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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Device Evaluation

Future CARDIOLOGY

Optimizer Smart in the treatment of moderate-to-severe chronic heart failure

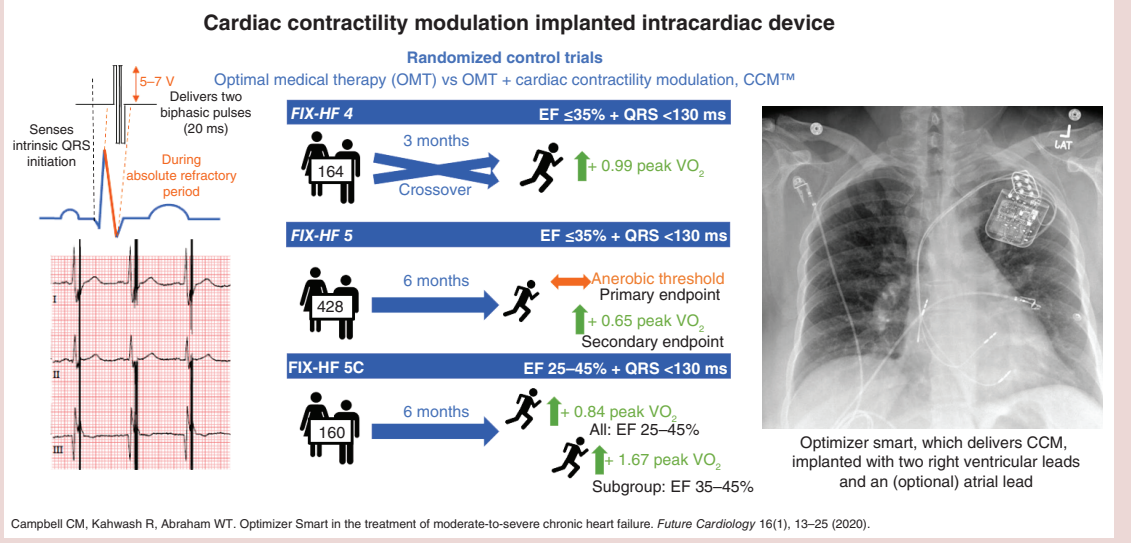
Courtney M Campbell*,[1], Rami Kahwash[1] & William T Abraham[1]

[1]Department of Internal Medicine, Division of Cardiovascular Medicine, The Ohio State University Wexner Medical Center, 200 Davis Heart & Lung Institute, 473 W 12th Ave, Columbus, OH 43210, USA

*Author for correspondence: courtney.campbell@osumc.edu

Cardiac contractility modulation, also referred to as CCM™, by the Optimizer Smart device is an innovative intracardiac device-based therapy that has been recently US FDA-approved for the treatment of patients with chronic heart failure, left ventricular ejection fraction (LVEF) between 25 and 45%, QRS <130 ms who remain symptomatic despite optimal medical therapy. Clinical trials demonstrate that CCM therapy is safe and effective in reducing heart failure hospitalization and improving heart failure symptoms, quality of life and functional performance. This novel device-based therapeutic offers benefits to patients who do not otherwise qualify for cardiac resynchronization therapy. CCM expands the indication beyond the traditional LVEF cutoff of 35% to a newer group including patients who fall in midrange LVEF group, up to 45%.

Graphical abstract:



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Heart failure affects over 6 million adults in the USA with projections for increases to over 8 million by 2020 [1]. Approximately, 50% of people diagnosed with heart failure die within 5 years [1]. Our current medical management is inadequate to address this growing public health crisis. The medication regimen for systolic heart failure is strikingly limited: consisting of β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockade and mineralocorticoid receptor antagonists. Diuretics only provide symptomatic relief. Sacubitril/valsartan and ivabradine are the only new medications for heart failure in two decades.

Future Medicine

Cardiac resynchronization therapy (CRT) offers a device-based therapy for patients with ejection fraction (EF) of ≥35% and wide QRS (>130 ms in left bundle-branch pattern) that improves cardiac function, quality of life and decreases hospitalization and morbidity [2–4]. For the majority of heart failure patients, CRT device is not indicated: only a third of heart failure patients meet criteria [5]. The implantable cardiac contractility modulation, CCM™, fills this device-based therapeutic gap. CCM devices received the European Conformity (CE) mark in October 2016 and recently received the US FDA approval in March 2019. CCM devices are included in the European Society of Cardiology 2016 Heart Failure Guidelines, and CCM inclusion in the next update of the American Heart Association and American College of Cardiology guidelines is anticipated [6,7].

CCM is an innovative intracardiac device-based therapy that has been evaluated in the treatment of patients with chronic heart failure, left ventricular ejection fraction (LVEF) ≥25 and ≤45%, QRS <130 ms who remain symptomatic despite optimal medical therapy (OMT) [8–10]. In this patient population, clinical trials [8–10] showed that CCM therapy is safe and effective in reducing heart failure hospitalization and improving heart failure symptoms, quality of life and functional performance.

CCM consists of a specialized implantable pulse generator capable of delivering nonexcitatory electrical impulses to the interventricular septum through standard pacing leads [11]. These impulses are timed, so they occur during the absolute refractory periods of the myocytes' action potential. These impulses activate intracellular signals that favorably alter gene expression and enhance calcium delivery, which in turn increase myocardial contractility and cardiac efficiency without increasing metabolic demand [12].

In this review, we will discuss the development of the Optimizer Smart CE device for CCM in heart failure with an emphasis on clinical trials and future development.

Cardiac contractility modulation

Mechanism of action

The development of CCM therapy is based on observations first made in the 1960s. In the last two decades, a series of publications have expanded on these initial observations and propelled the development of the novel intracardiac CCM device. The molecular mechanism of action is not definitively understood, but many experiments have delineated how CCM changes the biology of the failing heart and the preclinical data have been previously reviewed [13]. CCM therapy increases contractility, enhances cardiac myocyte calcium handling, and improves gene expression profiles without increasing myocardial oxygen demand.

Early studies demonstrated that extracellular electrical stimulation during the absolute refractory period of calf or sheep ventricular bundles resulted in increased contractile strength and prolonged action potential duration [14]. More recent studies showed that following CCM therapy, the contraction force of healthy rabbit papillary muscles was increased within a single beat and steady state was achieved within 6–8 beats [15]. The loss of effect within a couple of beats was similarly rapid. Similar positive inotropic effects were seen when CCM was applied to failing human left ventricular trabeculae from patients with end-stage heart failure, obtained at time of transplantation [15]. Strikingly, the average EF improved from 31 to 41% in 1 h and 44% after 6 h of CCM therapy in dogs with chronic heart failure [16]. EF improvement was maintained during 3 months of therapy [17]. In the acute setting, CCM contractility improvement was shown to be β1-adrenergic receptor dependent [18]. In these studies, epicardial CCM stimulation was applied to isolated rabbit hearts. Basal and mid stimulation resulted in a more robust contractility response compared with apical stimulation. The magnitude of the effect correlated with increased levels of norepinephrine in samples of coronary effluent [18]. The gradient of response mirrors the distribution of sympathetic nerve fibers – the highest nerve density in basal regions and lower nerve density in apical regions [19]. Furthermore, the effects were abolished in the presence of metoprolol, a β1-adrenergic receptor antagonist. However, CCM therapy has been effective in the setting on concomitant β-blocker therapy suggesting an additional β1-adrenergic receptor independent mechanism [20].

CCM therapy enhances cardiac myocyte calcium handling both acutely and chronically. In early experiments using Langendorff-perfused ferret hearts, aequorin luminescence was used to show increased intracellular calcium levels after acute CCM stimulation [15]. The positive inotropic effect of CCM was blocked with the addition of ryanodine, which blocks calcium release from the sarcoplasmic reticulum [15,20]. Verapamil, which blocks L-type calcium channels and consequently myocyte calcium entry, also blocked CCM inotropic effects [20]. Furthermore, the inotropic effects are likely calcium-dependent as the contractility force improvement by CCM plateaued when supraphysiologic levels of calcium were used in experiments [21]. After 3 months of CCM therapy, dogs with heart failure had increased mRNA and protein levels of the SERCA-2a, phosphorylated PLN and RYR [17]. SERCA

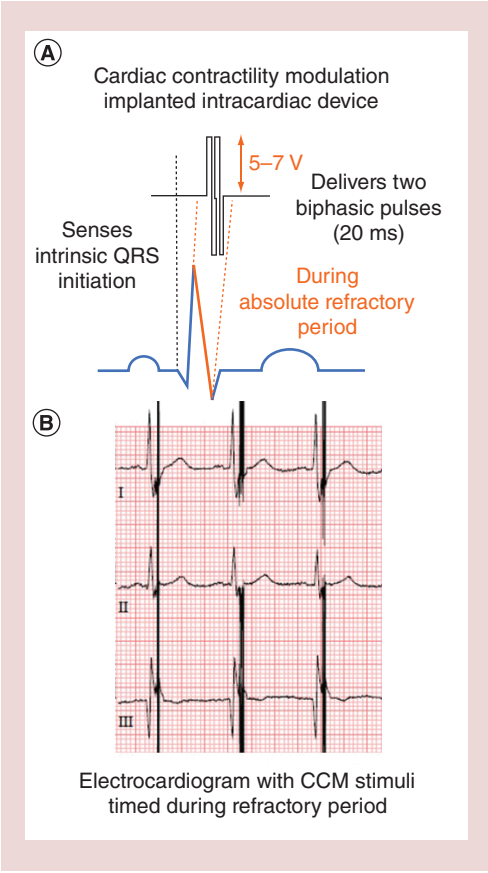

Figure 1. Cardiac contractility modulation stimulation. (A) Cardiaccontractility modulation implanted intracardiac device senses the intrinsic QRS initiation and then delivers two biphasic pulses of 5–7V over a total of 20 ms during the absolute refractory period. **(B)** Electrocardiogram leads I, II, III from a patient with an implanted CCM device demonstrating the CCM stimuli timed during the refractory period.
CCM: Cardiac contractility modulation.

allows calcium to return to the sarcoplasmic reticulum and unphosphorylated PLN inhibits SERCA. Together, these protein changes augment calcium handling within the myocyte. NCX, increased in heart failure, was decreased after CCM therapy [22]. Importantly, these protein levels were comparable to healthy controls and increased compared with sham-operated dogs with failing hearts. Similar changes of mRNA expression from endomyocardial biopsies were seen in a study of 11 patients with systolic heart failure after 3 months of CCM therapy [23]. Levels of *SERCA2*, *PLN* and *RYR* were increased. Beyond calcium-handling proteins, CCM has been shown to decrease expression of cardiac maladaptive fetal genes [17,23] and normalize expression of calcium-binding proteins [24].

Despite positive inotropic effects, CCM does not change myocardial oxygen consumption [25,26]. In an elegant study, myocardial oxygen consumption was measured before and after CCM therapy for 2 h in dogs with heart failure and for 30 min in humans [26]. Coronary blood flow was estimated using calculation based on the average peak flow velocity of the left main coronary. Oxygen content was measured from samples from the coronary artery and the coronary sinus. The product of the coronary blood flow and the arteriovenous oxygen content difference was used as a measure of myocardial oxygen consumption. In both dogs with induced heart failure and humans with chronic systolic heart failure, improvement was seen in left ventricle systolic function without an increase in myocardial oxygen consumption. In a larger study of 21 patients, ^{11}C-acetate positron emission tomography imaging was used to evaluate myocardial oxygen consumption [25]. No difference was seen in oxygen consumption or work metabolic index when the CCM device was on or off. This effect is in contrast to inotropic medications, like dobutamine or milrinone, which increase contractility with an increase in myocardial oxygen consumption and result in increased mortality [27].

The optimizer device

The CCM intracardiac delivery via the Optimizer system by Impulse Dynamics (Stuttgart, Germany) is an innovative device-based therapy that has undergone improvements in each generation. Two high voltage (4.0–7.5 V) biphasic electric signals of approximately 20 ms duration are delivered to the right ventricle septal wall during the absolute refractory period (Figure 1) [28,29]. This signal is nonexcitatory and thus does not result in a new

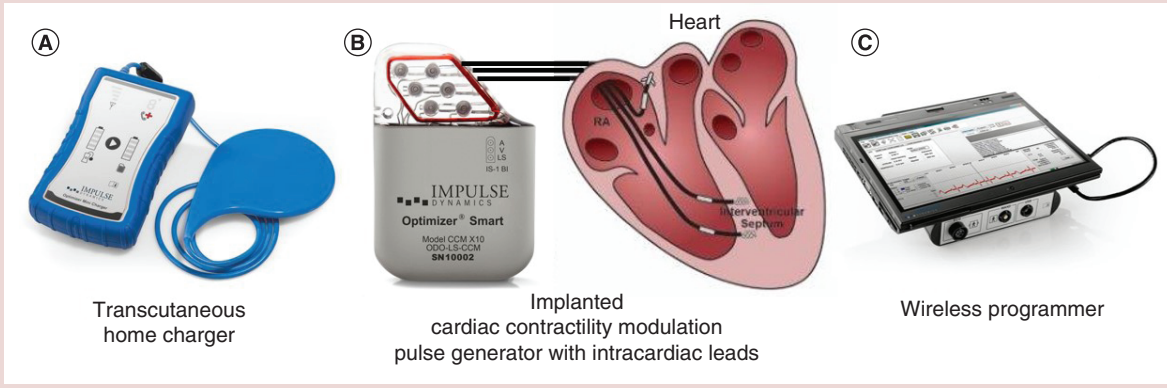

Figure 2. Optimizer system. (A) Current Optimizer System devices with transcutaneous home charger, **(B)** Optimizer Smart implanted cardiac contractility modulation pulse generator with intracardiac lads, and **(C)** wireless programmer. Images from Impulse Dynamics. Reproduced with permission from Impulse Dynamics.

contraction [30]. For comparison, this voltage is approximately 100-times the amount of energy delivered during a standard pacemaker impulse. The maximum rate of the device is programmed to 90–110 beats per minute to avoid therapy delivery during a slow ventricular tachycardia. This therapy is delivered throughout the day for 7–12 h based on patient preferences and physician discretion [11].

The CCM device is similar to other intracardiac devices, such as a pacemaker or defibrillator, with a pulse generator and intracardiac leads (Figure 2) [11]. The Optimizer IV CE device consisted of three leads: atrial sensing, ventricular sensing and ventricular pacing. The most recent version of the device, Optimizer Smart CE, has only two right ventricular septal leads that are both used for sensing and pacing with an optional atrial lead [31]. Implantation of the Optimizer system is similar to other intracardiac devices [11]. In most cases, local anesthesia and conscious sedation can be used. The ventricular bipolar screw-in leads are placed transvenously in the right ventricular septum. The generator is typically placed in the right pectoral region given that many eligible patients also have another intracardiac device implanted in the left pectoral region (Figure 3). Importantly, the generator of the Optimizer system has a rechargeable battery. The patient can recharge the battery at home, which needs to be done on a weekly basis [11,32]. This advance is in contrast to other intracardiac devices that require periodic generator changeout procedure at the end of battery life. Compared with other intracardiac devices, the rechargeable feature is advantageous in that future procedures are not necessary. However, patients may find a weekly 40–60 min charging session to be onerous.

Randomized clinical trials

Initial human clinical studies of CCM demonstrated improved cardiac contractility with temporarily placed electrodes in patients with heart failure [29,33,34]. In early feasibility studies that were unblinded and uncontrolled, there were no overt safety issues, no proarrhythmic effects an<d suggested improvement in clinical heart failure parameters [28,34]. Here, we discuss in detail the randomized clinical trials that demonstrate CCM therapy improves exercise tolerance, as measured by peak ventilatory oxygen uptake (peak VO_2) and by the six-minute walk test (6MWT), and quality of life, as assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) in patients with symptomatic moderate to severe heart failure despite OMT with normal QRS.

Pilot study

In 2006, the first prospective randomized, double-blind pilot study of CCM therapy established feasibility and safety of CCM therapy applied for 6 months [35]. Inclusion criteria included symptomatic moderate-to-severe heart failure with LVEF of ≤35% despite OMT and an implanted cardiac defibrillator (ICD). OMT was defined as treatment with a diuretic, a β-blocker and an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker. Exclusion criteria included CRT, peak VO_2 <11 ml/kg/mg, atrial fibrillation or ≥8900 premature ventricular contractions (PVCs) on a 24-h Holter monitor. Patients had to be clinical stable with no recent hospitalization within 30 days, myocardial infarction within 3 months or adjustments made to OMT within 30 days. 49 patients

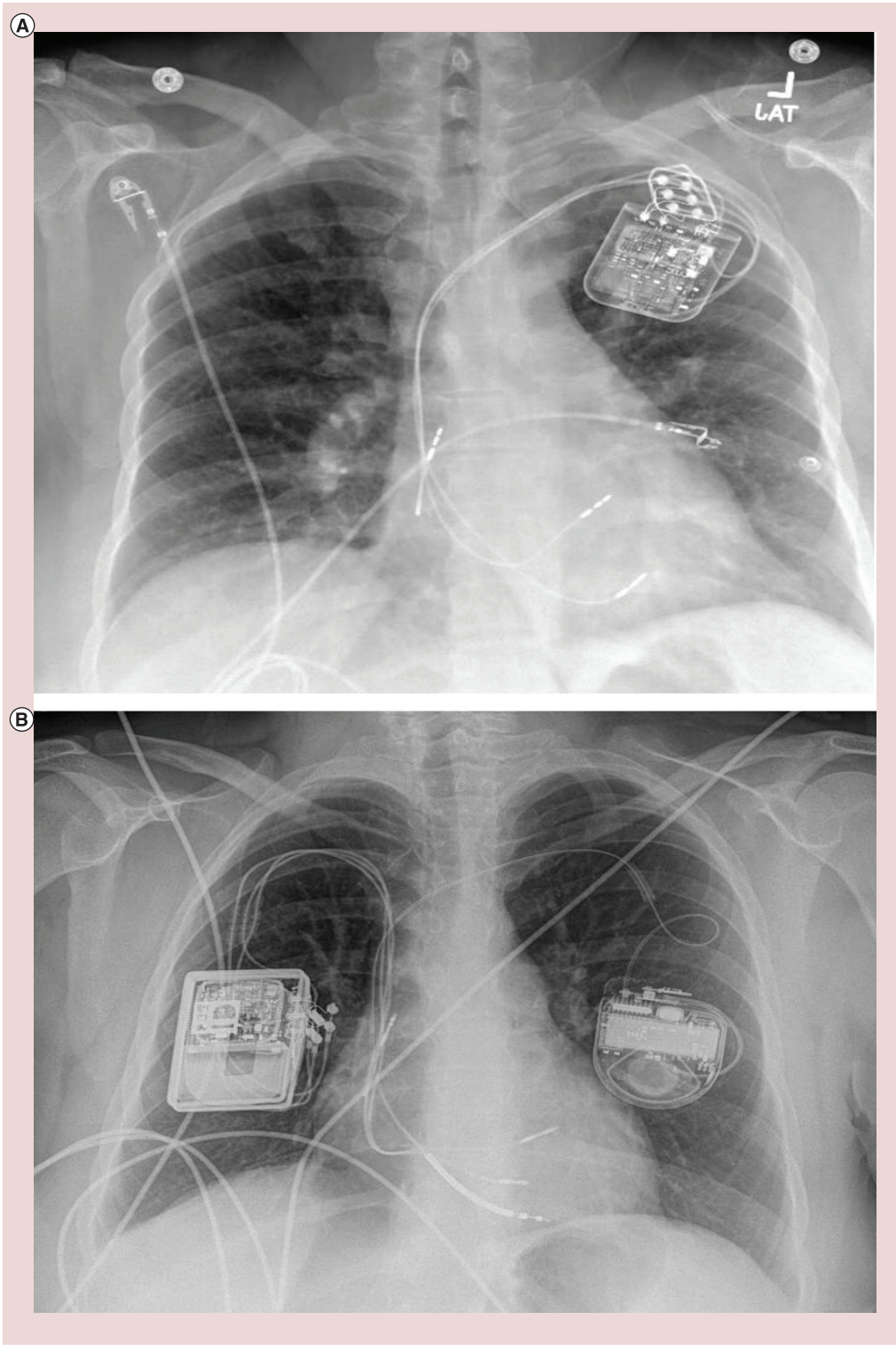

Figure 3. Implanted Optimizer Smart on chest x-ray. Chestradiographs of patient with ejection fraction >35% implanted with Optimizer Smart cardiac contractility modulation device with pulse generator in left pectoral region and three intracardiac leads: one in the right atrium and two in the right ventricle interventricular septum **(A)** and patient with ejection fraction <35% with implanted Optimize IV cardiac contractility modulation device with pulse generator in right pectoral region and three intracardiac leads: one in the right atrium and two in the right ventricle interventricular septum plus a standard implanted cardiac defibrillation with generator in left pectoral region and single implanted cardiac defibrillation lead in the right ventricle.

were enrolled and had CCM device (with three leads) implanted. Patients were assessed at baseline, 3 and 6 months with 6MWT, MLHFQ, echocardiogram, peak VO_2 and Holter monitor. In half of the patients, the device was turned on. The primary safety outcome was any hospitalization. Patients with the CCM device had a significantly decreased event-free survival (i.e., less hospitalizations). No significant difference was seen in Holter monitor recordings. The study was not powered to evaluate clinical efficacy. There was a trend of clinical improvement, but no statistical significance between control and CCM therapy patients.

FIX-HF-4

The safety and efficacy of CCM was further established in a feasibility study with a randomized, double-blind, crossover design in the FIX-HF 4 trial conducted in Europe and published in 2008 [9]. Inclusion criteria included symptomatic heart failure (New York Heart Association functional class ≥II), LVEF ≤35% and peak VO_2 between 10 and 20 ml O_2/min/kg. Patients were required to be on OMT including diuretic, a β-blocker and an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker. Pre-existing ICD or pacemaker was allowed. Exclusion criteria included CRT device, atrial fibrillation or ≥8900 PVCs on a 24-h Holter monitor. 164 patients were enrolled and received CCM implantation (with three leads). Half were randomized to have the device turned on for 3 months and then off for 3 months. The other half had the device off for 3 months and then turned on for 3 months. Before, at 3 and 6 months, the enrolled patients were assessed by 6MWT, peak VO_2 and MLHFQ. The coprimary end points were improvements peak VO_2 and MLHFQ. A significant placebo effect was seen in both groups at 3 months with modest improvements in peak VO_2 (0.40 and 0.37 ml/kg/min). Patients who were switched to active treatment after 3 months demonstrated maintenance or continued clinical improvement in all parameters. In those patients for whom CCM therapy was turned off after 3 months, their clinical status decreased back toward baseline. At 6 months, patients with active CCM therapy had an increased difference in peak VO_2 of 0.99 ml/kg/min compared with patients whose device was turned off. Importantly, there was no significant difference in adverse events between either group. Also, there was no change in ICD firing, arrhythmia burden or PVCs as measured by Holter monitor.

FIX-HF-5

The pivotal FIX-HF-5 trial, published in 2011, evaluated the safety and clinical benefits of CCM with OMT versus OMT in a large randomized, unblinded patient population [8]. An unblinded trial design was chosen primarily as the optimal way to assure device safety over the 1-year time frame. In total, 428 patients were recruited. Inclusion criteria were similar to FIX-HF-4 trial except NYHA class limited to III or IV, EF ≤35% and extended peak VO_2 to include ≥9 ml/kg/min. The study's primary clinical end point was ≥20% improvement in ventilatory anaerobic threshold (VAT). VAT is considered to be an unbiased measure of exercise tolerance not subject to the placebo effect but also has not been measured in any prior large-scale heart failure study. Before implantation, at 3 and 6 months, the enrolled patients were assessed by 6MWT, VAT, peak VO_2, echocardiogram and MLHFQ. FIX-HF-5 did not meet its primary end point. However, the secondary end points were achieved with improved peak VO_2 (by 0.65 ml/kg/min; $p = 0.024$), and improved MLHFQ (by -9.7 points; $p < 0.0001$) compared with OMT. The study met the primary safety end point of noninferiority of all-cause mortality and hospitalizations compared with OMT. Interestingly, a subgroup analysis of the FIX-HF-5 trial showed that clinical benefits were more pronounced in patients with higher range LVEF (≥25%) [36]. Most prominently, peak VO_2 improved by 1.31 ml/kg/min ($p = 0.001$) compared with OMT.

Individual meta-analysis of randomized control trials

In 2014, the meta-analysis of individual patient data from the three CCM randomized clinical trials was published [37]. Pooled analysis of 641 participants reviewed the efficacy of CMM on functional capacity, by the objective measures of peak VO_2 and 6MWT and quality of life by the MLHFQ. Baseline characteristics of the participants were similar between trials. Most patients had ischemic cardiomyopathy and were NYHA class III. Overall, significant changes were seen in each parameter: peak VO_2 increased by + 2.6% (14.5–14.7 ml/kg/min; $p = 0.006$), 6MWT distance improved by + 10% (344–367 m; $p = 0.05$) and MLHFQ improved by -22% (55–40; $p < 0.0001$). In subgroup analysis, patients older than 60 and patients with LVEF 25–45% had significantly improved peak VO_2. Significant improvement in 6MWT was seen in the subgroups of male gender, patients with ischemic cardiomyopathy, and LVEF 25–45%. With MLHFQ, all age groups and both genders had significant

improvement. Patients with ischemic etiology and LVEF less than 25% also had significant improvement on MLHFQ.

FIX-HF-5C

Based on the FIX-HF-5 and the individual meta-analysis observations, the FIX-HF-5 confirmatory study published in 2018 was designed to address CCM benefits in the subgroups that emerged as the high responders in the FIX-HF-5 study: specifically, those with mild-to-moderate reduction in LVEF (25–45%) [38]. Inclusion criteria were similar to previous studies: NYHA class III or IV symptoms despite OMT, EF 25–45% and normal sinus rhythm with QRS ≤130 ms. Patients with EF less than 35% were required to have an ICD. 160 patients were enrolled in the USA and EU in a randomized, unblinded fashion. Patients were randomized to continued OMT (n = 86) or CCM (n = 74). Patients were assessed with peak VO_2 (the primary end point), MLHFQ, NYHA functional class and 6MWT. Assessments were completed at baseline and then at 3- and 6-month postimplantation of the three lead Optimizer IV CE system. The study met its primary end point with an improvement in peak VO_2 with a difference between groups of 0.84 ml O_2/kg/min (95% Bayesian credible interval: 0.123–1.552). Statistically significant differences were also seen in quality of life by MLHFQ with -11.7 point improvement ($p < 0.001$). Patients with CCM were 5.97-times more likely to improve at least one NYHA functional class compared with OMT ($p < 0.001$). The average 6MWT improved by 43 meters ($p = 0.02$). In FIX-HF-5 and FIX-HF-5C, there were 96 patients with EF greater than 35% (49 OMT, 47 CCM). In comparison, 275 patients had EF less than 35% (145 OMT, 130 CCM). In patients with EF greater than 35–45%, better CCM efficacy results were seen in each parameter with pronounced improvement in peak VO_2 to 1.76 ml O_2/kg/min difference from control ($p = 0.009$). Furthermore, the composite end point of cardiovascular deaths and heart failure hospitalizations was lower in the CCM group with a great than 50% reduction from 10.8 to 2.9% event rate. Thus, FIX-HF-5C showed that CCM improves exercise tolerance and quality of life when compared with OMT and led to fewer hospitalizations.

Long-term outcomes

While randomized clinical trials have shown improvement in heart failure morbidity end points, CCM survival benefits and long-term sustainability of clinical effects have remained not fully addressed in a prospective fashion due to short-term follow-up of prior randomized clinical trials (Table 1) [8–10,12,16]. Both retrospective and prospective observational studies start to address these questions.

A retrospective study of 68 patients with a CCM device and mean follow-up of 4.5 years demonstrated lower mortality rates than predicted by the Seattle Heart Failure Model (SHFM) [39]. Kaplan–Meier analysis of mortality rate of 14.2% at 5 years versus predicted 27.7% by SHFM. In single-center retrospective study, 81 patients with CCM sustained improvements in EF, quality of life (MLHFQ), symptoms, exercise tolerance through an average of 3-year follow-up. These patients had mortality rates lower than predicted by the Meta-Analysis Global Group in Chronic (MAGGIC) heart failure score. However, there was not a significant change in peak VO_2 [40].

CCM-REG

The largest study to address long term outcomes is the CCM-$REG_{25\text{-}45}$. CCM-$REG_{25\text{-}45}$ is a multicenter prospective observational registry designed to address long-term (3-year) mortality of patients who received CCM as part of routine clinical indication in Europe compared with the predicted mortality assessed by the SHFM [41]. 140 were enrolled in the overall cohort (CCM-$REG_{25\text{-}45}$), among them: 83 patients were in the CCM-$REG_{25\text{-}34}$ subgroup and 57 patients were in the CCM-$REG_{34\text{-}45}$ subgroup. Patients were well treated in accordance to GDMT at time of enrollment (>90% received RAAS inhibitors and β blockers). The study showed that observed survival in the overall group (CCM: 25–45%) and in the lower LVEF group (CCM: 25–34%) were similar to predicted survival by the SHFM (P: NS for both). Interestingly, in the CCM-REG 35–45% group, observed survival was significantly higher than predicted survival by the SHFM ($p = 0.046$). The study also showed significant improvement in NYHA functional class and quality of life assessed by MLHFQ, as well as marked reduction in heart failure hospitalization rate in the 2 years following CCM implant across all LVEF ranges.

The study results provide further insight into the clinical benefits of CCM among patients selected in a practice setting and strengthen CCM position as an emerging therapy in heart failure therapeutic algorithm. In this study, the investigators have not only emphasized the outcome of prior randomized studies that substantiated CCM effectiveness in reducing heart failure hospitalization and improving symptoms and quality of life in patient with

Table 1. Randomized Controlled Trials for Cardiac Contractility Modulation.

Trial name	Patients enrolled and follow-up	Inclusion	Design	End points	Results	Ref.
Pilot study	49 (6 months)	NYHA class III or IV LVEF <35% QRS <130 ms	Randomized, double-blind, pilot study	NYHA class 6MWT Cardiopulmonary stress test (peak VO_2) MLHFQ Holter monitoring	6MWT, peak VO_2 and anaerobic threshold increased more in the treatment group than in control, but were not statistically significant (small sample size) NYHA and MLHFQ improved similarly in the two groups More patients in the treatment group were free of hospitalization for any cause at 6 months No change in ectopy was observed	[35]
FIX-HF-4	164 (3 months)	NYHA class II or III LVEF ≤ 35% QRS <130 ms	Randomized, double-blind, crossover study	Peak VO_2 MLHFQ 6MWT Safety (adverse events)	Exercise tolerance (peak VO_2) and quality of life (MLHFQ) were significantly better, while patients were receiving active treatment with CCM for a 3-month period No significant differences between ON and OFF phases in the number or types of adverse events	[9]
FIX-HF 5	428 (6 months for VAT, Peak VO_2, MLWFQ) (12 months for all-cause mortality and hospitalization)	NYHA class III or IV LVEF ≤35% QRS <130 ms	Prospective, randomized study comparing CCM plus OMT to OMT alone	Primary clinical: – VAT Secondary clinical: – Peak VO_2 – MLHFQ Primary safety: – Composite 12-month noninferiority of all-cause mortality and hospitalizations, 12.5% allowable delta	While VAT did not improve at 6 months, CCM significantly improved peak VO_2 over OMT 48% of OMT and 52% of CCM patients experienced a safety end point, which satisfied the noninferiority criterion	[8]
FIX-HF-5C	160 (6 months)	NYHA class III or IV EF 25–45% QRS <130 ms	Prospective, randomized study of comparing CCM plus OMT to OMT alone	Primary clinical: – Peak VO_2 – 6MWT Primary safety: – Composite of cardiovascular death and heart failure hospitalizations	The difference in peak VO_2 between groups was 0.84 (95% Bayesian credible interval: 0.123–1.552) ml O_2/kg/min, satisfying the primary end point MLHFQ, NYHA functional class and 6-min hall walk all improved in the treatment versus control group The composite of cardiovascular death and HF hospitalizations was reduced from 10.8 to 2.9% (p = 0.048)	[38]

6MWT: Six-minute walk test; CCM: Cardiac contractility modulation; HF: Heart failure; EF: Ejection fraction; LVEF: Left ventricular ejection fraction; MLHFQ: Minnesota living with heart failure questionnaire; NYHA: New York Heart Association; OMT: Optimal medical therapy; VAT: Ventilatory anaerobic threshold.

moderately reduced EF and narrow QRS but they also showed that those benefits were sustained after 2 years of follow-up and were present among all LVEF spectrum. Most importantly, this study establishes the long-term safety profile of CCM therapy that extends to 3 years of follow-up as compared with maximum of 1 year of follow-up in prior randomized trials [8–10].

Despite its prospective design, the study is a single-arm observational analysis that compared observed outcome against predicted model. SHFM is well-validated predictor of heart failure mortality and widely used in clinical settings. Yet the absence of an actual concurrent-matched control arm significantly weakens the validity of the study results. Objective measurement of functional capacity such as metabolic exercise testing or 6-min hallway walk could have provided more rigorous evidence of functional improvement.

Expanded optimizer use

The clinical trials to date demonstrate safety and efficacy of CCM therapy for patients with symptomatic moderate-to-severe heart failure with an EF 25–45% in normal sinus rhythm and narrow QRS (<130 ms). However, CCM therapy may be beneficial patients with atrial fibrillation or patients with wide QRS (>130 ms) based on recently published case series.

Atrial fibrillation

Timing algorithms for delivery the CCM signal rely on sequential sensing of the p-wave and depolarizations of each ventricular lead. This reliance means that patients with high burdens of atrial fibrillation were excluded from

clinical trials. A small case series of five patients demonstrated that the algorithm could be successful adjusted to recognize paced atrial stimulation [42]. In these patients with atrial fibrillation and heart failure, they were upgraded to a CRT device with an atrial lead. The atrial sensitivity was set low resulting in compulsory atrial stimulation followed by biventricular pacing. The CCM system was implanted and recognized the atrial stimulation resulting in properly deployed CCM therapy. In this case series, patients did have improvement of clinical symptoms by NYHA class and MLHFQ. In another case series, one heart failure patient with persistent atrial fibrillation was implanted with a CCM device [43]. Because of intermittent ventricular depolarization sensing, CCM stimulation only occurred in 74% of QRS complexes. The treatment window was extended to allow for more therapeutic stimulation. The patient had improvement in his NYHA class and exercise tolerance.

CRT nonresponders

To benefit from CRT, a patient should have a left bundle-branch block (wide QRS: >130 ms), normal sinus rhythm and LVEF less than 35% [44]. Of those with CRT, up to a third are nonresponders and do not benefit from CRT [4,45,46]. In a small feasibility study, CCM devices were implanted in 16 patients who did not respond to CRT and optimized medical therapy [47]. Acute CCM response was noted, but no long-term follow-up on efficacy was evaluated. No electrical interference was noted between CCM and CRT systems, but cardiac event rates were high. In a more recent open-label, treatment-only, feasibility study, 17 CRT nonresponders had CCM implanted [48]. Patients were assessed at baseline and 6 months after CCM therapy. EF trended up. Significant improvements were shown in NYHA class, MLHFQ, 6MWT and peak VO_2 [48].

Optimizer Smart use

The clinical trials used to gain FDA approval of the Optimizer system used the three lead Optimizer IV CE. The current version of the device, Optimizer Smart CE, only uses two ventricular leads with an optional atrial lead. In a case series of five patients with different clinical patterns of heart failure with EF less than 35%, this newest-generation Optimizer Smart CE device was used [43]. In the patient with permanent atrial fibrillation, CCM was only activated in 74% of beats during the therapy delivery interval, but the patient had improvement in both NYHA class and 6MWT. Although no improvement was seen in patients with EF less than 25% in the randomized control trial, three patients with EF of 20% and CRT nonresponders were included. One of these patients died during the study. The other two patients had striking increases in EF, NYHA and 6MWT. All four surviving patients reached NYHA functional class II from class III/IV.

Future perspective

CCM is a novel, innovative device-based therapy for heart failure recently approved by the FDA in March 2019. Based on the most recent randomized clinical trials, CCM can benefit patients with symptomatic heart failure despite optimized medical therapy with normal sinus rhythm and QRS less than 130 s. The significance of CCM is that it provides additional device-based therapeutic benefits to patients who do not otherwise qualify for CRT (narrow QRS). CCM also expands the indication beyond the traditional LVEF cutoff of 35% to a newer group including patients who fall in midrange LVEF group, up to 45%. Importantly, these studies were conducted in era prior to extensive use of sacubitril/valsartan and ivabradine. Further prospective trials that address mortality in a prospective randomized fashion on background of current medical therapies are needed to confirm survival benefits.

With recent FDA approval, the adoption of this technology will soon be widespread (Figure 4). Infrastructure will be needed to support implementation of this novel device. Electrophysiologists will need some training in implantation of CCM devices. Device clinic staff will also need training in interrogation, evaluation and optimization of CCM. As implantation and interrogation techniques are similar to the ICD and CRT procedures, we anticipate a straightforward implementation process and infrastructure development.

Future changes can be anticipated in the refinement of this technology. A small randomized control trial of 48 patients found that the efficacy and safety of CCM was similar when the signal was delivered through a single ventricular lead rather than dual ventricular leads [49]. Thus, future models will likely consist of a single ventricular lead. In addition, a device that combines ICD and CCM in a single lead is currently under investigation. Given that many patients with an ICD could qualify for a CCM, this combination lead may become the new industry standard within the next decade.

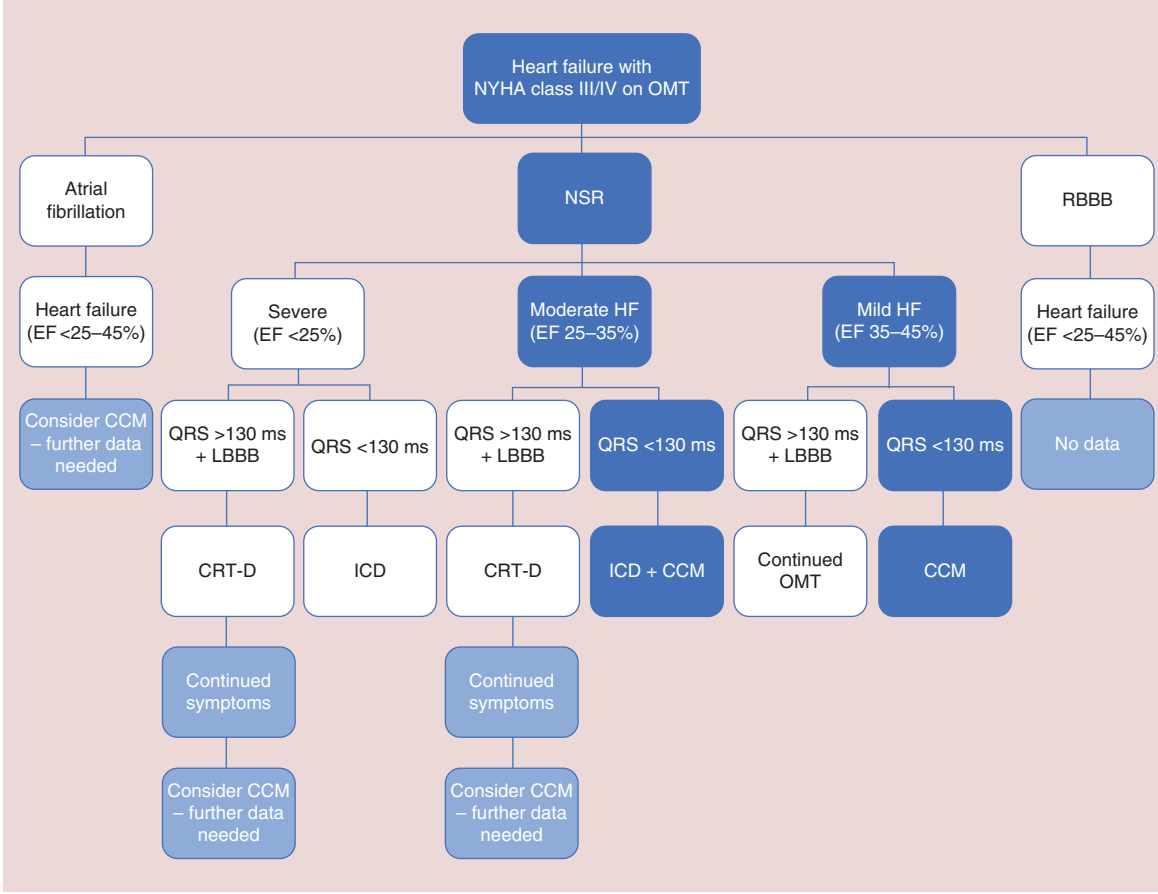

Figure 4. Intracardiac device-based therapy decision making pathway. Decision making pathway for intracardiac device-based therapy for patients with heart failure based on based on EF and electrocardiogram characteristics. Dark blue boxes indicate FDA-approved CCM indications. Light blue boxes are supported by very limited case reports and need further studies.
CCM: Cardiac contractility modulation; CRT: Cardiac resynchronization therapy; EF: Ejection fraction; HF: Heart failure; ICD: Implanted cardiac defibrillator; LBBB: Left bundle branch block; NSR: Normal sinus rhythm; NYHA: New York Heart Association; OMT: Optimal medical therapy; RBBB: Right bundle branch block.

CCM's potential benefit in atrial fibrillation is promising. In a few published cases, patients with atrial fibrillation had improvement in functional status with CCM. One patient had clinical benefit with only intermittent CCM delivery during frequent atrial fibrillation. Given that CCM therapy is only activated 8–12 h per day in patients with normal sinus rhythm, this decreased delivery percentage may not be detrimental. In contrast, CRT requires more than 90% capture for benefit, and the therapy is delivered constantly. Another alternative for patients with atrial fibrillation is to use an atrial lead with decreased atrial sensing with atrial pacing to maximize CCM delivery. Larger randomized studies should be anticipated exploring this potential benefit group.

Patients who currently qualify for CRT should be considered in future studies. Nonexcitatory CCM therapy is distinctly different than excitatory CRT. Theoretically, there is no reason both therapies cannot be of benefit to the same patient. Despite the current need for up to six implanted leads, initial studies in CRT nonresponders already show promise for CCM in this population. Whether patients who benefit from CRT can also benefit from CCM remains to be evaluated and would be more feasible with a single CCM lead system. One can postulate that a combination ICD-CCM lead could become an integral part of CRT with defibrillator (CRT-D).

Patients with reduced EF and a right bundle-branch block should also be investigated. These patients have a wide QRS but do not qualify for CRT and have not been included in any of these device trials. A few cases of patients with wider QRS despite CRT show benefit [43,47,48]. It seems reasonable that patients with right bundle-branch block may also benefit.

Although clinical trials did not show benefit in patients with EF less than 25%, published cases do show some striking results in patients with these low range EFs. These results suggest that EF may not be the definitive method to determine which patients may respond to CCM therapy. Improvements in our understanding of heart failure etiology and stratification with molecular mechanisms or markers may lead to better insights into the CCM benefit population.

Lastly, CCM has global effects on the heart. All studies and trials have focused on left ventricular failure. No studies have evaluated CCM effects on patients with right ventricular failure, which has no good treatment options, or diastolic heart failure. Assessment of CCM in these patient population should not be overlooked in future endeavors.

Executive summary

Cardiac contractility modulation

- Cardiac contractility modulation, also referred to as CCM™, device sends nonexcitatory impulses that are delivered during the absolute refractory period of the myocytes' action potential.
- CCM impulses activate intracellular signals that favorably alter gene expression and enhance calcium delivery, which in turn increase myocardial contractility and cardiac efficiency without increasing metabolic demand.
- The newest generation CCM, Optimizer Smart European Conformity (CE), consists of a rechargeable implanted pulse generator, two right ventricular septal leads and an optional atrial lead.

Randomized control trials

- For patients in normal sinus rhythm with QRS less than 130 ms and who have left ventricular ejection fraction between 25 and 45% who remain symptomatic despite optimal medical therapy, randomized clinical trials have demonstrated safety and efficacy of CCM by increased peak ventilatory oxygen, improved Minnesota Living with Heart Failure Questionnaire scores and fewer hospitalizations.

Long-term outcomes

- Long-term safety and benefits have been evaluated in observational studies of up to 3 years, but studies to confirm survival and clinical benefits need to be completed in a prospective, randomized fashion.

Expanded Optimizer Smart CE use

- Small case report series have shown benefit in patients with atrial fibrillation and patients that did not respond to cardiac resynchronization therapy.

Future perspective

- In the next decade, CCM will see refinement including the possible addition of cardiac defibrillation capabilities, wider-spread adoption and expansion/refinement of clinical benefit for the heart failure population.

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In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

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