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Review

Cardiac Contractility Modulation in Patients with Heart Failure with Reduced Left Ventricular Ejection Fraction

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Abstract: Cardiac contractility modulation is an innovative therapy conceived for the treatment of heart failure. It is a device-based therapy, employing multiple electrodes to deliver relatively high-voltage (~7.5 V) biphasic signals to the endocardium of the right ventricular septum, in order to improve heart failure symptoms, exercise capacity and quality of life. Multiple clinical and mechanistic studies have been conducted to investigate the potential usefulness of this technology and, as of now, they suggest that it could have a place in therapy and meet a relevant medical need for a specific sub-category of underserved heart failure patients with reduced left ventricular ejection fraction. More studies are needed to further investigate its effect on outcomes such as mortality and rate of hospitalizations.

Keywords: cardiac contractility modulation; heart failure; HFrEF

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1. Introduction

Heart failure is one of the major causes of morbidity and mortality in the general population; it has a heavy impact on healthcare-related costs and its prevalence has been steadily increasing in the last 40 years [1–4]. This increase has many hypothesized causes, the most notable ones being the progressive ageing of the population, the prolonged survival of heart failure patients associated with new therapies and improved care and (somehow paradoxically) the constant improvements in the management of acute cardiovascular conditions like myocardial infarction, whose mortality keeps decreasing at the cost of higher post-acute morbidity [5–7]; the latter hypothesis, though, has been much debated [8].

Heart failure is a complex clinical syndrome enveloping different clinical phenotypes carrying diverse prognosis and requiring different treatments; various disease subcategories have been identified over the years, and the latest guidelines differentiate clinical entities according to left ventricular ejection fraction (heart failure with reduced, mid-range or preserved ejection fraction), time-course of the disease (acute or chronic) and symptomatic severity (New York Heart Association (NYHA) class) [9]. This manuscript will focus on chronic heart failure with reduced ejection fraction (HFrEF), with only sparse reference to other sub-categories of heart failure.

A plethora of evidence-based therapeutic strategies are nowadays available for the treatment of HFrEF, and medical devices are part of the guideline-directed therapy ad-

vised by scientific societies. Implantable cardioverters-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) have a clear role in therapy with very specific indications: ICDs are recommended for prevention of sudden death in patients with ischemic or dilated cardiomyopathy (with some limitations), while CRT is indicated for patients with an intraventricular conduction delay (QRS > 130 ms) and the recommendation is stronger in case of a left bundle branch block (LBBB) morphology [9–11]. CRT's indications, though, leave many patients ineligible: patients with medically refractory disease without intraventricular conduction delay are not eligible for CRT therapy and, apart from optimal medical therapy, no strategy has until recently been available for relieving symptoms or improving quality of life in this subset of patients. The recommendation against CRT in patients with normal QRS morphology dates back to the EchoCRT trial, which not only revealed how these patients had no clear benefit from CRT, but it also found a statistically significant association between the CRT arm and an excess of deaths. This was later confirmed by subsequent subgroup analysis [12,13]. One more element that should be taken into account is that, apart from patients not eligible for CRT per guideline recommendations, there is a proportion of subjects that, after CRT implantation, show no benefit from this therapy and are considered non-responders (ranging from 20 to 40% of implanted patients according to different studies) [14–17].

In this therapeutic gap, Cardiac Contractility Modulation (CCM) could potentially play a relevant role. CCM is an emergent therapy, it employs standard pacing electrodes to deliver non-excitatory high-voltage biphasic impulses (~7.5 V/20 ms) duration during the absolute refractory period of the action potential of cardiac myocytes (Figure 1, see "Technical aspects" for more detailed information) [18–20].

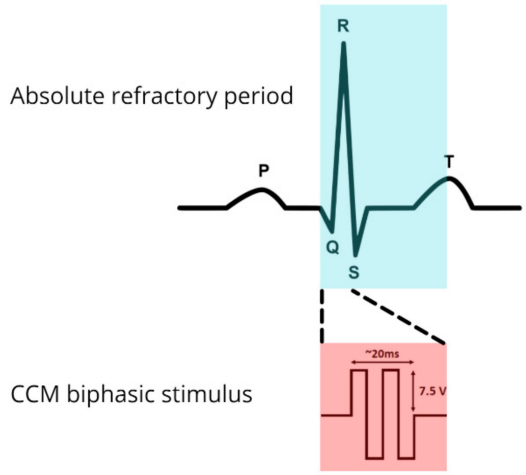

Figure 1. Cardiac contractility modulation biphasic stimulus located on an electrocardiogram strip.

The first in-human experience with CCM dates back to 2001: CCM was investigated in candidates for an electrophysiological study (EP) study and its efficacy was evaluated by measuring aortic and intracardiac pressures and by evaluating echocardiographic changes before, during and after the application of CCM. This study showed promising results, in that it demonstrated how this therapy could improve the contractile capabilities of the failing left ventricle [21].

After this first experience, much research work has been conducted in the CCM domain and many improvements have been introduced. The most notable studies belong to the FIX-HF series, with the last study (FIX-HF-5C2) published in 2020 [22].

In 2019, after a considerable amount of evidence had been collected, the first device capable of delivering CCM was approved by the Food and Drug Administration (FDA): the OPTIMIZER Smart System (Impulse Dynamics Inc., Orangeburg, NY, USA) [23].

2. Underlying Mechanisms

A wealth of in vitro and in vivo experimental evidence has been collected concerning the effects of CCM during the last twenty years; this technique has demonstrated its efficacy at a cellular and macroscopic level and these studies have given many insights into the mechanisms of action underlying the observed effects.

The effects of CCM observed in vitro and in animal model are not completely understood. Various theories have been advanced, and it appears that CCM improves calcium handling in the cardiac myocyte (this theory is further supported by the observation of the abovementioned effect of ryanodine administration) and that interferes in the phosphorylation of cardiac phospholamban [24–26]. Pathological studies have revealed how in specimens of myocardium that underwent 3 months of CCM, there was an increased expression of SERCA2a, phospholamban, and RyR2. It appears then that CCM is capable of reverting the cardiac fetal gene program associated with heart failure [27,28].

Among the numerous in vivo experimental observations, we hereby review the most significant ones: CCM improved isometric contraction strength in rabbit papillary muscle and in myocytes obtained from the failing human myocardium; it also ameliorated isovolumic pressure generation in Langendorff-perfused ferret hearts and LV function improvements were elicited in dogs where HF was induced by coronary microembolization [29–31]. In Langendorff-perfused ferret hearts, the improvements evoked by CCM persisted after inotrope administration (epinephrine and digitalis, with additive effects of drugs and CCM) and were markedly blunted after exposure to ryanodine [32].

The effects of CCM appear to be pleiotropic in that it also appears to modify the expression of cytoskeletal proteins and myofilaments, possibly reducing fibrosis and further improving contractility [33]. The reverse remodeling observed with CCM looks very much like the one induced by CRT in patients with a mildly prolonged QRS (while it is much more pronounced in CRT patients with a marked QRS prolongation) [34].

At a macroscopic level, several features appear striking and potentially very favorable. CCM improves myocardial contractility without increasing myocardial oxygen consumption unlike, for example, inotrope administration [35,36]. Moreover, the improvements in myocardial contraction are not confined to the site where CCM is delivered, they are in fact global, including regions remote to the impulse delivery; this appears to be of the utmost importance considering how every single myocardial segment contributes to the pump function [37].

3. Technical Aspects

The implantation procedure of a device capable of delivering CCM is very much like the implantation of a dual-chamber pacemaker, the only difference being the placement of the two right ventricular leads that are positioned in such a way that impact on LV function is ensured [20]. The necessity of two leads in the right ventricular chamber has been questioned in 2016 by Röger et al. [38], who showed how a CCM system employing a single right ventricular lead had similar efficacy and safety compared to the traditional two-lead system, paving the way for future modifications of the stimulation protocol, and to a combined device for patients with ICD indication, which could benefit by both therapies with two endovascular leads only.

Different devices and different CCM protocols have been used in the previous years. From the "Scepter" employed by Pappone et al. in 2001 [21] to newer and more sophisticated devices like the "Optimizer" system by Impulse Dynamics, many improvements have been introduced.

A device capable of delivering CCM usually consists of an implantable pulse generator (IPG) with a rechargeable battery. Signal delivery happens through a variable number of leads and this feature has been the object of much research and many improvements since CCM was first experimented.

The first CCM devices employed a 3-lead system, with one lead in the right atrium (sensing lead) and two into the right portion of the ventricular septum that delivered the

actual electrical impulses. The most recent device to be introduced in the research setting (FIX-HF-5C2 study) is the new-generation 2-lead Optimizer system, which, at once, reduced the likelihood of lead-related adverse events (such as systemic infection and superior vena cava thrombosis), known to be higher in dual-chamber lead systems [39,40] and made it possible for patients affected by atrial fibrillation and atrial flutter to receive CCM therapy (because the atrial sensing is not necessary for this device to function) [22].

The energy delivered with CCM is about a hundred times the amount of that delivered during a standard pacemaker impulse, yet these signals do not start a depolarization because the stimulus is delivered during the absolute refractory period of ventricular cardiomyocytes, about 30–40 ms after detection of local electrical activity (during phase 2 of the action potential of cardiac myocytes) [41,42].

The arrhythmogenic potential of CCM has been demonstrated as very low since the very first studies and CCM delivering devices have safety features meant to avoid the induction of malignant arrhythmias [21,41,42].

CCM impulses have an immediate effect on myocardial contractility and the efficacy and feasibility of this technique are established by measuring peak + dP/dt_{max} with a Millar micromanometer right after lead implantation (within ~10 min) [20,43]. Generally, investigators have employed a cut-off of a $\geq$5% increase in peak + dP/dt_{max} to classify the patient as responder and further proceed with the implantation. If this increase could not be documented, either lead repositioning or suspension of the procedure are considered viable options [26,44].

In 2017, a detailed guide for device implantation was produced by Kuschyk et al., covering all technical aspects ranging from pocket preparation and lead positioning to device programming and postoperative care [20]. We strongly recommend referring to this work for an extensive procedural guide.

4. Clinical Significance

Due to the impressive heterogeneity of the available clinical studies involving CCM, we hereby present two synoptic tables synthesizing the different studies investigating CCM in various clinical scenarios and in different patients with the aim of giving an overview on the large CCM research landscape. We used the MEDLINE database to search for studies investigating cardiac contractility modulation; search term was "cardiac contractility modulation" and studies that were either not interventional or did not investigate mortality or cardiovascular outcomes were excluded. Nineteen studies were selected and are represented in Table 1. As observable, these studies have many different features such as criteria of inclusion and exclusion, duration of follow-up, type of device, type of recruitment, CCM stimulation protocol, blinding or unblinding, presence of control group, type of treatment in the control group, outcomes measured and sample size. It is also notable that most of these studies (except four) were conducted on less than a hundred patients and still showed in most cases significant changes in quality of life and in cardiopulmonary performance.

Table 1. Major findings and study design of clinical trials investigating CCM.

Author	Study Design	Sample Size	Quality of Life	Functional Capacity					
			MLWHF	6MWT	NYHA Class	PVO2	EF	Mortality	Other Findings
Pappone C et al. (2001)	- Acute feasibility Study to assess haemodynamics after CCM - EF < 35% - Ischemic or non-ischemic etiology	15	NA	NA	NA	NA	NA	NA	- Significant ($p < 0.05$) increases in LV + dp/dt_{max}. - No change in rate of arrhythmias
Pappone C et al. (2002)	- Acute feasibility Study to assess haemodynamics after CCM - Three CCM protocols: LV (epicardial), RV and CCM + BVP - EF < 35% - Ischemic or non-ischemic etiology	24	NA	NA	NA	NA	NA	NA	- Significant increase both with LV and RV CCM stimulation in dp/dt_{mx} ($p < 0.01$) - Additional increase in dp/dt_{mx} in BVP +CCM vs. BVP alone
Stix G et al. (FIX-HF-3, 2004)	- Feasibility study (8 weeks follow-up) - NYHA III and EF < 35% - Refractory to pharmacological therapy	25	Significantly improved vs. baseline (43 ± 22 vs. 25 ± 18, $p = 0.01$)	Significantly improved vs. baseline (evaluated in 7 patients, (441 ± 86 m vs. 465 ± 81 m, $p = 0.02$)	NA	NA	Significantly improved vs. baseline, (22 ± 7 vs. 28 ± 8, $p = 0.0002$)	NA	NA
Neelagaru et al. (pilot Study for FIX-HF-5, 2006)	- Randomized, double-blind feasibility Study (6 months follow-up) - NYHA III-IV and EF < 35% - Patients in OMT	49	Similar change in both group (decrease from baseline values by 16.2 ± 5.9 in the control group vs. 18.3 ± 4.8 CCM group)	Greater improvement in CCM group than in control group approximately of 15 m (p = NS)	Similar improvement in both group	Greater improvement in CCM group (+0.2 $mLO_2/kg/min$) than in control group (p = NS)	NA	NA	- Greater improvement in CCM group in terms of VAT (0.8 $mLO_2/kg/min$, p = NS) despite that the baseline patient characteristics were better in control group.
Nägele H et al. (2008)	- Feasibility Study to explore CCM in CRT on responders (3 months follow-up) - NYHA III-IV - Patients with BVP and OMT	16	NA	NA	Significantly improved vs. baseline (from 3.4 to 2.8, $p < 0.01$)	NA	Significantly improved vs. baseline (from 27.3 ± 5 to 31.1 ± 6, $p < 0.01$)	Three patients (19%) died suddenly presumably due to electromechanical dissociation after 318, 104, and 81 days	- Significant increases in LV + dp/dt_{max} (+14%, $p < 0.01$) - No electrical interference between CRT and CCM - No inappropriate shocks

Table 1. *Cont.*

Author	Study Design	Sample Size	Quality of Life	Functional Capacity					
			MLWHF	6MWT	NYHA Class	PVO2	EF	Mortality	Other Findings
Borggrefe MM et al. (FIX-HF-4, 2008)	- Randomized, double-blind crossover Study (6 months follow-up with crossover CCM ON/OFF at 3 months) - NYHA $\geq$ 2 - EF < 35% - Peak VO_2 between 10 and 20 mL O_2/min/kg.	181	Significant greater improvement in CCM group (from 36.5 $\pm$ 27.1 to 26.1 $\pm$ 15.1, $p < 0.05$) considering Group 2 (Sham to CCM)	Greater improvement in CCM group (Not Statistically tested)	Improvement in both groups (Not statistically tested)	Significant greater improvement in CCM group (from 13.6 $\pm$ 2.7 to 12.7 $\pm$ 3.1, $p < 0.05$), considering Group 2 (Sham to CCM)	NA	NA	- The placebo effect ends at 3 months as in the Phase II of the Study after crossover was no longer present
Yu CM et al. (2009)	- To assess the impact of CCM on LV size and myocardial function - Echo 3D and TDI assessment at baseline and after 3 months	30	Not significantly improved vs. baseline (23 $\pm$ 19 vs. 20 $\pm$ 18, $p = 0.577$)	Significantly improved vs. baseline (331 $\pm$ 85 vs. 358 $\pm$ 83, $p = 0.015$)	83% of patients improved $\geq$1 class ($p < 0.01$)	Not significantly improved vs. baseline (15.9 $\pm$ 4.7 vs. 14.3 $\pm$ 4.6 mL/kg/min, $p = 0.059$)	Significantly improved vs. baseline, (29.0 $\pm$ 6.5 vs. 33.1 $\pm$ 6.5, $p < 0.001$)	NA	- TDI indexes showed improved systolic function and no changes in diastolic function and in dyssynchrony.
Schau T et al. (2011)	- Retrospective Study to evaluate the impact of CCM on Cardiac and all-cause mortality in HF patients	54	NA	NA	NA	NA	NA	Data suggested no worsening of survival in the treatment of patients with end-stage HF by CCM.	NA
Kadish A et al. (FIX-HF-5, 2011)	- Randomized, unblinded, controlled trial comparing CCM to OMT alone (6 months follow-up)	428	Significant greater improvement in CCM group (−9.7 points, $p < 0.01$)	Greater improvement in CCM group than in control group (p = NS)	Significant greater improvement $\geq$1 class in CCM group (49.2% vs. 34.4%, $p < 0.01$)	Significant greater improvement in CCM group (+0.65 mL/kg/min, $p = 0.024$)	NA	NA	- VAT did not improve at 6 months
Röger S et al. (2014)	- Non randomized Study to assess the impact of CCM on QRS duration and intraventricular conduction (2.8 years of follow-up)	70	NA	NA	NA	NA	NA	NA	- No significant changes in QRS duration were found compared to baseline

Table 1. *Cont.*

Author	Study Design	Sample Size	Quality of Life	Functional Capacity					
			MLWHF	6MWT	NYHA Class	PVO2	EF	Mortality	Other Findings
Kuschyk J et al. (2015)	- Long-term (34 months) retrospective single-site analysis on the efficacy of CCM in HF patients	81	Significantly improved vs. baseline (from 49.9 to 32.2, $p < 0.01$)	NA	74% of patients improved ≥1 class at 6 months follow-up	Trend of Increase vs. baseline (from 13.9 ± 3.3 to 14.6 ± 3.5 mL/kg/min ($p = 0.1$)	Significantly improved vs. baseline (from 23.1 to 29.4, $p < 0.01$)	Mortality rates at 1 and 3 years were 5.2% and 29.5% compared to mortality rates estimated from the MAGGIC risk score of 18.4% ($p < 0.001$) and 40% (p = ns), respectively	- Significant improvements in NT-ProBNP value (from 4395 ± 3818 to 2762 ± 3490 ng/L ($p < 0.05$)
Kloppe A et al. (2016)	- Retrospective Study evaluating survival in CCM patients with HF (until 5 year follow-up) - NYHA II-III - QRS < 130 ms	68	NA	NA	NA	NA	NA	Mortality rates (Kaplan–Meier analysis) at 1, 2 and 5 years were lower with CCM than predicted by SHFM for the cohort ($p = 0.007$).	NA
Liu M et al. (2016)	- Case-control Study of HF patients with CCM vs. OMT - EF < 40%	82	NA	NA	NA	NA	NA	All-cause mortality was lower in the CCM group than the control group ($p = 0.001$).	NA
Kloppe A et al. (2016)	- Randomized study (6 months of follow-up) comparing 5 vs. 12 h per day of CCM treatment for HF patients.	19	Improvements of both groups (5 h vs. 12 h) with −18.5 vs. −15.2 respectively, p = NS (not statistically tested vs. baseline)	Improvements of both groups (5 h vs. 12 h) with +32.4 vs. +29.6 respectively, p = NS (not statistically tested vs. baseline)	Improvements of both groups (5 h vs. 12 h) with −0.88 vs. −0.83 respectively, p = NS (not statistically tested vs. baseline)	Improvements of both groups (5 h vs. 12 h) with +0.8 vs. +2.3 respectively, p = NS (not statistically tested vs. baseline)	Improvements of both groups (5 h vs. 12 h) with −1.25 vs. +5.75 respectively, p = NS (not statistically tested vs. baseline)	NA	- There were no significant differences, either clinically or statistically, between the groups receiving CCM for 5 h/day vs. 12 h/day.
Röger S et al. (2016)	- Randomized comparison of signal delivery through one vs. two ventricular leads (Follow-up of 6 months).	48	Significantly improved in both groups vs. baseline (−14 ± 20 vs. −16 ± 22, $p < 0.05$)	NA	Significantly improved in both groups vs. baseline (−0.7 ± 0.5 vs. −0.9 ± 0.7, $p < 0.05$)	Trend of Increase of both groups vs. baseline (0.34 ± 1.52 vs. 0.10 ± 2.21 mL/kg/min, p = NS)	NA	NA	NA

Table 1. *Cont.*

Author	Study Design	Sample Size	Quality of Life	Functional Capacity					
			MLWHF	6MWT	NYHA Class	PVO2	EF	Mortality	Other Findings
Muller D. et al. (2017)	- Prospective registry study evaluating the effect of CCM on NYHA functional class, EF, 6MWT peak VO_2 and MLHFQ at 6, 12, 18 and 24 months. - Patients were stratified according to EF and three subgroups were identified.	143	Significantly improved vs. baseline (from 45.4 ± 19.6 to 31.2 ± 22.5, $p < 0.01$) at 24 months	NA	Significantly improved vs. baseline (from 2.9 ± 0.5 to 2.2 ± 0.8, $p < 0.01$) at 24 months	NA	Significantly improved vs. baseline (from 28.3 ± 6.4 to 34.9 ± 8.8, $p < 0.01$) at 24 months	NA	NA
Abraham WT et al. (FIX-HF-5C, 2018)	- Randomized (CCM vs. OMT) unblinded clinical trial (Follow-up at 6 months) that sought to confirm that CCM's efficacy is maximal in patients with EF between 25% and 45%. - NYHA class III–IV - QRS duration <130 ms - EF between 25% and 45%	160	Significantly improved vs. control group (+18.5 in CCM group vs. +7.5 in control group, $p < 0.001$)	Significantly improved vs. control group, (+43.0 ± 80.7 m in CCM group vs. +9.3 ± 87.4 m in control group, $p = 0.0093$)	Improved by ≥1 class in 81% in CCM group compared to 42% in control group ($p < 0.001$)	Greater improvement in CCM group vs. control group (15.042 vs. 14.206 $mLO_2/kg/min$, respectively)	NA	The composite of cardiovascular death and HF hospitalizations was reduced ($p = 0.048$).	NA
Kuschyk J et al. (2019)	- Non-randomized unblinded study (Follow-up of 6 months) evaluating CCM in CRT-non-responders	17	Significantly improved vs. baseline (−15.9 ± 16.1, $p = 0.02$)	Significantly improved vs. baseline (+52 ± 60 m, $p = 0.008$)	Significantly improved vs. baseline (−0.33 ± 0.49 ($p = 0.02$)	Significantly improved vs. baseline (+1.1 ± 1.6 $mLO_2/kg/min$, $p = 0.03$)	Not significantly improved vs. baseline (2.9 ± 5.8%, $p = 0.08$)	NA	NA

Table 1. *Cont.*

Author	Study Design	Sample Size	Quality of Life	Functional Capacity					
			MLWHF	6MWT	NYHA Class	PVO2	EF	Mortality	Other Findings
Anker S et al. (CCM-REG25-45, 2019)	- Prospective registry study (Follow-up of 3 years) evaluating the effect of CCM on hospitalizations and mortality in patients with HF and an EF $\leq$ 45%. - Two cohorts were identified according to EF: CCM-REG 25-34 and CCM-REG35-45	140	Significantly improved in overall cohort (-17.1 point, $p < 0.001$) at 24 months	NA	Significantly improved in overall cohort (-0.8, $p < 0.001$) at 24 months	NA	Significantly improved in overall cohort (from 32.8 $\pm$ 4.9 at baseline to 35.8 $\pm$ 8.2 at 6 months, $p = 0.003$)	Survival was significantly better than predicted by SHFM only in the CCM-REG$_{35\text{-}45}$ subgroup ($p = 0.046$).	- Less hospitalizations in the 2 years following CCM implantation vs. the year before ($p < 0.0001$).
Wiegn P et al. (FIX-HF-5C2, 2020)	- Nonrandomized unblinded study (Follow-up of 6 months) evaluating safety, performance and efficacy of CCM delivered by the 2-Lead Optimizer Smart System.	60	NA	NA	Improved by $\geq$1 class in 83.,1% in 2-lead device group compared with 42.7% in the control group ($p < 0.001$)	Significantly improved vs. baseline (+1.72 mL/kg/min) greater in 2-lead device group vs. control group	NA		- CCM delivery did not differ significantly between 2- and 3-lead systems (comparable number of CCM signals/day). - There were decreased Optimizer-related adverse events with the 2-lead system compared with the 3-lead system ($p = 0.03$).
Tschöpe C et al. (2020)	- Subgroup analysis (Follow-up of 6 months) in patients with EF between 40 and 45%, from the FIX-HF-5, FIX-HF-5C, and FIX-HF-5C2 studies.	53	Decreased from baseline in CCM group and control group, for a between-group treatment effect non-significantly ($p = 0.10$)	Significantly improved in the CCM group with a net between-group treatment effect of 53.9 $\pm$ 74.2 m ($p = 0.05$).	Improvement of $\geq$1 class from baseline in 80.6% in CCM group compared with 57.1% in the control group vs. baseline	Improved in CCM group and declined in the control group for a net between-group treatment effect of 2.0 $\pm$ 2.8 mL/kg/min ($p = 0.02$)	NA	Freedom from cardiovascular mortality (97.2% vs. 100%; $p = 0.51$) and freedom from the composite of HF hospitalization or cardiovascular mortality (91.7% vs. 93.8%; $p = 0.79$) did not differ between groups	NA

Captions: 6MWT: 6 Minute Walk Test Distance; BVP: Biventricular Pacing; CCM: cardiac contractility modulation; CRT (-D, -P, -NR): Cardiac Resynchronization Therapy (-Defibrillator, -Pacemaker, -Non-Responders); + dP/dtmax: maximal rate of rise of pressure; EF: left ventricular Ejection Fraction; EP: Electrophysiologic; HF: Heart failure; LV: Left Ventricle; MAGGIC: Meta-Analysis Global Group in Chronic; MLHFQ: Minnesota Living with Heart Failure Questionnaire; OMT: Optimal medical therapy; Peak VO_2: Peak Oxygen uptake; RV: Right Ventricle; SHFM: Seattle Heart Failure Model; TDI: Tissue Doppler Imaging; VAT: Ventilatory Anaerobic Threshold.

According to the latest studies, and specifically to the FIX-HF-5 study that first introduced this concept, the subgroup of patients that seem to benefit the most from this technique are NYHA II–III patients with an EF between 35 and 45% [19,45,46]. It is on these findings that the FDA formulated its approval in 2019 and patients with an EF between 35 and 45% are specifically mentioned in the FDA label for use in the USA.

A recent individual patient metanalysis by Giallauria et al. examined all the published randomized clinical trials comparing CCM to either sham or OMT (i.e., FIX-HF 5 pilot, FIX-HF 4, FIX-HF 5 and FIX-HF 5C) [41,46–48] and included the recent non-randomized FIX-HF-5C2 study. This work analyzed the effects of CCM on an aggregate of 861 patients (801 without those of FIX-HF-5C2) and pooled analysis showed that CCM significantly improved peak VO_2 (mean difference +0.93, 95% CI 0.56 to 1.30 mL/kg/min), 6-min walk test distance (mean difference +17.97, 95% CI 5.48 to 30.46 m), and quality of life measured by Minnesota Living With Hearth Failure Questionnaire (mean difference 7.85, 95% CI 10.76 to 4.94) [49]. These results confirmed and further extended the findings of a previous meta-analysis by the same group, which included three trials (with the same inclusion criteria) and showed similar results [50].

The impact of CCM on cardiovascular outcomes such as mortality and hospitalizations need further investigation. In Table 1, the relevant clinical studies on CCM were reported and only six of the included works investigated the effect of CCM therapy on mortality and/or other cardiovascular outcomes [46,51–55]. The overall effect seems favorable, but specifically designed studies are strongly encouraged in order to confirm the potential role of CCM in reducing adverse outcomes in heart failure.

Defining potential responders and non-responders to CCM therapy will be crucial for optimal decision-making and more data are needed in order to establish which patients are most likely to benefit from device implantation [56]. Management algorithms have been proposed by several authors based on available evidence, but many grey zones still exist and the effect of CCM in some patients, like those with a right bundle branch block or patients that stay symptomatic after CRT implantation, still remains to be elucidated. The decision-making pathway proposed in 2020 by Campbell et al. provides a good overview of the actual and potential place in therapy of CCM according to the state-of-the art research [57].

5. Future Perspectives

Scientific societies are leaning towards an evidence-driven consensus that CCM could fill a gap in HF therapy [58] and the recent approval of CCM by the FDA paves the way for future opportunity of studying long-term outcomes in patients with CCM.

Although data on mortality outcomes is still poor, research on heart failure suggests that peak VO_2 is a significant prognostic determinant in heart failure [59,60]; thus, based on the demonstrated positive effects on exercise capacity, it could be speculated that by increasing peak VO_2, CCM is likely to improve survival in eligible patients. Its role in HF with preserved ejection fraction, which is becoming more and more prevalent, remains to be elucidated [4,61].

As of now, evidence suggests that the subgroup that benefits the most from CCM is made up of patients with a left ventricular ejection fraction between 25 and 45% [62,63], with recent real-world studies showing even more impressive effect in a subgroup of patients with an ejection fraction between 35 and 45% [55]. Still, most studies analyzed very small cohorts; therefore, adequately powered long-term studies are eagerly awaited in order to confirm and extend previous findings, by clearly depicting the clinical efficacy and the risk/benefit ratio associated with the procedure and identifying possible non-responders. In addition, the additive beneficial effect of exercise-based Cardiac Rehabilitation on symptoms relief and outcome remains to be elucidated.

6. Conclusions

Additional evidence is needed to find CCM's place in therapy; adequately powered studies are required to fully understand the role of this novel therapy. Several safe and effective therapies have been investigated and approved for HF treatment. The recent approval of Sacubitril-Valsartan made it clear that HFrEF treatment can in fact be improved in order to transform the ominous prognosis that this syndrome carries into a more favorable one. Still, much remains to be done, in that some patients find themselves in a state of limbo, without access to further therapies or procedures. CCM could find its place in meeting a relevant medical need, by providing an effective therapy to patients that would otherwise have no therapeutic option left.

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