

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

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## 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 ≥25% and ≤45% were randomized to continued medical therapy (control, n = 86) or CCM (treatment, n = 74, unblinded) for 24 weeks. Peak VO<sub>2</sub> (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<sub>2</sub> between groups was 0.84 (95% Bayesian credible interval: 0.123 to 1.552) ml O<sub>2</sub>/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/>).

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

**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<sub>2</sub>** = 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<sub>2</sub>) 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:

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