary artery bypass grafting; CHF, chronic heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; QRS, QRS duration on electrocardiogram; and RER, respiratory exchange ratio.

*Compared with FIX-HF-5C2 Optimizer Group via Fisher exact test for binary variables and 2-sample *t*-test for continuous variables.

the FIX-HF-5C2 population and the entire FIX-HF-5C cohort is provided in Table I in the Data Supplement; no additional differences between baseline studies were identified beyond those noted above.

FIX-HF-5C2 subjects were receiving guideline-recommended medical therapy (Table II in the Data Supplement) that were similar to the FIX-HF-5C subjects except for greater use of combined angiotensin receptor/neprilysin inhibitor and antiarrhythmic agents (mainly amiodarone); increased angiotensin receptor/neprilysin inhibitor use is due to the later start date of the study, while antiarrhythmic use was due to the higher prevalence of atrial fibrillation.

The study protocol stipulated that medical therapy was to remain constant unless mandated by clinical care considerations. The numbers of medication adjustments between baseline and 24 weeks are detailed in Table III in the Data Supplement. For each drug class, the number of instances of dose increases was reasonably well balanced by the number of dose decreases; for this analysis, any increase or decrease of dose was counted. There were 2 cases where angiotensin receptor blockers were switched to sacubitril/valsartan and one case of an opposite switch.

Device Performance

The average daily number of CCM signals delivered during the 24-week study period is summarized in Table 5. The devices are programmed to deliver CCM therapy 5 hours per day, delivered evenly across each 24-hour period. Assuming an average heart rate of 72 bpm (from Table 4), the expected daily number of beats eligible for CCM signal delivery is 21 600. As summarized in Table 5, the average daily number of beats was just under 20 000 (95% of predicted), and this did not differ significantly between the FIX-HF-5C (3-lead system) and FIX-HF-5C2 (2-lead system) studies. Based on formal statistical testing detailed in the Methods, the average daily amount of CCM delivery through 24 weeks is equivalent between the 2-lead (FIX-HF-5C2 study) and 3-lead (FIX-HF-5C study) Optimizer systems since the 95% CI of the difference between the 2 groups lies wholly within the interval Θ_L, Θ_U (ie, −2448, 2448). Also, importantly, as detailed in Table 5, the amount

Table 5. Number of CCM Signals Delivered in 24 Weeks; Comparison Between 2- and 3-Lead Systems, With and Without Permanent Atrial Fibrillation

CCM Signal Delivery	FIX-HF-5C2			FIX-HF-5C	
	All (n=59)	NSR (n=50)	Atrial Fibrillation (n=9)	NSR (n=67)	Difference*
Mean±SD	19892±3472	19921±3377	19734±4187	19583±4998	310±4352
(Min, max)	(11618, 28284)	(11618, 28284)	(12787, 24578)	(3645, 31009)	
(95% CI)	(18988 to 20797)	(18961 to 20881)	(16515 to 22952)	(18364 to 20802)	(−1228 to 1847)

CCM indicates cardiac contractility modulation; and NSR, normal sinus rhythm. *Difference between all patients of FIX-HF-5C2 and CCM-treated patients of FIX-HF-5C.

of CCM signal delivery did not differ significantly between subjects with or without permanent atrial fibrillation.

Peak VO_2

Baseline peak VO_2 was similar between FIX-HF-5C2 2-lead Optimizer patients and FIX-HF-5C control patients at baseline (Figure 1A, showing mean±SD values at each timepoint). As detailed above, follow-up results for the primary analysis were available from 52 of these subjects. Peak VO_2 increased progressively over time in the 2-lead Optimizer group (by 1.13 mL/kg per minute from baseline to 24 weeks) but declined in the FIX-HF-5C control group (by 1.18 mL/kg per minute from baseline to 24 weeks). The primary end point, a Bayesian analysis of the difference between groups (Figure 1B) was 1.08 (95% Bayesian credible interval [BCI]: 0.38–1.78) mL/kg per minute at 12 weeks and this increased to 1.72 (95% BCI, 1.02–2.42) mL/kg per minute by 24 weeks, both of which were highly statistically significant (Bayesian posterior probability of superiority equals 1.00, exceeding the threshold of 0.975 required to demonstrate superiority). Additional details concerning the Bayesian prior distribution, the observed data, and the Bayesian posterior distribution combining the prior and the observed data are provided in Figure I in the Data Supplement and accompanying figure legend. Thus, based on the prespecified primary efficacy end point, exercise tolerance improved in response to CCM treatment provided by the 2-lead Optimizer system relative to FIX-HF-5C control patients.

Several supplemental sensitivity analyses were performed to test the robustness of the findings. First, a sensitivity analysis was conducted for the primary analysis that included a Bayesian analysis with covariate adjustment for heart failure etiology and baseline ejection fraction. In all cases, the posterior probability for superiority of the 2-lead Optimizer system versus FIX-HF-5C control patients was 1.00, exceeding the threshold of 0.975 required to demonstrate superiority. Second, a supporting non-Bayesian (frequentist) estimate of benefit without 30% borrowing from FIX-HF-5 data was comparable (2.21 mL/kg per minute) with a *P* value <0.001, indicating that borrowing was not necessary to achieve statistical significance with respect to the primary efficacy end point. Third, upon inclusion of the 4 inadequate CPX tests, the frequentist estimate of the benefit was 2.09 mL/kg per minute ($P<0.001$). Finally, an assessment of treatment effects at 12 and 24 weeks based on frequentist mixed modeling was performed to assesses the impact of baseline characteristics that differed (at $P<0.1$) between control and FIX-HF-5C2 treatment patients noted above. This analysis, detailed in Table IV in the Data Supplement, showed that DM had a statistically significant but small effect on the treatment results.

An additional analysis showed that respiratory exchange ratios (index of subject effort) were similar between 2-lead Optimizer and FIX-HF-5C control subjects both at baseline (1.15±0.06 versus 1.14±0.07; $P=0.50$) and at 24 weeks (1.16±0.04 versus 1.16±0.07; $P=0.96$). Finally, the duration of exercise increased from baseline to 24 weeks by 1.31±2.08 minutes in CCM-treated subjects with the 2-lead Optimizer system, compared with a 0.60±2.31 minute in FIX-HF-5C control subjects.

NYHA

NYHA improved by at least 1 functional class in 83.1% of subjects treated with the 2-lead Optimizer system at 24 weeks compared with only 42.7% in the FIX-HF-5C control group ($P<0.001$; Figure 2). A greater proportion of patients in the control group showed no change in NYHA (56% versus 17%). Finally, NYHA worsened in 1% of control patients versus 0% of treatment patients. Thus, overall, there was a greater shift toward lower NYHA in the 2-lead Optimizer group than in the FIX-HF-5C control group ($P<0.001$).

Primary Safety End Point Analysis

The primary safety end point was the composite of the percentage of subjects in the 2-lead Optimizer group who experienced an Optimizer device- or procedure-related complication through the 24-week follow-up period as determined by the Events Adjudication Committee. There was only 1 complication observed which was a hematoma at the Optimizer implant site requiring the patient to remain in the hospital overnight for observation. The hematoma

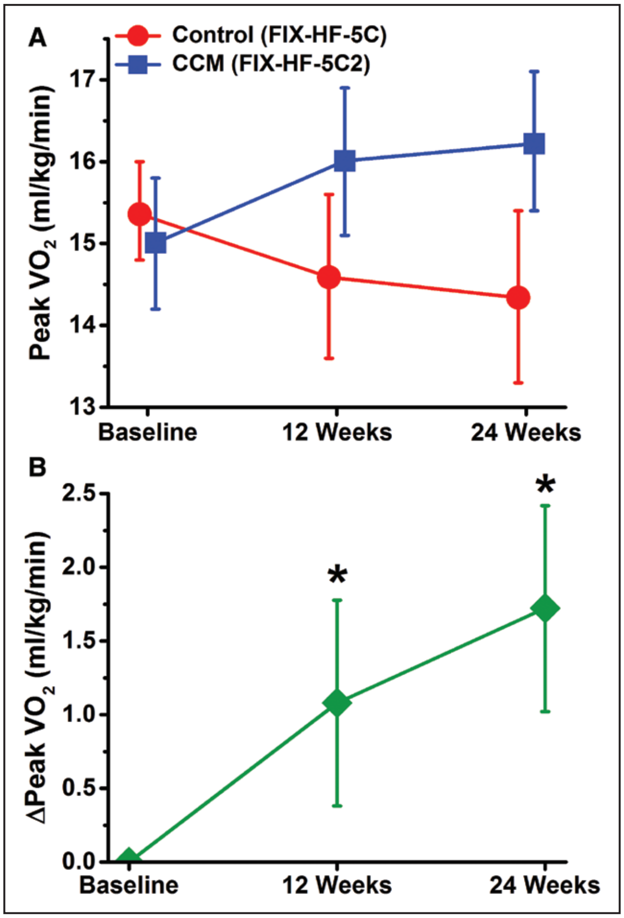

Figure 1. A, Peak VO_2 over time comparing control group from FIX-HF-5C and the CCM treatment group from the FIX-HF-5C2 study.
Values represent mean±SD frequentist values at each timepoint. One side of error bars are shown for clarity. **B**, Between-group treatment effects (ie, difference between CCM treatment and control group and 95% CIs) over time as estimated by the primary Bayesian analysis. *Indicate statistically significant treatment effect. CCM indicates cardiac contractility modulation.

resolved without treatment and there were no further complications in this case. Thus, the complication rate was 1.7% (1/60 [CI, 0.0%–8.9%]). This compares favorably with the 10.3% (CI, 4.2%–20.1%) complication rate seen in 3-lead Optimizer subjects in the FIX-HF-5C study (P=0.07).

Secondary Safety End Points

As noted above, there were no deaths during the 24-week study period in the 2-lead Optimizer subjects; in contrast, there were 4 deaths in the FIX-HF-5C control subjects during the same period of follow-up. Serious adverse events were tabulated by treatment group and were compared by Fisher exact test (Table 6). There were no significant differences between the 2-lead Optimizer (FIX-HF-5C2) subjects and FIX-HF-5C control or 3-lead Optimizer (FIX-HF-5C) subjects with the exception that there were fewer Optimizer device-related events with the

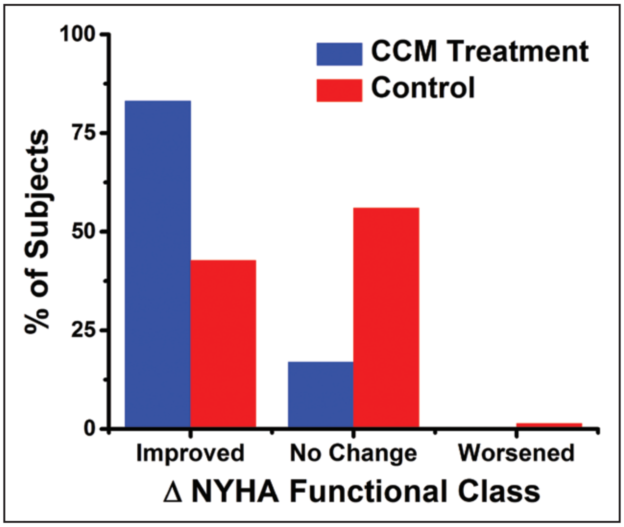

Figure 2. Distributions of changes of New York Heart Association (NYHA) class at 24 wks in control and CCM groups.
The differences between these distributions were statistically significant (P<0.001). CCM indicates cardiac contractility modulation.

2-lead system (P=0.03). It is notable that a majority of the Optimizer device-related events with the prior FIX-HF-5C 3-lead system study were due to lead dislodgements and lead fractures; there were no device-related complications reported with the 2-lead device. Importantly, there were no occurrences of premature ventricular contractions or ventricular tachycardia events in the FIX-HF-5C2 study.

DISCUSSION

The present results demonstrate that compared with the prior 3-lead system, the 2-lead Optimizer Smart device delivers equivalent amounts of CCM treatment, while device-related events are decreased, presumably related to having 1 less lead; increased experience among implanters could also have contributed to the improved safety profile. Compared with the results of the prior FIX-HF-5C study, the improvements in peak VO_2 and NYHA appear to be equivalent (or greater) with the 2-lead system. In addition, device performance did not differ between patients with normal sinus rhythm or atrial fibrillation. As such, the present study represents a significant advance for patients who qualify for CCM treatment and potentially expands the eligible pool of patients to those with permanent atrial fibrillation.

The prior Optimizer system required an atrial lead for sensing of a P wave, the timing of which relative to the depolarizations at the 2 right ventricular septal leads, was part of the algorithm that ensured CCM signal delivery during the myocardial absolute refractory period. Elimination of the atrial lead was made possible through modifying the algorithm to eliminate the atrio-ventricular timing criteria, while at the same time strengthening the criteria used to evaluate the timing and sequence between the 2 right

Table 6. Adjudicated Serious Adverse Events From Study Day 0 to 168

	FIX-HF-5C2 Optimizer		FIX-HF-5C Optimizer			FIX-HF-5C Control		
Variable	No. Events	No. and % of Subjects* (CI)	No. Events	No. and % of Subjects* (CI)	*P* Value†	No. Events	No. and % of Subjects* (CI)	*P* Value†
All	26	19 (31.7%) (20.3%–45.0%)	29	20 (27.0%) (17.4%, 38.6%)	0.572	27	19 (22.1%) (13.9%, 32.3%)	0.250
General Medical	8	7 (11.7%) (4.8%–22.6%)	7	7 (9.5%) (3.9%–18.5%)	0.779	8	7 (8.1%) (3.3%–16.1%)	0.571
Arrhythmia	3	2 (3.3%) (0.4%–11.5%)	3	3 (4.1%) (0.8%–11.4%)	1.000	2	2 (2.3%) (0.3%–8.1%)	1.000
Worsening heart failure	7	5 (8.3%) (2.8%–18.4%)	4	3 (4.1%) (0.8%–11.4%)	0.466	8	7 (8.1%) (3.3%–16.1%)	1.000
General cardiopulmonary	2	2 (3.3%) (0.4%–11.5%)	4	3 (4.1%) (0.8%–11.4%)	1.000	2	2 (2.3%) (0.3%–8.1%)	1.000
Bleeding	1	1 (1.7%) (0.0%–8.9%)	0	0 (0.0%) (0.0%–4.9%)	0.448	1	1 (1.2%) (0.0%–6.3%)	1.000
Neurological	1	1 (1.7%) (0.0%–8.9%)	0	0 (0.0%) (0.0%–4.9%)	0.448	0	0 (0.0%) (0.0%–4.2%)	0.411
Thromboembolism	1	1 (1.7%) (0.0%–8.9%)	1	1 (1.4%) (0.0%–7.3%)	1.000	1	1 (1.2%) (0.0%–6.3%)	1.000
Local infection	1	1 (1.7%) (0.0%–8.9%)	1	1 (1.4%) (0.0%–7.3%)	1.000	4	4 (4.7%) (1.3%–11.5%)	0.649
Sepsis	1	1 (1.7%) (0.0%–8.9%)	1	1 (1.4%) (0.0%–7.3%)	1.000	1	1 (1.2%) (0.0%–6.3%)	1.000
ICD or pacemaker system malfunction	1	1 (1.7%) (0.0%–8.9%)	2	2 (2.7%) (0.3%–9.4%)	1.000	0	0 (0.0%) (0.0%–4.2%)	0.411
Optimizer system malfunction	0	0 (0.0%) (0.0%–6.0%)	6	6 (8.1%) (3.0%–16.8%)	0.033		…	

ICD indicates implantable cardioverter-defibrillator.
*Number and percent of subjects. Subjects are counted only once within each category.
†Compared with FIX-HF-5C2 Optimizer Group via Fisher exact test.

ventricular leads. In addition to prior significant bench-top and preclinical testing of that algorithm, the present results indicating no occurrences of premature ventricular contractions or ventricular tachycardia events in the FIX-HF-5C2 provides important additional safety information.

The Bayesian model-based mean change in peak VO_2 from baseline to 24 weeks in the FIX-HF-5C2 study increased by 0.80 (95% BCI, 0.18–1.40) mL/kg per minute, whereas the model-based mean change in peak VO_2 from baseline to 24 weeks in the FIX-HF-5C control group decreased by 0.93 (95% BCI, −1.46 to −0.39). The corresponding treatment effect (ie, the Bayesian primary analysis model-based mean difference in peak VO_2 change at 24 weeks between the FIX-HF-5C2 treatment group and the FIX-HF-5C control group) was 1.72 (95% BCI, 1.02–2.42) mL/kg per minute. This was supported by a frequentist analysis (ie, no borrowing), which showed a 2.21 mL/kg per minute CCM treatment effect. This effect is larger than the Bayesian model–based mean treatment effect identified in the prior FIX-HF-5C study: 0.84 mL/kg per minute (95% BCI, 0.12–1.52). The larger mean treatment effect identified in the present study is due to the fact that peak VO_2 in the FIX-HF-5C2 patients increased significantly over baseline at 24 weeks, whereas there was almost no change from baseline in the FIX-HF-5C CCM patients. It can only be speculated as to why the treatment group appeared to have behaved differently in the FIX-HF-5C and FIX-HF-5C2 studies. Placebo effect is unlikely since both studies were unblinded and the same core laboratory oversight was applied in both studies. One difference between studies was that in FIX-HF-5C, patients underwent 2 CPX tests at each time point in addition to a 6-minute walk test; in FIX-HF-5C2, only one CPX test was performed at each timepoint and there was no 6-minute walk test. This methodological difference could have influenced patient performance on serial tests; results in the FIX-HF-5C2 could have been more reflective of habituation on repeated tests, whereas the more frequent exercise testing used in the FIX-HF-5C study could have blunted this effect. Nevertheless, the less frequent CPX testing schedule used in the FIX-HF-5C2 study is more reflective of how patients are evaluated serially in clinical practice and in most prior clinical trials.

Limitations

The main limitation of the present study is that it was a nonrandomized, unblinded study with a relatively small number of patients that used a historical control group from the prior FIX-HF-5C study. The 2 studies are reasonably contemporaneous, having been completed <2 years of each other. The only significant difference in background medical therapy was a slightly greater use of valsartan/sacubitril in the current study (15% versus 4%) due to its introduction into clinical practice toward the completion of enrollment into the FIX-HF-5C study. In addition, there were some imbalances in baseline characteristics between the prospective treatment and retrospective control groups (Table 4; Table I in the Data Supplement); however, frequentist mixed modeling of the results by sequential addition of baseline characteristics showing differences between groups showed little impact of these differences on the results (Table IV in the Data Supplement). Regarding unblinding, this aspect is similar to the prior FIX-HF-5C study, so we consider it unlikely that it would have influenced the comparisons made between the 2 studies.

Conclusions

The 2-Lead Optimizer Smart system reduces the total lead requirement from 3-leads to 2-leads and enables CCM signal delivery in patients with atrial arrhythmias. Compared with the 3-lead system, the 2-lead system delivers comparable amount of CCM signals, is equally safe, and improves peak VO_2 and NYHA functional class. Device-related adverse effects related to leads are less than with the 3-lead system. The availability of the 2-lead system therefore represents a significant advance in the development of cardiac contractility modulation therapy for patients with heart failure.

ARTICLE INFORMATION

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