Regarding the included study, Impulse Dynamics is providing this information for educational purposes only. Some or all the studied uses of the Optimizer described in the article have not been approved or cleared by the FDA.

INDICATIONS

The safety and performance of the OPTIMIZER Smart System is based on clinical investigations conducted with the prior generation devices, the OPTIMIZER IVs and III Systems, given the similarities between the Systems with regard to function, intended use, design characteristics, and the CCM™ signals. Summaries of these studies are available on Impulse Dynamics' website. (http://www.impulse-dynamics.com/int/for-physicians/clinical-data/)

The OPTIMIZER Smart System, which delivers CCM™ therapy, is indicated to improve 6-minute hall walk distance, quality of life and functional status of NYHA Class III heart failure patients who remain symptomatic despite guideline directed medical therapy, who are in normal sinus rhythm, are not indicated for CRT, and have an LVEF ranging from 25% to 45%.

The OPTIMIZER Smart system delivers non-excitatory CCM™ signals to the heart and has no pacemaker or ICD functions.

CONTRAINDICATIONS AND PRECAUTIONS

Use of the OPTIMIZER Smart system is ***contraindicated*** *in:*

1. Patients with permanent or long-standing persistent atrial fibrillation or flutter
2. Patients with a mechanical tricuspid valve
3. Patients in whom vascular access for implantation of the leads cannot be obtained

WARNINGS

Potential Complications of Device Implantation

Just like any surgical procedure, implantation of an OPTIMIZER Smart IPG is associated with a certain risk. Complications of IPG implantation reported in the literature include but are not limited to: arrhythmias induced by the IPG, including life-threatening arrhythmias (e.g., ventricular fibrillation), infection, skin necrosis, device migration, hematoma formation, seroma and histotoxic reactions (also see: Potential Adverse Effects in the Appendix).

Programming high sensitivities (i.e., sensitivity settings less than 2 mV) may increase the system's susceptibility to electromagnetic interference, which could either inhibit or trigger signal delivery.

Acute and chronic complications reported in the literature include, but are not limited to: lead fracture, lead displacement, atrial or ventricular perforation, and rare cases of pericardial tamponade. Perforation of the ventricular wall can induce direct stimulation of the phrenic nerve or the diaphragm. An impedance change demonstrated on a check-up can be indicative of lead fracture, lead displacement, or perforation (also see: Potential Adverse Effects in the Appendix).

In very rare cases (<1%), transvenous lead placement can also lead to venous thrombosis and subsequent SVC syndrome.

Loss of sensing shortly after implant can be the result of lead displacement. In addition, loss of CCM™ signal delivery could be due to a lead fracture.

Atrial and Ventricular Arrhythmias Potentially Caused by Lead Implantation

As noted above, the use of transvenous leads may lead to arrhythmias, some of which may be life-threatening such as ventricular fibrillation and ventricular tachycardia. The use of screw-in leads such as those used for CCM™ signal delivery also have the potential of causing conduction disturbances such as bundle branch block. These can be minimized by performing the implant with the use of fluoroscopic guidance, ensuring that the leads are in appropriate position prior to fixation and by limiting the number of lead manipulations. Please read and follow all directions of the original Physician Manual for the leads that you intend to use to minimize adverse events connected to lead implantation.

Ventricular Arrhythmias Potentially Caused by CCM™ Signals

CCM™ signals are of greater strength than that of typical pacing pulses and are thus capable of eliciting activation of cardiac tissue when delivered outside of the absolute refractory period. CCM™ signals delivered outside of the ventricular absolute refractory period thus have the potential of causing signal-induced arrhythmias (some of which may be life-threatening, such as ventricular fibrillation and tachycardia). For this reason, it is imperative that CCM™ signal delivery parameters be chosen carefully. Most importantly, the various settings related to conditions that inhibit CCM™ signal delivery (e.g. Long AV Delay, Short AV Delay, LS Alert Window, refractory periods, and IEGM sensitivities) must be selected to allow delivery of CCM™ signals only on normally conducted (e.g. non-arrhythmic) beats, but inhibit them on beats of suspected ectopic or premature origin.

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In addition, CCM™ signals may cause changes in the electrical conduction of tissue. For this reason, the delivery of CCM™ signals to the ventricular septum has the potential of causing bundle branch block that could lead to bradycardia. Through similar mechanisms, CCM™-induced changes in the electrical conduction of the myocardium have the potential of inducing tissue refractoriness that may facilitate the induction of reentrant tachyrrhythmias. It is recommended that the patient's rhythm be monitored carefully for changes in rhythm when CCM™ signals are delivered during lead implantation, as well as during first activation of the OPTIMIZER Smart IPG and subsequent follow-up visits. Changes in ventricular rhythm caused by the delivery of CCM™ signals may require relocating the leads, as well as reprogramming the CCM™ delay and amplitude to settings that do not cause changes in the patient's ventricular rhythm.

Atrial Arrhythmias Potentially Caused by CCM™ Signals

Atrial and supraventricular arrhythmias could theoretically be initiated when CCM™-induced ventricular activity is conducted retrograde to the atria, resulting in premature atrial depolarization. The OPTIMIZER Smart IPG may sense the ventricular activation resulting from the retrograde-induced atrial event and deliver CCM™ as programmed. In addition, strong CCM™ signals delivered through leads implanted in basal position close to the atria have the potential of directly stimulating the atria. If CCM™ delivery causes atrial activation through either of these mechanisms, and the atrial signal is then conducted to the ventricles, the cycle may develop into a condition similar to pacemaker-mediated tachycardia (PMT).

The main variables that may have an impact on CCM™ events leading to atrial activation are the location of lead placement on the right ventricular septum, CCM™ amplitude, and CCM™ delay. To prevent the occurrence of atrial arrhythmias due to CCM™ signal delivery, it is recommended that basal lead implant locations be avoided. The potential for direct atrial activation by CCM™ signals can be tested during the implant by delivering the strongest possible CCM™ signal 20 to 30 ms longer than the LS-CCM delay with which the IPG will be ultimately programmed, as long as this delay places the CCM™ signal, including its 40 ms balancing phase, completely within the ventricular absolute refractory period, and monitoring for atrial activations. In such a case, the delay should be programmed to a longer value and lack of atrial activation confirmed. Besides proper lead location and CCM™ parameter programming, the "Atrial Tachycardia Rate" must be programmed to a sufficiently low value as a protective measure against atrial arrhythmias that could be induced by CCM™ signal delivery.

APPENDIX

Potential Adverse Effects

Examples of adverse effects that may occur as the result of the surgical procedure are listed below in the order of their clinical severity:

1. Death
2. Arrhythmias (brady- or tachyarrhythmias including fibrillation)
3. Stroke or TIA ("transient ischemic attack")
4. Respiratory/ventilatory failure
5. RA/RV perforation
6. Hemorrhage
7. Infection
8. Pleura or pericardial effusion
9. Pneumothorax

Examples of additional adverse effects potentially occurring secondary to CCM™ signal delivery are listed in the table below in the order of their clinical severity:

1. Abnormal cardiac function
2. Atrial and Ventricular Tachyarrhythmias
3. Atrial and Ventricular Bradyarrhythmias
4. Worsening heart failure
5. Myocardial tissue damage
6. Chest pain

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2. **Please document the time and place of the unsolicited request that preceded your distribution of this document.**
3. **Do not bring up or imply that CCM® therapy results in improved peak VO2.**
4. **If unsure about any of this, please consult with your manager at Impulse Dynamics.**

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Circulation

PERSPECTIVE

Cardiac Contractility Modulation in 2018

Martin Borggrefe, MD
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Cardiac contractility modulation (CCM) is a device-based therapy for heart failure (HF) that involves applying relatively high-voltage (≈7.5 V), long-duration (≈20 milliseconds), biphasic electric signals to the right ventricular septal wall during the absolute myocardial refractory period. Accordingly, CCM signals do not elicit a new contraction; rather, they influence the biology of the failing myocardium. CCM signals have been shown to induce an acute, mild augmentation of left ventricular (LV) contractile strength without an increase in myocardial oxygen consumption in both animal HF models[1] and patients with reduced ejection fraction (EF). Three-dimensional echocardiographic studies showed that CCM induces reverse LV remodeling and improves LVEF over time. The myocardial effects of CCM are multifactorial: Studies show effects on molecular, cellular, and extracellular properties that express themselves over different time frames. Acute effects appear to involve alterations of myocardial calcium handling, whereas over intermediate and longer time frames, CCM exerts a multitude of biochemical and molecular effects locally and remotely from the site of stimulation, including shifts of a large number of abnormally expressed genes toward normal, many of which involve pathways that regulate calcium cycling and myocardial contraction. Although the major clinical trials (reviewed below) have focused on patients with normal conduction, CCM effects appear to be additive to those of cardiac resynchronization therapy (CRT) when applied to patients with prolonged QRS duration.

Three randomized prospective studies have compared patients treated with guideline-directed optimal medical therapy (including an implanted cardiac defibrillator, when indicated) with those treated with optimal medical therapy plus CCM. The earliest of these, the FIX-HF-4 study, which was conducted in European Union, showed that 3 months of CCM treatment improved exercise tolerance and quality of life.[2] Although the FIX-HF-5 study, which randomized 428 patients who were followed up for 1 year, missed its US Food and Drug Administration–mandated primary end point (an analysis of anaerobic threshold measured on cardiopulmonary stress test), it showed significant improvements in the secondary end points of peak V_{O_2} and Minnesota Living With Heart Failure Questionnaire score with treatment effects of 1.4 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ and 11.8 points, respectively.[3] This study was also the first to show that patients with an LVEF between 35% and 45% benefited the most, whereas those with EF <25% derived inadequate benefit. Most recently, the FIX-HF-5C study (n=160), conducted in sites in the United States and European Union, was designed to confirm findings that CCM improves peak V_{O_2} and Minnesota Living With Heart Failure Questionnaire score in patients with LVEF between 25% and 45% and, secondarily, to confirm even larger effects in patients with LVEF of 35% to 45%.[4] The study used a bayesian statistical design, meaning that there was statistically appropriate pooling of data from the prior FIX-HF-5 study conducted in the United States.[3] Data from

Key Words: heart failure ■ myocardial contraction

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the combined study showed an ≈50% reduction in the composite end point of cardiovascular death and HF hospitalizations. FIX-HF-5C met its primary and secondary end points, showing treatment effects in the entire cohort (LVEF, 25%–45%) amounting to 0.84–mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ improvements in peak Vo_2 (P=0.011) and 11.7-point incremental improvement over the control group in Minnesota Living With Heart Failure Questionnaire score (P<0.001), as well as a 24.6-m improvement in the 6-minute walk test (P=0.006). For patients with LVEF of 35% to 45%, the incremental improvements were 1.8 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ for peak Vo_2 (P=0.009), 14.9 points for the Minnesota Living With Heart Failure Questionnaire score (P=0.003), and 57.1 m for the 6-minute walk test (P=0.003). This study also showed an ≈50% reduction in the composite end point of death and HF hospitalizations.

In addition to these randomized studies, a number of real-world registry studies have shown that CCM-mediated improvements in symptoms, exercise tolerance, and quality of life are sustained through 2 years of follow-up.[5] They have also shown that patients with EF between 35% and 45% have even greater clinical improvements than those with LVEF <35% and that for all patients CCM reduces the rate of HF hospitalizations compared with the year before treatment.

In addition, in patients with LVEF of 35% to 45%, 3-year mortality is less than predicted by both the Meta-Analysis Global Group in Chronic Heart Failure score and the Seattle Heart Failure Model score, whereas the effect for those patients with an LVEF of 25% to 35% does not reach statistical significance.

As a result of the earliest of the studies noted above, CCM has been made available to patients in countries that recognize the CE Mark and in China, India, Brazil, the Middle East, and Australia. CCM was already mentioned in the European Society of Cardiology guidelines for the management of patients with HF. CCM is currently under review for approval by the US Food and Drug Administration.

The algorithm in the Figure summarizes a suggested pathway for how CCM fits, compared with CRT, in the treatment of patients with HF in New York Heart Association functional class III or ambulatory class IV despite optimal medical therapy with an EF ≤45%. It is important to note that there are variations in clinical practice between the United States and the European Union and that CCM is not yet approved in the United States. Thus, the actual indications for use in the United States are not yet defined; therefore, the suggested algorithm needs to be considered accordingly. Nevertheless, in both regions, optimal medical therapy generally consists of a diuretic, a β-blocker, an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, or valsartan combined with sacubitril and, when tolerated, a mineralocorticoid receptor inhibitor. If the QRS

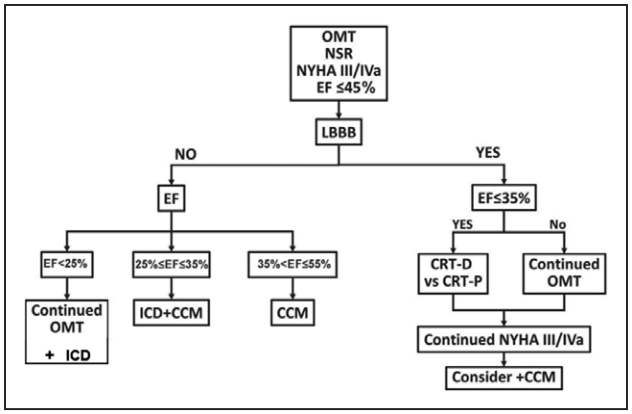

Figure. Suggested pathway for how cardiac contractility modulation (CCM) fits, compared with cardiac resynchronization therapy (CRT), in the treatment of patients with heart failure.
CRT-D indicates cardiac resynchronization therapy–defibrillator; CRT-P, cardiac resynchronization therapy–pacing; EF, ejection fraction; ICD, implanted cardiac defibrillator; LBBB, left bundle-branch block; NSR, normal sinus rhythm; NYHA, New York Heart Association; and OMT, optimal medical therapy.

complex shows a left bundle-branch block pattern (with QRS duration ≥150 milliseconds) and the LVEF is ≤35%, CRT-pacing is indicated, typically in combination with a CRT-defibrillator. However, CRT is not indicated for patients with normal QRS duration, and studies show that it may be harmful even for patients with a narrow QRS and echocardiographic evidence of contractile dyssynchrony. It is for such patients that clinical trials show that CCM provides benefit, particularly those with LVEF between 25% and 45%. For patients with an LVEF of 25% to 35%, CCM can be safely combined with an implanted cardiac defibrillator, and for patients with an LVEF of 35% to 45%, CCM is offered as the only device-based therapeutic option. In addition, particularly in the European Union, CCM may be considered an option for patients not responding to CRT and those without an indication for CRT who continue to have symptomatic HF.

CRT has proved to be an effective treatment for patients with left bundle-branch block, normal sinus rhythm, and LVEF ≤35%. However, a majority of HF patients are not indicated for CRT, and for these patients, CCM is an option. Further studies are underway to help define expanded roles for routine use of CCM in combination with CRT and in patients with HF and preserved LVEF.

ARTICLE INFORMATION

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Disclosures

Dr Borggrefe reports honoraria/lecture fees from Boston Scientific, Medtronic, Impulse Dynamics, St. Jude Medical, CVRx, Biotronic, Pfizer, Bayer, and Böhringer-Ingelheim. Dr Mann reports honoraria from CVRx, LivaNova, and Bristol Meyers Squibb.

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