Taylor & Francis
Taylor & Francis Group

Expert Review of Medical Devices

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierd20

Cardiac contractility modulation for the treatment of moderate to severe HF

Ishu V. Rao & Daniel Burkhoff

To cite this article: Ishu V. Rao & Daniel Burkhoff (2021) Cardiac contractility modulation for the treatment of moderate to severe HF, Expert Review of Medical Devices, 18:1, 15-21, DOI: 10.1080/17434440.2020.1853525

To link to this article: https://doi.org/10.1080/17434440.2020.1853525

EXPERT REVIEW OF MEDICAL DEVICES
2021, VOL. 18, NO. 1, 15–21
https://doi.org/10.1080/17434440.2020.1853525

Taylor & Francis
Taylor & Francis Group

REVIEW

Cardiac contractility modulation for the treatment of moderate to severe HF

Ishu V. Rao[a] and Daniel Burkhoff[b]

[a]Medical Director and Vice President of Clinical Affairs, Impulse Dynamics, Marlton, NJ, USA; [b]Heart Failure, Hemodynamics and MCS Research, Cardiovascular Research Foundation, New York, NY, USA

ABSTRACT

Introduction: Heart failure (HF) affects over 6 million Americans and approximately 650,000 new cases are diagnosed annually, with patients evenly split between HFrEF and HFpEF. Recent advances in therapy for these patients have been limited to pharmaceutical agents, with CRT remaining the most reliable device therapy option since its advent almost twenty years ago. In 2019, after almost two decades without the introduction of a new device therapy for the treatment of moderate HF, the FDA approved CCM® therapy, delivered by the Optimizer Smart device, for patients with NYHA Class III HF who are on guideline-directed medical therapy (GDMT), in normal sinus rhythm (NSR), and with EF ranging from 25% to 45%, and who are ineligible for CRT.

Areas covered: Multiple clinical trials support the use of CCM to improve quality of life, functional class, and 6-min hall walk distance. This article will discuss the science behind CCM therapy, the presumed mechanisms of action, the pre-clinical studies that shaped subsequent endeavors, and the clinical trials that support its use.

Expert opinion: The introduction of CCM therapy bridges a therapeutic gap for patients with few or no other therapeutic options for NYHA III heart failure.

ARTICLE HISTORY
Received 17 September 2020
Accepted 17 November 2020

KEYWORDS
Cardiac contractility modulation; CCM; heart failure; HFrEF; HFpEF; optimizer; SERCA2a

1. Introduction

HF affects over 6 million Americans and over 25 million individuals worldwide. HF has been categorized phenotypically into HFrEF (HF with reduced ejection fraction) describing the population of patients with EF ≤ 35%; HFpEF (HF with preserved ejection fraction) describing patients, typically, with EF ≥ 45%; and the recently coined HFmrEF (HF with moderately reduced ejection fraction) describing patients with EF 35–45%.

For patients with compromised ventricular function, the cornerstones of therapy have long included beta-blockers, ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists[1]. More recently, promising data has added ARNis [2] and SGLT2i [3] to an ideal medication regimen. A subset of patients with EF ≤ 35% and significant conduction delay have gleaned benefit from CRT. However, despite advances in science, technology, and skillset, 30% of patients do not respond to CRT, and this number has been surprisingly constant since the inception of the therapy [4].

CCM has been studied in pre-clinical and clinical studies over the past two decades and has now been found to benefit a population of patients characterized as having:

- NYHA Class III status
- EF 25–45%
- Normal sinus rhythm
- No indication for CRT

This article will outline the salient points surrounding CCM therapy.

2. Body of review

2.1. Overview of the market

Despite widespread adoption of GDMT and CRT, a large patient population continues to experience symptomatic HF. CRT and left ventricular assist devices (LVADs) are established mainstays of device therapy for HF. However, 30% of patients do not respond to CRT, and LVAD therapy is restricted to a small proportion of patients with advanced, end-stage HF. The population of patients in the US that have NYHA III CHF and HFrEF who would not qualify for CRT is estimated to be well over 600,000 individuals, about twice the number of patients that qualify for CRT.

2.2. Introduction to the device

CCM is delivered by the Optimizer Smart device. The system is comprised of a pulse generator (produced by Impulse Dynamics) and two commercially available pacemaker leads that are placed using techniques similar to pacemaker and defibrillator implantation. As with pacemaker implantation, the Optimizer Smart implantation procedure requires an upper chest incision and insertion of two pacing leads via subclavian venous system vascular access. The only tangible departure from the pacemaker

CONTACT Ishu V. Rao i.rao@impulse-dynamics.com Impulse Dynamics, Marlton, NJ 08053-3449, USA

Supplemental data for this article can be accessed here.

Article highlights

- CCM is a novel therapy that uses high voltage currents delivered during the absolute refractory period (ARP) of the cardiac cycle.
- The Optimizer Smart device and two commercially available pacing leads with low polarization coating are implanted in a procedure similar to dual-chamber pacemaker implantation, with complication rates and recovery times that parallel that procedure.
- The mechanisms of action are felt to be twofold:
  - Improvement of calcium handling within the myocyte.
  - Normalization of abnormal gene expression seen in HF.
- The improvement in contractility does not come at the expense of increased myocardial oxygen consumption (MVO_2).
- Clinical trials have demonstrated improvement in peak VO_2, six-minute walk distance (6 MW), and New York Heart Association (NYHA) functional class.
- Patients indicated for CCM include those with:
  - NYHA Class III status.
  - EF 25–45%.
  - Normal sinus rhythm at the time of implantation.
  - No current indication for CRT.

implantation procedure is that, rather than single leads implanted into atrium and ventricle, both leads are actively fixed into the right ventricular septum. Resource utilization, including catheterization laboratory time and materials, are nearly identical, and no special training is required for the lab staff supporting the procedure. Pre-operative preparation and post-operative recovery are similar, and the procedure can be performed with minimal sedation. Not surprisingly, the 30-day significant adverse event (SAE) rate of Optimizer implantation parallels that of dual-chamber pacemaker implantation, with both reported at approximately 9% [5,6].

The device delivers high output biphasic (±7.5 V), long duration (20 ms) electrical impulses during the absolute refractory period (ARP) of the cardiac cycle. Though the impulses are 300 times the typical pacing capture threshold for ventricular tissue, the therapy is non-excitatory given the timing of impulse delivery.

A unique feature of the Optimizer Smart device is its rechargeable battery. Because of the high amount of current delivered, standard battery technology would result in prohibitively frequent generator replacements. The proprietary rechargeable battery is labeled for 15 years of longevity while requiring the patient to charge with a portable device for only 1 h per week.

Though ostensibly similar to pacemaker therapy (both include pulse generators with two pacing leads; both deliver electrical impulses to the ventricular myocardium; the implantation procedures are virtually identical), CCM is contrasted from pacing in many ways:

- CCM does not result in wave front propagation or myocardial excitation.
- Both leads are implanted into the right ventricular septum, ideally separated by at least 2 cm.
- The Optimizer Smart is not capable of delivering pacing impulses.
- In the US, therapy is delivered intermittently in five 1-h periods spread equally throughout the 24-h clock.

In early studies, efficacy was evaluated at various 'doses' of CCM ranging from 3 to 12 h per day. No detectable difference was found between 5 and 12 h. Studies in the US were done with 5-h CCM therapy per day (which is the currently approved dose in the US), whereas in EU most recent studies have been done with 7 h per day. In either case, hours of daily delivery can be increased based on clinical response.

Because of the ease of implantation and safety profile of Optimizer Smart implantation (complication rates mirror those of dual-chamber pacemaker procedures), CCM therapy is appropriate for virtually all indicated patients. Current indications are as noted above.

While current FDA labeling states that patients must be in NSR at the time of Optimizer implantation, this may be the result of cardioversion, even at the time of the procedure. As such, only patients with permanent, non-cardiovertible atrial fibrillation (AF) are currently excluded from receiving CCM therapy. Data from the recent FIX-HF-5-C2 trial that studied the two-lead system (i.e., no atrial lead) included 15% of patients with permanent AF; the results showed that this system provided equivalent doses of CCM to patients with AF as to those in normal sinus rhythm, with similar efficacy and safety profiles [7]. This study led to FDA approval for the two-lead system in October 2019.

Subgroup analysis from the FIX-HF-5 trial showed that patients with EF < 25% did not show significant benefit from CCM (though it should be noted that they did not do worse, either) and as such, are not included in the regulatory labeling [8].

Though many patients eligible for CCM have existing defibrillators in place, clinical studies showed that addition of an Optimizer implant on the contralateral side was safe. No reports of tricuspid regurgitation were seen in the 283 patients in the FIX-HF-5 and FIX-HF-5 C trials who received Optimizer devices and had concomitant ICDs, despite having a total of three leads crossing the tricuspid valve.

An economic analysis performed in Great Britain concluded that CCM therapy was likely to be cost-effective for the indicated population in that country's healthcare system [9]. Institutions that currently implant pacemakers can adopt CCM therapy delivery into their programs with no additional equipment needs (other than the Optimizer Smart IPG) and minimal need for additional training of personnel.

2.3. Clinical profile and post-marketing findings

2.3.1. Early bench studies

Studies which spawned the concepts which would give rise to CCM were first conducted in the 1960s by EH Wood and colleagues [10]. Using the sucrose gap technique, superfused thin bundles of sheep and calf ventricular fibers were studied in a muscle bath to evaluate the effects of varying action potential voltage and duration on contractile force. These experiments showed that when voltage of the action potential plateau (phase 3) was increased, contractile force also increased. Further studies showed that this was due to increased calcium loading of the sarcoplasmic reticulum.

Subsequent studies in rabbit cardiac muscle fibers that employed field stimulation in the muscle bath (instead of sucrose gap technique) showed that similar effects on contractility could be achieved when muscles were subjected to high-intensity electrical fields during the plateau of the action potential. Such studies were replicated in failing human cardiac muscle obtained following explantation of hearts at the time of orthotopic transplantation [11]. The extracellular fields were called cardiac contractility modulation (CCM) signals.

2.3.2. Mechanism of action

Mechanisms which resulted in clinical improvement were felt to fall into two categories:

(1) Improvement in calcium handling
(2) Normalization of pathologic HF gene expression

2.3.2.1. Improvement in calcium handling.

Force production in the cardiac myocyte depends largely on calcium concentration in the cytosol of the cell. The process of contraction begins when a triggering amount of calcium enters the cell via the L-type calcium channel and triggers the ryanodine receptor on the sarcoplasmic reticulum (SR) to release its calcium content to the cytosol. It is this calcium that is responsible for facilitating actin-myosin cross-bridging, which leads to filament sliding and force production. Calcium must be removed from the cytosol to allow filament dissociation. Reuptake of calcium into the SR is facilitated by the protein SERCA2a.

CCM has been found to phosphorylate the protein phospholamban which, in its unphosphorylated state, acts to inhibit the function of SERCA2a. Once phosphorylated, phospholamban dissociates from SERCA2a and its ability to pump calcium back into the SR is increased, thus improving calcium reuptake into the SR.

2.3.2.2. Normalization of pathologic HF gene expression.

In the failing heart, gene expression is pathologically altered. One class of genes that are affected are the genes responsible for calcium cycling, such as the ryanodine receptor and SERCA2a, which are abnormally downregulated in HF, while other 'fetal genes' associated with increased stress are abnormally upregulated. The end result is a downward spiral of ventricular dysfunction and pathologic remodeling.

Endomyocardial biopsies obtained from a subset of 11 patients who participated in the FIX-HF-4 trial were evaluated for changes in gene expression [12]. The HF gene expression profile was found to be reversed (toward normal) in patients who received CCM. Further, it was seen that these effects were present with CCM delivery but waned after cessation of therapy. Other studies confirmed that protein expression followed gene expression, so the beneficial effects of normalization of gene expression could be expected to translate to clinical benefit.

A biopsy study in dogs was performed to elucidate (a) the local and remote effects of CCM on gene expression, and (b) whether said effects evolved over time. Not surprisingly, acute gene expression (at the time of device implantation and therapy initiation) revealed local improvement (at the lead implantation site) but no such activity was demonstrated at a remote site. However, after 3 months, both local and remote sites showed improved gene expression, implying that a global effect occurred, possibly due to secondary beneficial systemic effects of improved LV function [13].

2.3.2.3. Myocardial oxygen consumption.

CCM implanted in seven dogs (compared to seven sham treatment animals) showed improved metrics of left ventricular function as well as decreased myocardial oxygen consumption. Subsequent studies in humans (utilizing right and left heart catheterization in one study of 9 patients and PET scans in another study of 23 patients) confirmed that no increase in MVO_2 occurred with use of CCM [14]. Though pharmacologic inotrope therapy also improves ventricular contractile function, the parallels to CCM likely end there. Inotropes have been shown to increase MVO_2 [14] and arrhythmias [15], while CCM notably does neither. CCM more closely mimics beta-blocker therapy or CRT, both of which improve cardiac performance and revert gene expression profile toward normal without the expense of increased MVO_2.

2.3.3. Reverse remodeling

Though none of the clinical trials (detailed below) evaluated echocardiographic metrics of left ventricular function as a prespecified endpoint, a number of studies examined the effects of CCM on ventricular performance.

The aforementioned study of 14 dogs (seven sham and seven with CCM therapy), assessed LVEF, LVESV, and LVEDV [14]. The CCM dogs showed an absolute improvement of 6% in LVEF, representing a 10% increase when compared to the sham dogs. Similarly, there was a 15 ml difference in LVESV, and an 11 ml difference in LVEDV, both favoring CCM.

Reverse remodeling was assessed by Yu et al. in 30 human patients who received CCM therapy, where LVESV improved by 11.5% and LVEF improved by almost 5%[16]. Additionally, myocardial contraction was improved in all LV wall segments, not simply limited to the site of lead implantation; thus, providing additional evidence of the global positive impacts of CCM. The authors concluded that CCM may contribute to reverse remodeling and improvement in systolic function.

2.3.4. Timing of benefit

Improvements of myocardial properties observed with CCM progress over time. These effects have been consistently observed over three timeframes.

Within minutes to hours, local electrotonic spread results in phosphorylation of key proteins, improvement of calcium handling, and augmented local contractility. Some of the immediate beneficial changes are triggered by neurohormonal adjustments that occur because of activation of afferent parasympathetic signals due to augmented contraction in the interventricular septum.

Within weeks, reversal of the abnormal gene expression associated with HF takes place. This includes the phenotypic reversal of the fetal gene program to a more normal adult program.

Finally, within months, evidence of reverse remodeling becomes apparent. Patients often begin to experience benefit within weeks of therapy initiation with further increase occurring over time.

2.3.5. Clinical trials

Clinical trials of CCM began with human studies in the early 2000s that proved feasibility in small patient cohorts. Thereafter, the FIX-HF-4 study was conducted, which randomized 164 patients in a double-blind, double-crossover design [17]. It enrolled subjects with EF ≤ 35% with NYHA Class II (24%) or III (76%) and randomly assigned them to Group 1 (N = 80, CCM ON 3 months, CCM OFF 3 months) or Group 2 (N = 84, reversed treatment sequence). The co-primary endpoints were changes in peak VO_2 and MLWHFQ. Peak VO_2 showed statistically significant superiority with CCM ON vs OFF, and MLWHFQ trended better when CCM was ON. The authors concluded that CCM was a safe and effective modality to treat HF when patients received CCM applied over a 3-month period.

The FIX-HF-5 pivotal study was a prospective, randomized, parallel group, controlled trial of 428 patients randomized to optimal medical therapy (OMT) plus CCM therapy (N = 215) vs OMT alone (N = 213) [9]. Enrolled patients had site investigator determined EF ≤ 35% and NYHA Class III or ambulatory IV symptoms despite GDMT. Because of the unblinded nature of the study, the FDA mandated that VO_2 at anaerobic threshold (VAT) serve as the primary endpoint as it was felt to be more objective. Secondary endpoints included peak VO_2, MLWHFQ, 6 MW, and NYHA class.

The study met its primary safety endpoint but not the unique primary endpoint. VAT had never been validated for use in HF trials and has since been abandoned for future trials [18]. VAT by its very nature is indeterminate in a large proportion of patients with HF, especially in those with limited exercise tolerance. This resulted in 30% missing or indeterminate data, leading to the primary endpoint not being met in the FIX-HF-5 study.

Despite this, peak VO_2 showed a significant difference of 1.31 ml/kg/min between treatment groups, and additionally, QoL score improved by nearly 10 points.

Subgroup analyses indicated that patients with LVEF ≥ 25% responded better in VAT, peak VO_2, QoL, 6 MW, and NYHA class compared with patients with EF < 25% (though there was no detrimental effect of CCM on the EF < 25% group). Further, core lab evaluation of the echocardiographic studies at enrollment showed that the patients' EFs ranged up to 45%. Serendipitously, these patients with higher EFs also showed significant improvement. These data informed subsequent trial design for the FIX-HF-5 C confirmatory trial.

FIX-HF-5 C[18] was a prospective, randomized, multicenter study of 160 patients with NYHA Class III and ambulatory IV symptoms and EF ranging from 25% to 45% who were randomly assigned with 1:1 allocation to either the CCM + OMT group (N = 74) or OMT alone (N = 86). The primary endpoint was defined as difference in peak VO_2, and a prespecified Bayesian statistical approach was used to leverage the peak VO_2 data from the FIX-HF-5 study. The prior data was weighted to contribute only 30% to the overall assessment, thus ensuring that the prospective FIX-HF-5 C data would not be dominated by the prior subgroup data.

The primary endpoint of difference in peak VO_2 was met with a between group difference of 0.84 ml/kg/min. Additionally, secondary and additional endpoints were also evaluated, with key results including:

- 33.7 m improvement in 6 MW in CCM vs OMT patients ($p = 0.0093$)
- 11.7 point improvement in MLWHFQ in CCM vs OMT patients ($p < 0.001$)
- NYHA Class improvement of ≥1 class in 81% of patients in CCM group vs 42% of patients in OMT group ($p < 0.001$)

CCM therapy in the FIX-HF-5 C trial compared very favorably against CRT therapy in the MIRACLE [19]trial:

- Peak VO_2: 0.84 ml/kg/min (CCM) vs. 0.9 ml/kg/min (CRT)
- 6 MW improvement: 33.7 m (CCM) vs. 29 m (CRT)
- MLWHFQ improvement: 11.7 points (CCM) vs. 9 points (CRT)
- NYHA Class improvement of ≥1 class: 81% (CCM) vs. 68% (CRT)

A post hoc analysis showed substantial improvement in the combined endpoint of cardiovascular death and HF hospitalization in patients treated with CCM compared to controls, though the benefit was derived almost entirely from a reduction in hospitalization.

Based on the results of the FIX-HF-5 C data, the FDA granted approval of the three-lead (one atrial lead for sensing, two ventricular leads for sensing and CCM delivery) system on 21 March 2019.

Though all prior trials were performed with the three-lead device, the atrial lead was used only to sense atrial activity. By using the sensed P-wave, it could be determined whether the subsequent QRS was of supraventricular origin, thus establishing a safe timing window for the delivery of CCM therapy. In addition to the sensed P-wave, a unique sensing algorithm utilizing the two ventricular leads was also employed to differentiate impulses of supraventricular (i.e., sinus rhythm or AF) vs. ventricular origin (i.e., PVCs). This proprietary sensing algorithm utilized a combination of wave front propagation and conduction velocity to determine atrial vs. ventricular site of origin. The algorithm using only two ventricular leads was found to be equally effective to the three-lead system. As such, a two-lead system configuration was evaluated for safety, efficacy, and ability to deliver adequate amounts of CCM therapy in the **FIX-HF-5 C2** trial [8]. This study enrolled 60 subjects in the same patient population as in the FIX-HF-5 C study. The patients all received CCM therapy and the same Bayesian statistical approach was used to compare efficacy and safety with cohorts from the FIX-HF-5 C trial.

The net difference in peak VO_2 between the treated patients and a retrospective control group was 1.72 ml/kg/min (using Bayesian statistical approach) in favor of CCM treatment. Additionally, the primary safety endpoint was reached, and equal amounts of CCM were delivered by the two-lead system as were delivered by its three-lead predecessor in the prior studies.

One unique difference in the enrollment criteria was the allowance for patients with AF to be enrolled in the FIX-HF-5C2 trial. Fifteen percent of the 60 subjects (N = 9) carried the diagnosis of AF, and no decrease in CCM therapy delivery, efficacy, or safety were seen in this group, thus supporting the hypothesis that patients with AF could benefit from CCM as well.

2.3.6. Registry studies

Two multi-center registries of CCM therapy were sponsored by XXX and published to include data on 283 patients implanted with Optimizer devices.

The CCM-HF Registry was a 2-year multi-center registry of 143 patients with reduced LVEF treated with CCM. A total of 106 patients completed the 2-year follow-up [20]. NYHA class, 6 MW, QoL, LVEF, and peak VO_2 as well as serious adverse events and mortality rates were all recorded. Short term (6 months) and prolonged improvements in NYHA class, MLWHFQ score, and LVEF were demonstrated. The authors concluded that CCM therapy was a safe and effective treatment for patients with reduced EF HF and narrow QRS.

The CCM-REG registry was a multi-center observational study enrolling patients in whom the Optimizer system was implanted as part of routine care. Data were collected at routine care visits at baseline and every 6 months through a maximum of 2 years for functional parameters and 3 years for vital status.

A published analysis focusing on patients similar in profile to those in FIX-HF-5 C (i.e., those ineligible for CRT, with EF 25–45% and NYHA III/IV) included 140 such patients from 31 sites who met these criteria [21]. Patients were well treated on GDMT (>90% on ACE or ARB, 93% on beta blockers). Significant improvements were seen in NYHA class and MLWHFQ score.

Cardiovascular and HF hospitalization rates were evaluated by comparing the 12 months prior to device implantation against the subsequent 24 months. The combined endpoint was reduced by 71% in the entire cohort of patients with EF 25–45%, with an even greater benefit of 80% reduction seen in the population of patients with EF 35–45%.

In this real-world experience, the authors concluded that the results confirmed previous trial data, and that CCM therapy is a valuable device option for patients ineligible for CRT.

Of note, the finding that patients with a higher EF derive greater benefit from CCM has been observed repeatedly in multiple prior studies, including the FIX-HF-5 subgroup and FIX-HF-5 C study itself. Though unconfirmed, hypotheses for improvement in this group include improved lusitropy, possibly from phosphorylation of proteins such as titin that function in diastole, and augmentation of unrecognized poor contractile reserve.

2.4. Potential drawbacks and limitations

As previously described, the implantation procedure for the Optimizer Smart is strikingly similar to pacemaker implantation, and carries the same risks, 30-day SAE rates, and resource utilization. However, with the placement of two leads across the tricuspid valve, often in the presence of an existing defibrillator lead (over 90% of patients in the FIX-HF-5 and FIX-HF-5 C trials who received Optimizers had concomitant ICDs), the very reasonable concern of tricuspid valve insufficiency has been raised. However, in the 273 such patients in these trials, there were no reports of tricuspid regurgitation. Further, in a yet to be published European registry of 517 patients, there were no tricuspid valve-related SAEs.

Infection rates parallel those seen with de novo pacemaker implantation [5,6] and in the FIX-HF-5C trial were not significantly different from the control group. Incidence of thromboembolism also showed no significant difference between groups in the same trial.

Regarding the therapy itself, no detrimental effects have been reported. As noted, though patients with EF < 25% did not show significant benefit, they did not show deterioration with CCM therapy. In the FIX-HF-5C trial, 81% of patients experienced an improvement of at least one NYHA class (and 42% improved two classes), but of the non-responders, none worsened. Finally, there have been no reports of pro-arrhythmia related to CCM therapy in almost 5000 historical worldwide implants.

CCM's impact on heart failure in the era of newer pharmacologic heart failure therapy agents – such as angiotensin receptor-neprilysin inhibitors, SGLT2 inhibitors, and guanylate cyclase stimulators – cannot be assessed as the trials were largely conducted prior to the widespread use of these medications. Indeed, the full scope of utilization of these therapies is still evolving, and the role of CCM within that environment has yet to be determined.

2.5. Alternative devices

Patients with EF ≤ 35% and QRS ≥ 120 ms have been shown to benefit from Cardiac Resynchronization Therapy. However, despite advances in all aspects of therapy delivery, 30% of patients continue to show minimal or no response to CRT. Subsets of patients who reliably show substantial response include those with QRS ≥ 150 ms and those with LBBB conduction [22]. However, applying these criteria to the entire eligible cohort of patients necessarily results in a dramatic reduction in the number of patients who might be candidates for this therapy.

In the recently published BEAT-HF study, Baroreceptor Activation Therapy (BAT) benefited patients with EF ≤ 35% and NT-proBNP ≤1600 who were not indicated for CRT [23]. While the initial data appear to be promising, additional studies validating these results are needed. Further, limitations on patient selection, possibly due to coincident carotid artery disease, may pose barriers to therapy delivery. Nevertheless, BAT offers yet another option for device-based therapy for treatment of refractory heart failure.

2.6. Regulatory status

The Optimizer Smart System which delivers Cardiac Contractility Modulation therapy is indicated to:

- Improve functional status
- Improve 6-min hall walk distance, and
- Improve quality of life

for NYHA Class III HF patients who:

- Remain symptomatic despite guideline-directed medical therapy.
- Have a left ventricular ejection fraction ranging from 25% to 45%.
- Are in normal sinus rhythm.
- Are not indicated for Cardiac Resynchronization Therapy.

2.7. Conclusion

HF remains a growing problem in the US, with a prevalence of over 6 million patients nationally and an annual incidence of 650,000 cases. Despite new pharmacologic advances, NYHA III patients remain particularly difficult to treat. These patients remain symptomatic despite GDMT. CRT has been the mainstay of device therapy for these patients since its advent nearly two decades ago, but 30% of patients fail to respond. Until recently, no new device therapy has proven to be effective for this population.

CCM received FDA approval in 2019 for patients with NYHA Class III status who remained symptomatic on GDMT, were not candidates for CRT, who were in NSR at the time of device implantation, and who had EF 25–45%. The clinical trials supporting its use, including FIX-HF-5C and FIX-HF-5C2, showed improvement in functional status, 6-min hall walk, and quality of life.

3. Expert opinion

CCM arrives at a time when few effective therapies exist for patients with refractory NYHA Class III HF. The data from clinical trials of CCM compare favorably with the data that supported the use of CRT for two decades. Though mortality data have not yet been generated to show benefit for CCM, it must be remembered that CRT was in a similar situation at its inception yet proved to provide immense symptom relief for thousands of patients. With its wide range of EF inclusion (25–45%), CCM can benefit roughly twice as many patients as are currently indicated for CRT. Additionally, it should be appreciated that over 80% of patients improve at least one NYHA class, and over 40% of patients improve two classes. The ease of implantation, uneventful procedural recovery, extraordinary device longevity, and favorable risk profile all position CCM as an important tool in the treatment of HF patients.

The finding that CCM benefits are heightened in patients with progressively higher EFs has led to the design of an upcoming trial evaluating the benefits of CCM in the rapidly growing population of patients with HF and mid-range and preserved EFs. This trial seeks to evaluate CCM in patients with EF from 40% to 60%. There is great optimism that CCM will show benefit in patients across this EF spectrum, and for whom no treatment options exist at all.

As indicated above, CCM therapy is currently often delivered in patients in need of or already having a concomitant ICD. In the FIX-HF-5 and FIX-HF-5C trials, over 90% of patients required both CCM and ICD devices, thus necessitating bilateral implants. Impulse Dynamics is developing a combined single-chamber ICD-CCM device and anticipates initiating an IDE trial in 2021. With one device and two leads, it will offer the combined therapies of both devices in one unit. Additionally, this device will utilize the rechargeable battery for all non-life-supporting functions which is expected to leave the system with a 20-year battery longevity.

The next 5 years of advances in HF therapy can be expected to include expansion of indications for CCM to include patients with EF 25–60%, and Optimizer devices that incorporate existing therapies such as defibrillation and potentially standard pacing and CRT along with CCM in a single device.

Information resources

www.impulse-dynamics.com

Declaration of interest

I Rao is employed as the Medical Director of Impulse Dynamics; and is the owner of stock options in Impulse Dynamics. D Burkhoff is a consultant to Impulse Dynamics; and is the owner of stock options in Impulse Dynamics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart failure society of America. Circulation. 2017;136(6):e137–e161.
2. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993–1004.
3. JJV M, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008.
4. Daubert C, Behar N, Martins RP, et al. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. Eur Heart J. 2017;38(19):1463–1472.
5. Abraham WT, Kuck KH, Goldsmith RL, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation. JACC Heart Fail. 2018 Oct;6(10):874–883. Epub 2018 May 10. PMID: 29754812
   • **These citations reference articles which presented the results of clinical and registry trials which shaped the regulatory approval and clinical acceptance of CCM therapy.**
6. Cantillon DJ, Exner DV, Badie N, et al. Complications and health care costs associated with transvenous cardiac pacemakers in a nationwide assessment. JACC Clin Electrophysiol. 2017 Nov;3(11):1296–1305. . Epub 2017 Aug 30. PMID: 29759627.

7. Wiegn P, Chan R, Jost C, et al. Safety, performance, and efficacy of cardiac contractility modulation delivered by the 2-lead optimizer smart system: the FIX-HF-5C2 study. Circ Heart Fail. 2020;13(4):e006512.
   • These citations reference articles which presented the results of clinical and registry trials which shaped the regulatory approval and clinical acceptance of CCM therapy.
8. Abraham WT, Nademanee K, Volosin K, et al. Subgroup analysis of a randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. J Card Fail. 2011;17(9):710–717.
   • These citations reference articles which presented the results of clinical and registry trials which shaped the regulatory approval and clinical acceptance of CCM therapy.
9. Witte K, Hasenfuss G, Kloppe A, et al. Cost-effectiveness of a cardiac contractility modulation device in heart failure with normal QRS duration. ESC Heart Fail. 2019;6(6):1178–1187.
10. Wood EH, Heppner RL, Weidmann S. Inotropic effects of electric currents. I. Positive and negative effects of constant electric currents or current pulses applied during cardiac action potentials. II. Hypotheses: calcium movements, excitation-contraction coupling and inotropic effects. Circ Res. 1969;24(3):409–445.
11. Lyon AR, Samara MA, Feldman DS. Cardiac contractility modulation therapy in advanced systolic heart failure [published correction appears in Nat Rev Cardiol. 2014 Apr;11(4):188]. Nat Rev Cardiol. 2013;10(10):584–598.
   •• These citations reference articles which provide in-depth discussion on the scientific and mechanistic background and rationale for CCM therapy.
12. Butter C, Rastogi S, Minden HH, et al. Cardiac contractility modulation electrical signals improve myocardial gene expression in patients with heart failure. J Am Coll Cardiol. 2008;51(18):1784–1789.
   •• These citations reference articles which provide in-depth discussion on the scientific and mechanistic background and rationale for CCM therapy.
13. Imai M, Rastogi S, Gupta RC, et al. Therapy with cardiac contractility modulation electrical signals improves left ventricular function and remodeling in dogs with chronic heart failure. J Am Coll Cardiol. 2007;49(21):2120–2128.
   •• These citations reference articles which provide in-depth discussion on the scientific and mechanistic background and rationale for CCM therapy.
14. Headrick JP, Willis RJ. Relation between the O2 supply:demand ratio, MVO2, and adenosine formation in hearts stimulated with inotropic agents [published correction appears in Can J Physiol Pharmacol 1990 Jun;68(6):752]. Can J Physiol Pharmacol. 1990;68(1):110–118.
15. Overgaard CB, Dzavík V. Inotropes and vasopressors: review of physiology and clinical use in cardiovascular disease. Circulation. 2008;118(10):1047–1056.
16. Yu CM, Chan JY, Zhang Q, et al. Impact of cardiac contractility modulation on left ventricular global and regional function and remodeling. JACC Cardiovasc Imaging. 2009;2(12):1341–1349.
17. Borggrefe MM, Lawo T, Butter C, et al. Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure. Eur Heart J. 2008;29(8):1019–1028.
18. Kadish A, Nademanee K, Volosin K, et al. A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure [published correction appears in Am Heart J. 2011 Jun;161(6):1220]. Am Heart J. 2011;161(2):329–337.e3372.
   • These citations reference articles which presented the results of clinical and registry trials which shaped the regulatory approval and clinical acceptance of CCM therapy.
19. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346(24):1845–1853.
20. Müller D, Remppis A, Schauerte P, et al. Clinical effects of long-term cardiac contractility modulation (CCM) in subjects with heart failure caused by left ventricular systolic dysfunction. Clin Res Cardiol. 2017;106(11):893–904.
21. Anker SD, Borggrefe M, Neuser H, et al. Cardiac contractility modulation improves long-term survival and hospitalizations in heart failure with reduced ejection fraction. Eur J Heart Fail. 2019;21(9):1103–1113.
   • These citations reference articles which presented the results of clinical and registry trials which shaped the regulatory approval and clinical acceptance of CCM therapy.
22. Tracy CM, Epstein AE, et al.; 2012 Writing Group Members. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. J Thorac Cardiovasc Surg. 2012;144(6):e127–e145.
23. Zile MR, Lindenfeld J, Weaver FA, et al. Baroreflex activation therapy in patients with heart failure with reduced ejection fraction. J Am Coll Cardiol. 2020;76(1):1–13.