Cardiac Contractility Modulation Therapy

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DESCRIPTION

Impulse Dynamics offers cardiac contractility modulation (CCM) therapy to treat adults with moderate-to-severe chronic heart failure that is symptomatic despite optimal medical therapy. CCM delivers non-excitatory electrical signals to the right side of the intraventricular septum during the absolute refractory period of the ventricular contraction and does not trigger a new action potential. CCM signals are delivered by Impulse Dynamics' Optimizer system (i.e., Optimizer IVs), which is an implantable pulse generator. This device is implanted in a minimally invasive procedure under local anesthesia, typically in the right pectoral region. CCM has been evaluated in patients with heart failure with reduced ejection fraction (HFrEF) in New York Heart Association (NYHA) Classes II to IV with normal QRS duration (less than 120 ms). In contrast to a pacemaker or a defibrillator, the system is designed to modulate the strength of contraction of the heart muscle rather than the rhythm. CCM therapy is delivered at regular intervals throughout the day. The common patient profile for this therapy is

NYHA II to III, normal QRS, EF greater than 20 %, peak $VO_2 \geq 10$ ml/kg/min, and ventricular ectopies or bigeminies less than 10,000 per day.

Some individuals may also require and implantable cardioverter-defibrillator (ICD) device, or already have one implanted. The Optimizer IVs is designed to work in parallel with any ICD device and generally does not cause any interruption of ICD function. The Optimizer IVs is contraindicated for patients with permanent or long-standing persistent atrial fibrillation or flutter, mechanical tricuspid valve, no venous access, and device programmed to 100 % VVI pacing.

In 2021, Matta et. al. stated that cardiac contractility modulation (CCM) is a therapeutic option for patients suffering symptomatic congestive heart failure (CHF) with reduced LVEF who are not eligible for cardiac resynchronization. Data on mid-term follow-up were limited to small observational studies. In a pilot study, these researchers examined the impact of CCM on QOL, symptoms, exercise tolerance and left ventricular function in patients with CHF and moderate-to-severe left ventricular systolic dysfunction. Patients suffering CHF with LVEF of less than 45% and NYHA class of greater than II despite optimal medical therapy, underwent CCM implantation. Enrolled patients underwent baseline and 3-, 6- and 12-months evaluation with ECG, echocardiogram, clinical assessment, 6MWD and MLWHFQ. A total of 10 patients underwent CCM implantation. All subjects were actively treated with the optimal pharmacological therapy as tolerated and had at least 1 hospitalization for worsening HF during the previous year. After a mean follow-up of 15 months, 9 patients were alive, while 1 patient died for worsening HF precipitated by pneumonia. Among the remaining 9 patients, LVEF improved non-significantly from 29.4 ± 8 % to 32.2 ± 10 % ($p = 0.092$), 6MWD improved from 179 ± 73 m to 304 ± 99 m ($p < 0.001$), NYHA class reduced from 3.0 ± 0.4 to 1.6 ± 0.5 ($p = 0.003$) and MLWHFQ score improved from 59.6 ± 49 to 34.2 ± 32 ($p = 0.037$). Only 2 patients have been hospitalized during the 12 months. Overall, a net clinical benefit was detected in 6 out of 9 patients. The authors concluded that CCM could be effective in improving QOL, symptoms and exercise tolerance, and reduced hospitalizations in patients with symptomatic CHF on top of optimal medical and electrical therapy. Moreover, these researchers stated that a prospective registry has been designed to identify the subsets of patients gaining more benefit, and to evaluate the long-term effect of CCM on those clinical endpoints.

The authors stated that the findings of this study were subject to the limitations of an observational, non-randomized, registry study including the potential role of placebo effect. However, sustained improvements over 2 years in NYHA class, MLHFQ and, more objectively, LVEF, and the consistency of these findings among different patient subgroups suggested that clinical effects beyond placebo were operative. Furthermore, LVEF data were available only when this test was carried out as part of routine care, which accounted for the lower number of observations compared to NYHA class and MLHFQ that were collected at each visit. It should also be recognized that these findings were derived from completer analyses over time, which did not account for patients lost to follow-up or who had died. Similarly, effects of CCM on hospitalization rates were

based on comparison of patients' historical rates rather than on a parallel control group. However, similar findings were observed in the prior randomized clinical trial and had also been used as the primary analysis for other studies of HF therapies. Furthermore, changes in medications were not tracked during the follow-up period; however, there was very high usage of diuretics (90.7 %), angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) (90.7 %), beta-blockers (95.6 %) and mineralocorticoid receptor antagonists (68.4 %). Accordingly, there would have been very little opportunity for meaningful additions of drugs to the population as a whole; thus, changes in medications would unlikely have contributed to the sustained improvements in clinical status and hospitalizations noted during follow-up. Also noted that during the period of data collection neither sacubitril/valsartan nor sodium-glucose co-transporter 2 inhibitors were in widespread use, so these medications did not factor into the results. Finally, interpretation of effects on survival was based on the MAGGIC risk score, not a parallel control group. However, the MAGGIC score incorporates values of 13 independent, readily obtained clinical parameters. This is the most comprehensive and generalizable risk score currently available in the literature that has been based on 39,372 patients from 30 studies with a median follow-up of 2.5 years. Furthermore, the score was prospectively validated in a study of 51,043 patients. The MAGGIC score does not reflect the use of ICDs.

Kuschyk et. al. (2021) examined long-term effects of cardiac contractility modulation (CCM) delivered by the Optimizer Smart system on quality of life (QOL), left ventricular ejection fraction (LVEF), mortality and heart failure (HF) and cardiovascular hospitalizations. These researchers noted that CCM-REG is a prospective registry study including 503 patients from 51 European centers. Effects were examined in 3 terciles of LVEF (less than or equal to 25 %, 26 % to 34 % and greater than or equal to 35 %) and in patients with AF and normal sinus rhythm (NSR). Hospitalization rates were compared using a Chi-square test. Changes in functional parameters of NYHA class, MLHFQ and LVEF were assessed with Wilcoxon signed-rank test, and event-free survival (EFS) by Kaplan-Meier analysis. For the entire cohort and each subgroup, NYHA class and MLHFQ improved at 6, 12, 18 and 24 months ($p < 0.0001$). At 24 months, NYHA class, MLHFQ and LVEF showed an average improvement of 0.6 ± 0.7, 10 ± 21 and 5.6 ± 8.4 %, respectively (all $p < 0.001$). LVEF improved in the entire cohort and in the LVEF less than or equal to 25 % subgroup with AF and NSR. In the overall cohort, HF hospitalizations decreased from 0.74 [95 % CI: 0.66 to 0.82] prior to enrolment to 0.25 (95 % CI: 0.21 to 0.28) events per patient-year during 2-year follow-up ($p < 0.0001$). Cardiovascular hospitalizations decreased from 1.04 (95 % CI: 0.95 to 1.13) events per patient-year prior to enrolment to 0.39 (95 % CI: 0.35 to 0.44) events per patient-year during 2-year follow-up ($p < 0.0001$). Similar reductions of hospitalization rates were observed in the LVEF, AF and NSR subgroups. Estimated survival was significantly better than predicted by MAGGIC at 1 and 3 years in the entire cohort and in the LVEF 26 % to 34 % and greater than or equal to 35 % subgroups. The authors concluded that CCM therapy improved functional status, QOL, LVEF and, compared to patients' prior history, reduced HF hospitalization rates. Survival at 1 and 3 years was significantly better than predicted by the MAGGIC risk score.

In 2021, Nolan et. al. discussed the implications of recent technological advances in the care of patients with HF. These investigators stated that novel cardiac devices and technologies may offer an opportunity to improve outcomes. Baroreflex activation therapy and CCM may improve myocardial contractility by altering neurohormonal stimulation of the heart. Implantable pulmonary artery monitors and bi-atrial shunts may prevent HF admissions by altering the trajectory of progressive congestion. Phrenic nerve stimulation offers potentially effective treatment for co-morbid conditions. Smartphone applications offer an intriguing strategy for improving medication adherence. The authors concluded that novel HF technologies offer promise for reducing this public health burden. Moreover, these researchers stated that RCTs are needed for examining the future role of these novel therapies.

Colucci, in 2021 in an UpToDate review on Investigational and Emerging Strategies for Management of Heart Failure states the following: "cardiac contractility modulation" as one of the investigational and emerging strategies. It states that "Cardiac contractility modulation (CCM) is a device-based therapy for heart failure (HF) that mildly improves functional measures but an effect on long-term clinical outcomes has not been established and there is a significant risk of complications CCM is an option in patients with HFrEF with NYHA functional class III or IV symptoms despite optimal medical therapy. However, there are several limitations to the widespread use of CCM: the data regarding outcomes with CCM are limited and there is risk of bias due to lack of full blinding (i.e., control subjects did not receive a generator implant), and outcomes less susceptible to lack of blinding such as all-cause death and survival free of hospitalization were not improved. Accordingly, cardiac resynchronization therapy (CRT), which has more extensive supporting data, is the preferred approach in patients who qualify for CRT".

In 2020, Campbell et. al. stated that cardiac contractility modulation (CCM) by the Optimizer Smart device is an innovative intracardiac device-based therapy that has been recently received FDA approval for the treatment of patients with chronic HF (CHF), LVEF between 25 and 45 %, QRS of less than 130 ms who remain symptomatic despite optimal medical therapy. Clinical trials demonstrated that CCM therapy is safe and effective in reducing HF hospitalization and improving HF symptoms, QOL and functional performance. This novel device-based therapeutic offered benefits to patients who do not otherwise qualify for cardiac resynchronization therapy. CCM expands the indication beyond the traditional LVEF cut-off of 35 % to a newer group including patients who fall in midrange LVEF group, up to 45 %. The authors noted that CCM is a novel, innovative, device-based therapy for HF recently approved by the FDA in March 2019. Based on the most recent randomized clinical trials, CCM could benefit patients with symptomatic HF 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 cut-off of 35 % to a newer group including patients who fall in mid-range LVEF group, up to 45 %. More importantly, these studies were conducted in era before extensive use of

sacubitril/valsartan and ivabradine. These researchers stated that further prospective trials that address mortality in a prospective randomized fashion on background of current medical therapies are needed to confirm survival benefits.

In 2020, Wiegn et. al. noted that prior studies of cardiac contractility modulation (CCM) employed a 3-lead Optimizer system. A new 2-lead system eliminated the need for an atrial lead. These investigators examined the safety and effectiveness of this 2-lead system compared with the 3-lead system. Patients with NYHA III/IVa symptoms despite medical therapy, LVEF 25 % to 45 %, and not eligible for cardiac resynchronization therapy could participate. All subjects received an Optimizer 2-lead implant. The primary endpoint was the estimated difference in the change of peak VO2 from baseline to 24 weeks between FIX-HF-5C2 (2-lead system) subjects relative to control subjects from the prior FIX-HF-5C (3-lead system) study. Changes in NYHA classification was a secondary endpoint. The primary safety endpoint was a comparison of device-related adverse events (AEs) between FIX-HF-5C2 and FIX-HF-5C subjects. A total of 60 subjects, 88 % men, 66 ± 9 years old with LVEF of 34 ± 6 % were included. Baseline characteristics were similar between FIX-HF-5C and FIX-HF-5C2 subjects except that 15 % of FIX-HF-5C2 subjects had permanent AF versus 0 % in FIX-HF-5C. CCM delivery did not differ significantly between 2- and 3-lead systems (19,892 ± 3,472 versus 19,583 ± 4,998 CCM signals/day, CI of difference: -1,228 to 1,847). The change of peak VO2 from baseline to 24 weeks was 1.72 (95 % Bayesian CI: 1.02 to 2.42) ml/kg/min greater in the 2-lead device group versus controls. 83.1 % of 2-lead subjects compared with 42.7 % of controls experienced greater than or equal to 1 class NYHA improvement ($p < 0.001$). There were decreased Optimizer-related AEs with the 2-lead system compared with the 3-lead system (0 % versus 8 %; $p = 0.03$). The authors concluded that the 2-lead system effectively delivered comparable amount of CCM signals (including in subjects with AF) as the 3-lead system, was equally safe and improved peak VO2 and NYHA. Device-related adverse effects were less with the 2-lead system. The authors stated that the major drawback of this study was that it was a non-randomized, unblinded study with a relatively small number of patients ($n = 60$) that used a historical control group from the prior FIX-HF-5C study. The 2 studies were reasonably contemporaneous, having been completed less than 2 years of each other. The only significant difference in background medical therapy was a slightly greater use of valsartan / sacubitril in the current study (15 % versus 4 %) due to its introduction into clinical practice toward the completion of enrollment into the FIX-HF-5C study. Furthermore, there were some imbalances in baseline characteristics between the prospective treatment and retrospective control groups; however, frequentist mixed modeling of the results by sequential addition of baseline characteristics showing differences between groups showed little impact of these differences on the results. Regarding unblinding, this aspect was similar to the prior FIX-HF-5C study, so these investigators considered it unlikely that it would have influenced the comparisons made between the 2 studies.

In 2020, Giallauria et. al. performed a comprehensive individual patient data meta-analysis of all non-confounded prospective RCTs of CCM versus control that have measured functional capacity and/or QOL questionnaires in patients with HF. The

Cochrane Central Register of Controlled Trials, Medline, and Embase were searched in January 2020 to identify eligible RCTs. These researchers also asked the sole manufacturer of the device for their list of known trials. Primary outcomes of interest were peak VO2, 6MWD, and QOL measured by MLWHFQ, and all data were received as individual patient and individual time point data-points; MDs and 95 % CIs were calculated for continuous data using a fixed-effects model. A total of 5 trials were identified, 4 randomized studies enrolling 801 subjects for all endpoints of interest, and for peak VO2 alone (n = 60), there was an additional single arm non-randomized trial (FIX-HF-5C2) with a prospective comparison of its 24-week peak VO2 data compared with the control group of the FIX-HF-5C control patients. Pooled analysis showed that, compared with control, CCM significantly improved peak VO2 (MD +0.93, 95 % CI: 0.56 to 1.30 ml/kg/min, $p < 0.00001$), 6MWD (MD +17.97, 95 % CI: 5.48 to 30.46 m, $p = 0.005$), and QOL measured by MLWHFQ (MD -7.85, 95 % CI: -10.76 to -4.94, $p < 0.00001$). As a sensitivity analysis, these investigators excluded the FIX-HF-5C2 trial (only relevant for peak VO2), and the result was similar (MD +0.65, 95 % CI: 0.21 to 1.08 mL/kg/min, $p = 0.004$). The authors concluded that this meta-analysis showed statistically significant and clinically worthwhile beneficial effects of CCM in improving functional capacity, exercise tolerance, and QOL in HF patients. Moreover, these researchers stated that larger, well-conducted RCTs using a parallel double-blind design are needed to examine the effect of CCM on major mortality and morbidity outcomes before CCM can be widely recommended as an effective therapeutic option for HF patients. However, in those in whom conventional interventions are failing or contraindicated, these results suggested that worthwhile benefits could be expected. Studies in less compromised HF patients are also encouraged in order to explore a wider application of CCM in all stages of HF.

The authors stated that this meta-analysis had several drawbacks. Study cohorts are relatively young and predominantly male; thus, future data would be needed in older individuals and in more women. Patients with permanent AF were initially excluded because the original 3-lead OPTIMIZER device required detection of an appropriately timed P wave as part of a safety algorithm that ensures CCM signals are never delivered during the vulnerable period where they might trigger an arrhythmia. New algorithms have been developed to overcome this issue, and the FIX-HF-5C2 study included 9 patients with AF. Furthermore, the 2-lead system has been available and used in patients with AF in European Union for 10 years although, as of now, specific reports of the effects of CCM in patients with AF have not been completed. In addition, although no formal statistical heterogeneity was observed, the studies analyzed differed in study design limiting the ability to define representative results across different patient subgroups.

In 2019, Kuschyk et.al. noted that a significant proportion of patients receiving cardiac resynchronization therapy (CRT) are non-responders. In a multi-center, open-label, treatment-only, feasibility study, these researchers evaluated the efficacy of cardiac contractility modulation (CCM) in subjects with reduced LVEF who, despite CRT, continued to experience clinically significant symptoms. This was a trial of 17 CRT non-

responders who received CCM therapy. Changes in NYHA class, EF, MLWHFQ score, and exercise tolerance (6-minute walk test [6MWT] and pVo2) were analyzed over 6 months. Mortality and hospitalization rates were determined. Patients (82 % men) were 69.4 ± 9.6 years of age with baseline EF = 22.8 ± 6.5 %. Among primary endpoints, peak VO2 increased 1.1 ± 1.6 ml/kg/min ($p = 0.03$) and MLWHFQ improved (-16 ± 16 points; $p < 0.01$). Mean NYHA class improved (-0.33 ± 0.49; $p = 0.02$), 6MWT increased (52 ± 60 m; $p < 0.01$), while EF trended up (2.9 ± 5.8 %; $p = 0.08$) at 6 months. During the 6-month follow-up period, there were 18 hospitalizations in 9 subjects and 2 patients died. The authors concluded that patients with heart failure (HF) and reduced ejection fraction (EF) who remained moderately to severely symptomatic despite use of CRT, may benefit from CCM therapy with improvement in QOL and exercise tolerance. These researchers stated that a larger prospective study in this population is needed.

In 2019, Tint et. al. noted that heart failure (HF) is a major cause of morbidity and mortality throughout the world. Despite substantial progress in its prevention and treatment, mortality rates remain high. Device therapy for HF mainly includes CRT and the use of an ICD. Recently, however, a new device therapy cardiac contractility modulation (CCM) became available. These researchers presented a first case-series of patients with different clinical patterns of HFrEF, supported with the newest generation of CCM devices. A total of 5 patients with a LVEF of less than or equal to 35 % and a NYHA class of greater than or equal to III were supported with CCM OPTIMIZER SMART IPGCCMX10 at the authors' clinic. Subjects had a median age of 67 ± 8.03 years (47 to 80) and were all men (4 with ischemic etiology dilated cardiomyopathy). In 2 cases, CCM was added on top of CRT (non-responders), and, in 1 patient, CCM was delivered during persistent atrial fibrillation (AF). After 6 months of follow-up, the LVEF increased from 25.4 ± 6.8 % to 27 ± 9 %, and the 6MWT distance increased from 310 ± 65.1 m to 466 ± 23.6 m. One patient died 47 days after device implantation. The authors concluded that CCM therapy provided with the new model OPTIMIZER SMART IPG CCMX10 was safe, feasible, and applicable to a wide range of patients with HF. These researchers stated that further trials are needed to determine the magnitude of the effect of CCM provided by the new OPTIMIZER SMART IPG CCMX10 on HF in patients with AF or who fail CRT.

Mando et. al. (2019) carried out an updated meta-analysis of the randomized clinical trials (RCTs) to examine the safety and efficacy of cardiac contractility modulation (CCM) therapy. These investigators conducted a systematic review and meta-analysis of RCTs between January 2001 and June 2018. Outcomes of interest were peak VO2, 6-Minute Walk Distance (6MWD), Minnesota Living with Heart Failure Questionnaire (MLHFQ), HF hospitalizations, cardiac arrhythmias, pacemaker/ICD malfunctioning, all-cause hospitalizations, and mortality. Data were expressed as standardized mean difference (SMD) or odds ratio (OR). A total of 4 RCTs including 801 patients (CCM; n = 394) were available for analysis. The mean age was 59.63 ± 0.84 years, mean EF was 29.14 ± 1.22 %, and mean QRS duration was 106.23 ± 1.65 msec. Mean follow-up duration was 6 months. CCM was associated with improved MLWHFQ (SMD -0.69, $p = 0.0008$). There were no differences in HF hospitalizations (OR 0.76, $p = 0.12$), 6MWD

(SMD 0.67, p = 0.10), arrhythmias (OR 1.40, p = 0.14), pacemaker/ICD malfunction/sensing defect (OR 2.23, p = 0.06), all-cause hospitalizations (OR 0.73, p = 0.33), or all-cause mortality (OR 1.04, p = 0.92) between the CCM and non-CCM groups. The authors concluded that short-term treatment with CCM may improve MLFHQ without significant difference in 6MWD, arrhythmic events, HF hospitalizations, all-cause hospitalizations, and all-cause mortality. There is a trend towards increased pacemaker/ICD device malfunction. These researchers stated that larger RCTs might be needed to determine if the CCM therapy will be beneficial with longer follow-up.

Anker et al (2019) stated that CCM improved symptoms and ET and reduced HF hospitalizations over 6-month follow-up in patients with NYHA class III or IV symptoms, QRS of less than 130 ms and 25 % ≤ LVEF ≤ 45 % (FIX-HF-5C study). The current prospective registry study (CCM-REG) aimed to evaluate the longer-term impact of CCM on hospitalizations and mortality in real-world experience in this same population. A total of 140 patients with 25 % ≤ LVEF ≤ 45 % receiving CCM therapy (CCM-REG25-45) for clinical indications were included. Cardiovascular and HF hospitalizations, MLHFQ and NYHA class were assessed over 2 years. Mortality was tracked through 3 years and compared with predictions by the Seattle Heart Failure Model (SHFM). A separate analysis was performed on patients with 35 % ≤ LVEF ≤ 45 % (CCM-REG35-45) and 25 % ≤ LVEF < 35 % (CCM-REG25-34). Hospitalizations decreased by 75 % (from 1.2/patient-year the year before, to 0.35/patient-year during the 2 years following CCM, p < 0.0001) in CCM-REG25-45 and by a similar amount in CCM-REG35-45 (p < 0.0001) and CCM-REG25-34. MLHFQ and NYHA class improved in all 3 cohorts, with progressive improvements over time (p < 0.002); 3-year survival in CCM-REG25-45 (82.8 %) and CCM-REG24-34 (79.4 %) were similar to those predicted by SHFM (76.7 %, p = 0.16; 78.0 %, p = 0.81, respectively) and was better than predicted in CCM-REG35-45 (88.0 % versus 74.7 %, p = 0.046). The authors concluded that in real-world experience, CCM produced results similar to those of previous studies in subjects with 25 % ≤ LVEF ≤ 45 % and QRS < 130 ms; cardiovascular and HF hospitalizations were reduced and MLHFQ and NYHA class were improved. Overall mortality was comparable to that predicted by the SHFM but was lower than predicted in patients with 35 % ≤ LVEF ≤ 45 %. The authors stated that this study had several drawbacks. First, this was not a randomized study and there was no separate control group. Their choice of the SHFM to provide a basis for interpreting observed survival, while not as ideal as a control group, was chosen over the MAGGIC score since it provided more conservative estimates. These investigators also did not report any measure of functional capacity since this was not a standard clinical test and was required for the present registry study. Furthermore, the fact that this study was a voluntary registry collecting data from routine clinical visits imposed at least 2 limitations. First, study participation was offered to all patients implanted with an Optimizer at each participating center, approximately 30 % of patients did not agree to participate; there is no way to determine the characteristics of those that did not participate compared to those that did participate, and whether this created selection bias in the results. Second, several clinical parameters including hospitalizations, NYHA

class and MLHFQ scores were difficult to collect over the past 2 years. Interpretation of the changes in LVEF was limited by lack of an adjudicating echocardiography core (each site calculated this parameter separately) and by the relatively small number of LVEF values at later time-points, which increased the possibility of a type II error and of selection bias. For this reason, these investigators only reported changes for paired observations at 6 months. For similar reasons, the authors did not attempt to collect measures of ET that were not performed in the course of routine clinical care such as 6-minute hall walk or pVo2. In the context of randomized studies, core labs were used for analysis of endpoints such as LVEF, and adjudication committees were used to examine clinical endpoints; these were not utilized in the present study and were typically not used in real-world registry studies. It should also be noted that this registry was supported by Impulse Dynamics, Orangeburg, NY, through a clinical trials agreement with each enrolling site. Conflict of interest: Each of the following authors served as site principal investigators and received support from Impulse Dynamics for the registry study as part of a clinical trial agreement between their institution and Impulse Dynamics: M.B., H.N., M.A.O., S.R., A.G., B.A.R., and K.H.K. S.D.A. is a paid advisor for Impulse Dynamics and a member of a scientific steering committee. K.B.N., D.B., and B.R. are paid consultants to Impulse Dynamics. Impulse Dynamics provided support to the Medical College of Wisconsin for the consulting services of D.G.

Abraham et. al. (2018) sought to confirm a subgroup analysis of the prior FIX-HF-5 (Evaluate Safety and Efficacy of the OPTIMIZER System in Subjects with Moderate-to-Severe Heart Failure) study showing that cardiac contractility modulation (CCM) improved exercise tolerance (ET) and QOL in patients with EFs between 25 % and 45 %. A total of 160 patients with NYHA functional class III or IV symptoms, QRS duration of less than 130 ms, and EF of greater than or equal to 25 % and less than or equal to 45 % were randomized to continued medical therapy (control, n = 86) or CCM (treatment, n = 74, unblinded) for 24 weeks. Peak Vo2 (primary endpoint), Minnesota Living With Heart Failure questionnaire, NYHA functional class, and 6-min hall walk were measured at baseline and at 12 and 24 weeks. Bayesian repeated measures linear modeling was used for the primary end-point analysis with 30 % borrowing from the FIX-HF-5 subgroup. Safety was assessed by the percentage of patients free of device-related adverse events (AEs) with a pre-specified lower bound of 70 %. The difference in peak Vo2 between groups was 0.84 (95 % Bayesian CI: 0.123 to 1.552) ml O2/kg/min, satisfying the primary endpoint. Minnesota Living With Heart Failure questionnaire ($p < 0.001$), NYHA functional class ($p < 0.001$), and 6-min hall walk ($p = 0.02$) were all better in the treatment versus control group. There were 7 device-related events, yielding a lower bound of 80 % of patients free of events, satisfying the primary safety endpoint. The composite of cardiovascular death and HF hospitalizations was reduced from 10.8 % to 2.9 % ($p = 0.048$). The authors concluded that CCM was safe, improved exercise tolerance and QOL in the specified group of HF patients and led to fewer HF hospitalizations. Moreover, these researchers stated that future research is needed to examine the impact of CCM on mortality in the current target population. Furthermore, because CCM works through a mechanism completely different than cardiac resynchronization therapy (CRT), future research can examine the impact of CCM in

patients with prolonged QRS duration in addition to CRT, in particular in CRT non-responders.

In 2017, Muller et. al. evaluated clinical effects of long-term cardiac contractility modulation (CCM) in subjects with heart failure (HF) caused by left ventricular systolic dysfunction. Out of 143 subjects from 24 sites, 106 with HFrEF completed the 24-month follow-up which was recorded via a clinical registry. Recordings included NYHA class, MLWHFQ score, 6-min walk test (6MWT) distance, left ventricular ejection fraction (LVEF), and peak VO2 at baseline and 6-month intervals as clinically indicated. Serious adverse events, and all cause as well as cardiovascular mortality were recorded. Data are presented stratified by LVEF (all subjects, LVEF less than 35 %, LVEF greater than or equal to 35 %). The investigators found that baseline parameters were similar among LVEF groups. NYHA and MLWHFQ improved in all 3 groups at each time-point. LVEF in the entire cohort improved 2.5, 2.9, 5.0, and 4.9 % at 6, 12, 18, and 24 months, respectively. Insufficient numbers of subjects had follow-up data for 6MWT or peak VO2 assessment, precluding comparative analysis. Serious adverse events (n = 193) were observed in 91 subjects and similarly distributed between groups with LVEF less than 35 % and LVEF greater than or equal to 35 %, and similar to other device trials for HF: 18 deaths (7 cardiovascularly related) over 2 years. Overall survival at 2 years was 86.4 % (95 % confidence intervals [CI]: 79.3 to 91.2 %). The investigators concluded that in patients with HFrEF and persistent symptoms despite GDMT, CCM provided sustained improvement in both cardiac function and QOL. The benefit was present not only in subjects with baseline LVEF less than 35 %, but also in those with LVEF greater than or equal to 35 %. These data suggested that CCM may be beneficial in select patients with HF, narrow QRS, and symptoms despite OMT. Limitations of the study included: lack of a control group, improvement in NYHA, MLWHFQ, and LVEF could have resulted from the increased use of pharmacological treatment of HF in these patients, and registry follow-up testing was performed based on clinical need, which may have limited the number of patients available with outcomes data related to LVEF and exercise tolerance including 6MWT, and peak VO2.

Summary of Evidence

Based on review of the peer reviewed medical literature cardiac contractility modulation (CCM) is a device-based therapy for heart failure (HF) that mildly improves functional measures but an effect on long-term clinical outcomes has not been established and there is a significant risk of complications. CCM is an option in patients with HFrEF with NYHA functional class III or IV symptoms despite optimal medical therapy, However, there are several limitations to the widespread use of CCM: the data regarding outcomes with CCM are limited and there is risk of bias due to lack of full blinding (i.e., control subjects did not receive a generator implant), and outcomes less susceptible to lack of blinding such as all-cause death and survival free of hospitalization were not improved. Accordingly, cardiac resynchronization therapy (CRT), which has more extensive supporting data, is the preferred approach in patients who qualify for CRT. Larger, well-conducted randomized controlled trials (RCTs) using a parallel double-blind

design are needed to examine the effect of CCM on major mortality and morbidity outcomes before CCM can be widely recommended as an effective therapeutic option for HF patients. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

National Institute for Health and Clinical Excellence
In 2019, the National Institute for Health and Clinical Excellence (NICE) issued an interventional procedures guidance (IPG655) regarding cardiac contractility modulation device implantation for heart failure which states the following:

- The evidence on cardiac contractility modulation device implantation for heart failure raises no major safety concerns. However, the evidence on efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.
- Further research should ideally be in the form of randomized controlled trials. These should report details of patient selection, duration and timing of stimulation, and duration of effect of stimulation. Outcomes should include ejection fraction, oxygen consumption, New York Heart Association classification and patient-reported outcomes, including quality of life.

Regulatory Status
In March 2019, the U.S. Food and Drug Administration (FDA) granted Impulse Dynamics breakthrough device exemption for the OPTIMIZER® Smart Implantable Pulse Generator (Impulse Dynamics, Orangeburg, NY), with approved use in the treatment of individuals with chronic, moderate-to-severe (New York Heart Failure [NYHA] Class III or ambulatory Class IV) heart failure (HF) who remain symptomatic despite guideline-directed medical therapy (GDMT). Recipients must be in normal sinus rhythm with left ventricular ejection fraction (LVEF) from 25 to 45 percent and not considered a candidate for cardiac resynchronization therapy (CRT) to restore normal heart rhythm. The OPTIMIZER Smart System treatment, referred to as cardiac contractility modulation (CCM), delivers electrical signals to the ventricles during the ventricular absolute refractory period. The expected result is improvement in 6-mintue hall walking distance, quality of life, functional status, and exercise tolerance.

On October 26, 2021, the FDA approved a modification of labeling for the Optimizer Smart medical device, allowing the removal of "normal sinus rhythm" (NSR) from the indications for use statement.

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policies

- 02.02.19 Baroflex Stimulator Devices
- 02.02.21 Cardiac Hemodynamic Monitoring for the Management of Heart Failure in the Outpatient Setting
- 02.02.22 Non-invasive Heart Failure and Arrhythmia Management and Monitoring System

The use of cardiac contractility modulation therapy, administered by Impulse Dynamics OPTIMIZER Smart System is considered **investigational** for all indications, including but not limited to heart failure because the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 0408T Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes
- 0409T Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters, pulse generator only
- 0410T Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters, atrial electrode only
- 0411T Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters, ventricular electrode only
- 0412T Removal of permanent cardiac contractility modulation system; pulse generator only
- 0413T Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)
- 0414T Removal and replacement of permanent cardiac contractility modulation system pulse generator only
- 0415T Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)
- 0416T Relocation of skin pocket for implanted cardiac contractility modulation pulse generator
- 0417T Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent

programmed values with analysis, including review and report, implantable cardiac contractility modulation system

- 0418T Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, implantable cardiac contractility modulation system
- C1824 Generator, cardiac contractility modulation (implantable)
- K1030 External recharging system for battery (internal) for use with implanted cardiac contractility modulation generator, replacement only

SELECTED REFERENCES

- Yancy CW, Jessup M, Bozkurt B, et al.; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147-e239
- Butler J, Fonarow GC, Gheorghiade M. Need for increased awareness and evidence-based therapies for patients hospitalized for heart failure. JAMA. 2013;310:2035–2036.
- McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33:1787–1847.
- Kapelios C, Kontogiannis C, Nanas Y, Aravantinos D, Vlaras E, Tachliabouris I, Marinakis S, Charitos C, Nanas JN, Malliaras K. Profound pressure unloading induced by a novel implantable counterpulsation assist device in a porcine model of acute heart failure. Eur J Heart Fail. 2015;17(Suppl 1):120.
- Kapelios CJ, Terrovitis JV, Siskas P, Kontogiannis C, Repasos E, Nanas JN. Counterpulsation: a concept with a remarkable past, an established present and a challenging future. Int J Cardiol. 2014;172:318–325.
- 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. J Am Coll Cardiol. Aug 8 2017;70(6):776-803. PMID 28461007
- Dickinson MG, Allen LA, Albert NA, et al. Remote Monitoring of Patients with Heart Failure: A White Paper From the Heart Failure Society of America Scientific Statements Committee. J Card Fail. Oct 2018; 24(10): 682-694. PMID 30308242
- Abraham WT, Lindenfeld J, Reddy VY, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation in patients with moderately reduced left ventricular ejection fraction and a narrow QRS duration: Study rationale and design. Journal of cardiac failure. 2015;21(1):16-23.

- Abraham WT, Kuck K-H, Goldsmith RL, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation. Foot Ankle Surg. 2019;25(4):441-448.
- 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.
- Campbell CM, Kahwash R, Abraham WT, et al. Optimizer Smart in the treatment of moderate-to-severe chronic heart failure. Future Cardiol. 2020;16(1):13-25.
- Colucci WS. and emerging strategies for management of heart failure. UpToDate Inc., Waltham, MA. Last reviewed August 2021.
- Giallauria F, Cuomo G, Parlato A, et al. A comprehensive individual patient data meta-analysis of the effects of cardiac contractility modulation on functional capacity and heart failure-related quality of life. ESC Heart Fail. 2020;7(5):2922-2932.
- Impulse Dynamics. Cardiac contractility modulation: Innovative therapy for the treatment of chronic heart failure. Impulse Dynamics N.V. Available at: http://www.impulse-dynamics.com/us/wp-content/uploads/sites/3/2017/01/Therapy_Brochure_Optimizer_IVs_English_PDF.pdf.
- Impulse Dynamics. Evaluate safety and efficacy of the Optimizer system in subjects with moderate-to-severe heart failure: FIX-HF-5C (FIX-HF-5C). ClinciaTrials.gov Identifier: NCT01381172.
- Kuschyk J, Falk P, Demming T, et al. Long-term clinical experience with cardiac contractility modulation therapy delivered by the Optimizer Smart system. Eur J Heart Fail. 2021;23(7):1160-1169.
- Kuschyk J, Nagele H, Heinz-Kuck K, et al. Cardiac contractility modulation treatment in patients with symptomatic heart failure despite optimal medical therapy and cardiac resynchronization therapy (CRT). Int J Cardiol. 2019;277:173-177.
- Mando R, Goel A, Habash F, et al. Outcomes of cardiac contractility modulation: A systematic review and meta-analysis of randomized clinical trials. Cardiovasc Ther. 2019;2019:9769724.
- Mann JA, Abraham WT. Cardiac contractility modulation and baroreflex activation therapy in heart failure patients. Curr Heart Fail Rep. 2019;16(1):38-46.
- Matta M, Devecchi C, De Vecchi F, et al. Cardiac contractility modulation in left ventricular systolic dysfunction: one-year experience in a pilot study and design of a prospective registry. Minerva Cardioangiol. 2021;69(1):15-24.
- Muller 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. Clinical Research in Cardiology. 2017;106(11):893-904.
- Nolan MT, Tan N, Neil CJ. Novel non-pharmaceutical advancements in heart failure management: The emerging role of technology. Curr Cardiol Rev. 2021 Aug 31.

- Tint D, Florea R, Micu S. New generation cardiac contractility modulation device-filling the gap in heart failure treatment. J Clin Med. 2019;8(5).
- Tschope C, Kherad B, Klein O, et al. Cardiac contractility modulation: Mechanisms of action in heart failure with reduced ejection fraction and beyond. Eur J Heart Fail. 2019;21(1):14-22.
- 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.

POLICY HISTORY

Date	Reason	Action
January 2022	Annual Review	Policy Revised
January 2021	Annual Review	Policy Revised
January 2020	Annual Review	Policy Revised
January 2019	Annual Review	Policy Revised
January 2018	Annual Review	Policy Revised
January 2017	Annual Review	Policy Revised
September 2016	Interim Review	Policy Revised
January 2016		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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