NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of cardiac contractility modulation device implantation for heart failure

Heart failure means your heart is not able to pump blood around your body well enough. In this procedure, a device is placed under the skin of the chest and connected to the heart by 2 or 3 leads. It delivers electrical pulses that make the heart contract more strongly. The aim is to improve a person's ability to exercise and quality of life.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an

interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in November 2018.

Procedure name

- Cardiac contractility modulation device implantation for heart failure

Specialist societies

- The British Cardiovascular Intervention Society (BCIS)
- The British Cardiovascular Society (BCS)
- Society for Cardiothoracic Surgery in Great Britain and Ireland
- Royal College of Physicians
- Royal College of Physicians of Edinburgh
- Royal College of Physicians and Surgeons of Glasgow
- Royal College of Surgeons
- Royal College of Surgeons of Edinburgh.

Description of the procedure

Indications and current treatment

Heart failure is a complex clinical syndrome of symptoms and signs that suggest the heart is not working well enough, leading to reduced blood flow to body tissues. It can lead to oedema in the lungs (causing breathlessness) and swelling of the legs. Other symptoms include reduced ability to exercise, fatigue and malaise. Heart failure can be caused by structural or functional abnormalities of the heart.

NICE's guideline describes the diagnosis and management of chronic heart failure in adults. Treatments for heart failure include drugs to improve heart function, cardiac rehabilitation, cardiac resynchronisation therapy and cardiac transplantation. Cardiac contractility modulation device implantation may be an option for patients with advanced heart failure that hasn't responded to conventional therapy.

What the procedure involves

Cardiac contractility modulation device implantation for heart failure is usually done under local anaesthesia. A device similar to a pacemaker is implanted in the right or left pectoral region and is connected to 2 standard pacemaker leads that are threaded through veins into the right ventricle. The electrodes in the right ventricle are placed on the ventricular septum at least 2 cm apart. These sense ventricular activity and deliver cardiac contractility modulation signals. An optional additional lead may be used to sense atrial activity (usually placed in the right atrial appendage). 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. Pulses are delivered at regular intervals throughout the day.

The device is recharged using a home-based charger system, typically on a weekly basis. Charging sessions last about 40 to 60 minutes.

The aim is to improve the heart's contractility, therefore improving a person's ability to exercise and quality of life.

Outcome measures

NYHA classification

The New York Heart Association (NYHA) classification system is used to measure symptoms and loss of functionality caused by heart failure, in particular dyspnoea (breathlessness). It is a subjective outcome based on patient symptoms, as follows:

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Efficacy summary

Peak oxygen consumption

In a systematic review of 4 studies (n=723), there was a statistically significant increase in peak oxygen consumption in the cardiac contractility modulation (CCM) group compared with the control group (pooled standard mean difference=0.23, 95% confidence interval (CI) 0.07 to 0.4, p=0.006; I^2=0%, 3 studies).[1] In a randomised controlled trial (RCT) of 428 patients (also included in the systematic review), the peak oxygen consumption increased in the CCM group and decreased in the control group (difference 0.65 ml/kg/min, p=0.024). There was no statistically significant difference in the proportion of responders in each group (improved by 20% or more), which was 17.3% (31/179) and 13.7% (23/168) respectively, p=0.233.[2] In a randomised controlled trial (RCT) of 160 patients, the model-based estimated mean difference in peak oxygen consumption between CCM treatment and control groups was 0.84 ml O_2/kg/min (95% Bayesian credible interval 0.12 to 1.55).[3]

6-minute walk test distance

In the RCT of 428 patients, 34.2% (65/190) of patients in the CCM group and 29.5% (51/173) of patients in the control group (p=0.197) were classified as responders (40.0 metre increase) at 24 week follow-up.[2] In the RCT of 160 patients, the 6-minute walk test distance increased by 43.0 metres in the CCM group and 9.3 metres in the control group at 24 week follow-up (p=0.0093).[3]

Ventilatory anaerobic threshold (VAT)

In the RCT of 428 patients, the VAT decreased by 0.14 ml/kg/min in both groups at 24 week follow-up. VAT increased by 20% or more in 17.6% (28/159) of patients in the CCM group and 11.7% (18/154) of patients in the control group (p=0.093). At 50 weeks, 23.7% of patients in the CCM group and 14.4% of patients in the control group were responders with regard to VAT (p=0.027).[2]

NYHA class

In the RCT of 428 patients, the NYHA class improved by 1 class or more in 49.2% (94/191) of patients in the CCM group and 34.4% (63/183) of patients in the control group (p=0.0026) at 24 week follow-up.[2] In the RCT of 160 patients, the NYHA class improved by 1 class or more in 81% of patients in the CCM group and 42% of patients in the control group (p<0.001) at 24 week follow-up.[3] In a case series of 143 patients, the mean NYHA class reduced from 2.9 at baseline to 2.2 at 24 month follow-up (n=68; p<0.05).[6] In a case series of 140 patients, the NYHA class decreased by 0.8 at 24 month follow-up (p<0.001).[8]

Minnesota living with heart failure questionnaire (MLWHFQ)

In the RCT of 428 patients, the MLWHFQ reduced by 10 points or more in 56.1% (110/196) of patients in the CCM group and 41.8% (77/184) of patients in the control group (p=0.0037) at 24 week follow-up (lower scores indicate better quality of life).[2] In the RCT of 160 patients, the model-based mean difference in MLWHFQ between CCM treatment and control groups at 24 week follow-up was −11.7 points (95% CI −17.6 to −5.9; 1 sided p value <0.001).[3] In the case series of 143 patients, the MLWHFQ reduced by 13.6 points from baseline at 24 month follow-up (n=59; p<0.05).[6] In the case series of 140 patients, the MLWHFQ decreased by 17.1 points at 24 month follow-up (p<0.001).[8]

Survival

In the RCT of 160 patients, the overall survival was 98% in the CCM group and 95% in the control group at 24 week follow-up (p=not significant).[3] In the case series of 143 patients, 1 and 2 year survival were 94.2% (95% CI 88.8% to 97.1%) and 86.4% (95% CI 79.3% to 91.2%) respectively.[6] In the case series of 140 patients, survival at 1, 2 and 3 years was 91.6%, 86.2% and 82.8% compared with predicted survival (using the Seattle Heart Failure Model) of 91.3%, 83.7% and 76.7% respectively (p=0.1644).[8]

Left ventricular ejection fraction

In the case series of 143 patients, the left ventricular ejection fraction increased by 6.5% from baseline at 24 month follow-up (n=51; p<0.05).[6] In the case series of 140 patients, the left ventricular ejection fraction increased from 32.8% at baseline to 35.8% at 24 month follow-up (n=51; p=0.003).[8]

Safety summary

Mortality

The overall relative risk for all-cause mortality in patients who had a CCM device implanted was 0.70 (95% CI 0.47 to 1.04, p=0.078, I^2=26.7%, 4 studies) in a systematic review of 4 studies (n=723).[1] There were 6 deaths in an RCT of 160 patients: 2 in the CCM group (1 before the device was supposed to be implanted and 1 at 164 days after implantation because of sepsis after a cholecystectomy) and 4 in the control group (2 caused by cardiac pump failure, 1 after an ablation procedure for ventricular tachycardia and 1 caused by pulmonary complications after a noncardiac procedure).[3] All-cause mortality was 41% in the CCM group and 71% in the control group (p=0.001) in a non-randomised comparative study of 82 patients. Cardiovascular mortality was 34% in the CCM group and 51% in the control group (p=0.02) in the same study.[5] All-cause mortality was 7.4% (18/143) at 24 month follow-up in a case series of 143 patients (7 were classified as cardiovascular).[6] Observed mortality of 0%, 3.5% and 14.2% at 1, 2 and 5 years respectively was statistically significantly lower than the predicted mortality (using the Seattle Heart Failure Model) of 6.1%, 11.8% and 27.7% (p=0.007) in a case series of 68 patients.[7] Mortality was 12.9% (18/140) in a case series of 140 patients (11 deaths were cardiac related).[8]

Hospitalisation

The overall relative risk for all-cause hospitalisation in patients who had a CCM device implanted was 0.94 (95% CI 0.80 to 1.11, p=0.49, I^2=18.5%, 4 studies) in the systematic review of 4 studies (n=723).[1] Hospitalisation related to heart failure was reported in 46% of patients in the CCM group and 49% of patients in the control group (p=0.11) in a non-randomised comparative study of 82 patients.[5]

Worsening heart failure

The overall relative risk for worsening heart failure in patients who had a CCM device implanted was 0.99 (95% CI 0.72 to 1.37, p=0.974, I^2=0%, 3 studies) in the systematic review of 4 studies (n=723).[1] Worsening heart failure was reported in 26% (37/143) and 22.9% (32/140) of patients in the 2 case series of 143 and 140 patients respectively.[6,8]

Arrhythmia

The overall relative risk for arrhythmia in patients who had a CCM device implanted was 1.10 (95% CI 0.70 to 1.74, p=0.677, I^2=0%, 3 studies) in the systematic review of 4 studies (n=723).[1] Arrhythmia was reported in 10% (14/143) and 6.4% (9/140) of patients in the 2 case series of 143 and 140 patients respectively.[6,8]

General cardiopulmonary

General cardiopulmonary serious adverse events (such as chest pain and angina or pulmonary disease such as upper respiratory infection and pneumonia) were reported in 16% (23/143) and 17.1% (24/140) of patients in the 2 case series of 143 and 140 patients respectively.[6,8] 'General cardiopulmonary events' were reported in 20.0% (42/210) of patients in the CCM group and 21.7% (46/212) of patients in the control group in the RCT of 428 patients.[2]

Lead dislodgement, fracture, migration or revision

Lead dislodgement was reported in 7.4% (5/68) of patients who had a CCM device implanted in an RCT of 160 patients.[3] Lead migration or revision was reported in 7% (10/143) of patients in the case series of 143 patients.[6] Lead fracture or failure was reported in 1 patient in the case series of 140 patients.[8] Lead dislodgement was reported in 1.8% (3/164) of patients in the RCT of 164 patients.[4] Lead fracture or dislodgement was reported in 6.5% (14/215) of patients in the RCT of 428 patients. Lead perforation was reported in 1.0% (2/215) of patients in the same study. [2]

Generator erosion

Generator erosion was reported in 1 patient who had a CCM device implanted in the RCT of 160 patients.[3] Pocket dehiscence or erosion was reported in 1.4% (3/215) of patients in the RCT of 428 patients.[2]

Infection

Wound infection was reported in 4.9% (2/41) of patients who had a CCM device implanted in the non-randomised comparative study of 82 patients; the device was removed in both patients.[5] Infection was reported in 10% (14/143) of patients in the case series of 143 patients.[6] Infection (other than device pocket) was reported in 7.1% (10/140) of patients in the case series of 140 patients. Sepsis was reported in 1 patient in the same study.[8] Device pocket infection was reported in 2.4% (4/164) of patients in the RCT of 164 patients.[4] Pocket infection was reported in 1.0% (2/215) of patients in the RCT of 428 patients.[2] Localised infection was reported in 12.9% (27/210) of patients in the CCM group and 13.7% (29/212) of patients in the control group in the RCT of 428 patients. Sepsis was reported in 4.8% (10/210) and 1.0% (2/212) of patients respectively in the same study.[2]

Bleeding

Bleeding was reported in 3% (4/143) of patients in the case series of 143 patients.[6] Clinically significant bleeding was reported in 1.4% (2/140) of patients in the case series of 140 patients.[8] Bleeding at the device site was reported in 2.4% (4/164) of patients in the RCT of 164 patients.[4] Pocket bleeding was reported in 1 patient in the RCT of 428 patients.[2]

Device malfunction

Device malfunction was reported in 3% (5/143) of patients in the case series of 143 patients.[6] Implanted pulse generator problem was reported in 1 patient in the RCT of 428 patients.[2] 'Pocket stimulation' (not further defined) was reported in 1.0% (2/215) of patients in the RCT of 428 patients.[2]

Device-related events

Serious adverse events probably or possible related to the device were reported in 17% (25/143) of patients in the case series of 143 patients.[6] Device related serious adverse events (other than lead fracture or failure) was reported in 6.4% (9/140) of patients in the case series of 140 patients.[8]

ICD-related events

ICD or pacemaker related serious adverse events were reported in 5.2% (11/210) of patients in the CCM group and 2.8% (6/212) of patients in the control group in the RCT of 428 patients.[2] An ICD sensing defect was reported in 3.0% (5/164) of patients in the RCT of 164 patients.[4] ICD-related serious adverse events were reported in 3% (5/143) and 1.4% (2/140) of patients in the case series of 143 and 140 patients respectively.[6,8]

General medical

'General medical' serious adverse events (including renal failure, neurological dysfunction, peripheral arterial disease/event, stroke, and other non-cardiac medical abnormalities) were reported in 20% (28/143) and 25.0% (35/140) of patients in the 2 case series of 143 and 140 patients respectively.[6,8] 'General medical' adverse events (not further defined) were reported in 30.0% (63/210) of patients in the CCM group and 25.5% (54/212) of patients in the control group in the RCT of 428 patients.[2]

Other

Transient ischaemic attack or stroke was reported in 1.4% (2/140) patients in the case series of 140 patients. Thromboembolism (non-neurological) was reported in 1 patient in the same study.[8] Pericardial effusion was reported in 1 patient in the RCT of 164 patients.[4] Neurological dysfunction was reported in 1.4% (3/210) of patients in the CCM group and 5.7% (12/212) of patients in the control group in the RCT of 428 patients.[2]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse events: [add in anecdotal events]. They considered that the following were theoretical adverse events: [add in theoretical events].

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to cardiac contractility modulation device implantation for heart failure. The following databases were searched, covering the period from their start to 2 October 2018: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with heart failure.
Intervention/test	Cardiac contractility modulation device implantation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on about 1,200 patients from 1 systematic review, 3 randomised controlled trials (2 of which were also included in the review), 1 non-randomised comparative study (included in the review) and 3 case series.[1–8]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on cardiac contractility modulation device implantation for heart failure

Study 1 Liu X (2017)

Details

Study type	**Systematic review and meta-analysis**
Country	Not reported for individual studies
Recruitment period	Search date: May 2016
Study population and number	**n=723** (4 studies; n=82, 428, 164 and 49) **Adult patients with heart failure**
Age and sex	Mean age ranged from 52 to 64 years; % male ranged from 68% to 89%
Patient selection criteria	Age 18 years or above with documented heart failure (New York Heart Association classification III or higher). The following study designs were included: case-control, quasi-controlled trials, randomised controlled trials, long-term follow-up studies. Exclusion criteria described were designs such as case series, case reports, cross-sectional studies without comparison groups, crossover designs, and studies that aimed to validate or replicate the efficacy and safety of cardiac contractility modulation. No language restriction was set in advance.
Technique	All studies used the OPTIMIZER system (Impulse Dynamics) in the intervention group and control groups had sham treatment (device turned off) or optimal medical therapy alone.
Follow-up	**Ranged from 12 weeks to 70 months**
Conflict of interest/source of funding	Not reported for individual studies. The review work was supported by the Nature Science Foundation of Hubei Province and the Foundation Research Funds for the Central Research Funds for the Central Universities, China.

Analysis

Follow-up issues: Losses to follow-up were not discussed in the review. The authors stated that the risk of attrition bias was low.

Study design issues: Three of the included studies were described as randomised controlled trials, the fourth was described as a controlled trial. Primary safety outcomes were all-cause mortality, all-cause hospitalisations, and adverse events (worsening heart failure, arrhythmia, general cardiopulmonary events). The efficacy outcomes were peak oxygen consumption, 6-minute walk test distance, New York Heart Association (NYHA) classification, and echocardiography findings.

Study population issues: Most patients had chronic heart failure mainly resulting from an ischaemic cause and classified as NYHA III.

Other issues: the FIX-CHF-4 study was reported to have a sample size of 168 in the table of study characteristics, but the original paper reporting this study states the sample size was 164. The total number of patients was consistent with a sample size of 164.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **723** **Peak oxygen consumption** Pooled standard mean difference=0.23 (95% CI 0.07 to 0.4, p=0.006; I^2=0%, 3 studies) There was a statistically significant increase in peak oxygen consumption in the cardiac contractility modulation group compared with the control group. **6-minute walk test distance** Pooled standard mean difference=0.17 (95% CI 0.001 to 0.33, p=0.049; I^2=0%, 3 studies) (NB the body of the text and the abstract state that the standard mean difference is 0.924, 95% CI 0.001 to 0.334)	***Adverse events*** **Worsening heart failure** Overall RR=0.99 (95% CI 0.72 to 1.37, p=0.974; I^2=0%, 3 studies) **Arrhythmia** Overall RR=1.10 (95% CI 0.70 to 1.74, p=0.677; I^2=0.0%, 3 studies) **General cardiopulmonary events** (including severe cardiovascular clinical symptoms such as chest pain and angina or pulmonary disease such as upper respiratory infection and pneumonia) Overall RR=0.92 (95% CI 0.65 to 1.32, p=0.666; I^2=0.0%, 3 studies) **All-cause mortality** Overall relative risk (RR)=0.70 (95% Confidence interval [CI] 0.47 to 1.04, p=0.078; I^2=26.7%, 4 studies) **All-cause hospitalisations** Overall RR=0.94 (95% CI 0.80 to 1.11, p=0.49; I^2=18.5%, 4 studies)
Abbreviations used: CI, confidence interval; RR, relative risk	

Study 2 Kadish A (2011)

Details

Study type	**Randomised controlled trial (FIX-HF-5)**
Country	US (50 centres)
Recruitment period	2005 to 2007
Study population and number	**n=428** (215 cardiac contractility modulation [CCM] and optimal medical therapy versus 213 optimal medical therapy alone) **Patients with medically refractory heart failure with ejection fraction 35% or less**
Age and sex	Mean 58 years; 72% (309/428) male
Patient selection criteria	Patients ≥18 years old with ejection fraction ≤35%, New York Heart Association (NYHA) class III or IV symptoms despite medical treatment with angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker and beta-blockers for 3 months with a baseline peak oxygen consumption on cardiopulmonary stress testing ≥9 ml O_2/kg/min, normal sinus rhythm and not indicated for a cardiac resynchronisation therapy device (QRS <130 milliseconds). Unless there were extenuating circumstances, patients were required to have an implantable cardioverter defibrillator. Patients were excluded if they were hospitalised within 30 days of enrolment, were inotrope dependent, had >8,900 premature ventricular contractions per 24 hours on a baseline Holter monitor, had permanent atrial fibrillation, had a myocardial infarction within 90 days, had percutaneous coronary intervention within 30 days, or had coronary artery bypass surgery within 90 days of enrolment.
Technique	Device: OPTIMIZER system (Impulse Dynamics, US).
Follow-up	**12 months**
Conflict of interest/source of funding	The study was supported by a grant from Impulse Dynamics, US.

Analysis

Follow-up issues: In the CCM group, 3 patients died before the device could be implanted and 7 patients chose not to have the procedure. Device implantation was aborted in 2 patients, 1 because of right ventricular perforation and 1 because of a substantially prolonged PR interval (patients with PR interval >275 milliseconds were subsequently excluded). Of the 203 patients with a successful implant, 5 withdrew and 10 died so that 92.6% completed the follow-up period. In the control group, 17 patients withdrew and 7 died, so 88.7% of patients completed the follow-up period.

Study design issues: Randomised controlled trial; method of randomisation not described. Patients were not blinded to their treatment allocation. The primary effectiveness endpoint was the change from baseline in the ventilator anaerobic threshold (VAT) measured on cardiopulmonary stress testing. A patient was considered to be a 'responder' if VAT increased by 20% or more at 24 weeks. The primary analysis was based on the intent to treat population, and imputation was used to account for missing data. The primary safety endpoint was the composite event rate of all-cause mortality and all-cause hospitalisation. The following changes in secondary efficacy endpoints were considered to be a response: 20% increase in peak oxygen consumption, 10-point reduction in Minnesota living with heart failure questionnaire score, 1 class change in NYHA, and a 40 metre increase in 6-minute walk test distance.

Study population issues: The baseline characteristics were similar between the 2 treatment groups. 82% of patients had an implantable cardioverter defibrillator before entry into the study, 11% had 1 placed at the start of the study and 2% of patients had 1 implanted during the follow-up period.

Other issues: study is included in review by Liu X et al., 2017 (study 1).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **428 (215 versus 213)**

Ventilatory anaerobic threshold (VAT)
VAT decreased by 0.14 ml/kg/min in both groups at 24 weeks

Responder analyses at 24-week follow-up

Parameter	CCM group, n=215 n/N (%) LCL, UCL	Control group, n=213 n/N (%) LCL, UCL	Difference LCL, UCL (%)	p
VAT (ml/kg/min)	28/159 (17.6) 12.0, 24.4	18/154 (11.7) 7.1, 17.8	5.9 -2.0, 13.9	0.093
VAT (ml/kg/min) ITT	38/215 (17.7) 12.8, 23.4	28/213 (13.2) 8.9, 18.4	4.5 -2.4, 11.5	0.314
Peak oxygen consumption (ml/kg/min)	31/179 (17.3) 12.1, 23.7	23/168 (13.7) 8.9, 19.8	3.6 -4.1, 11.3	0.233
MLWHFQ	110/196 (56.1) 48.9, 63.1	77/184 (41.8) 34.6, 49.3	14.3 4.2, 24.1	0.0037
NYHA class	94/191 (49.2) 41.9, 56.5	63/183 (34.4) 27.6, 41.8	14.8 4.8, 24.5	0.0026
6-minute walk test distance (metres)	65/190 (34.2) 27.5, 41.4	51/173 (29.5) 22.8, 36.9	4.7 -4.9, 14.2	0.197

At 50 weeks, 23.7% of patients in the CCM group and 14.4% of patients in the control group were responders with regard to VAT (p=0.027).

Peak oxygen consumption increased in the CCM group and decreased in the control group (difference 0.65 ml/kg/min, p=0.024) but there was no statistically significant difference in the proportion of responders in each group (improved by 20% or more).

Patients with an ejection fraction ≥25% in the CCM group had a 12.2% greater responder rate than those in the control group.

Patients with NYHA class III in the CCM group had a 6.9% greater responder rate than those in the control group. Patients with NYHA class IV in the CCM group had a 7.3% lower responder rate.

Subgroup analysis – patients with ejection fraction ≥25% and NYHA class III (109 CCM versus 97 controls)

There were clinically and statistically significantly greater improvements in VAT (0.64 ml/kg/min, p=0.03 for the completed cases, p=0.024 for ITT with imputed missing data), increased peak oxygen consumption (1.31 ml/kg/min, p=0.001), improved MLWHFQ (10.8 points, p=0.003) and improved NYHA (-0.29, p=0.001) at 24 weeks.

Safety

All-cause hospitalisations and all-cause mortality (primary safety endpoint)
- CCM=52.1% (112/215)
- Control=48.4% (103/213)

p=0.03 for noninferiority

Device-related serious adverse events (number of patients)
- Lead fracture, n=3
- Right ventricular lead dislodgment, n=6
- Implanted pulse generator problem, n=1
- Right atrium lead dislodgment, n=5
- Pocket dehiscence or erosion, n=3
- Pocket infection, n=2
- Pocket stimulation, n=2
- Lead perforation, n=2
- Pocket bleeding, n=1
- Sensation because of CCM, n=2
- Extracardiac stimulation, n=1

Total incidence of lead complications=7%

Serious adverse events between study start date and 1 year follow-up; number of events (number of patients)

Adverse event category	CCM group n=210	Control group n=212
General cardiopulmonary event	60 (42)	58 (46)
Arrhythmias	40 (29)	30 (25)
Worsening heart failure	72 (50)	85 (50)
ICD/pacemaker system related	13 (11)	7 (6)
Bleeding	8 (6)	8 (8)
Localised infection	33 (27)	36 (29)
Sepsis	11 (10)	2 (2)
Neurological dysfunction	3 (3)	14 (12)
Thromboembolism (non-neurological)	3 (3)	5 (5)
General medical	98 (63)	81 (54)
Total	341 (129)	326 (115)
	p=0.66	

Between randomisation and the study start date, there were 22 events in 13 patients in the CCM group and 9 events in 8 patients in the control group (p=0.027).

Abbreviations used: CCM, cardiac contractility modulation; ICD, implantable cardioverter defibrillator; ITT, intention to treat; LCL, lower confidence limit; MLWHFQ, Minnesota living with heart failure questionnaire; NYHA, New York Heart Association; UCL, upper confidence limit; VAT, ventilator anaerobic threshold

Study 3 Abraham WT (2018)

Details

Study type	**Randomised controlled trial (FIX-HF-5C)**
Country	US
Recruitment period	Not reported
Study population and number	**n=160** (74 cardiac contractility modulation [CCM] and optimal medical therapy versus 86 optimal medical therapy alone) **Patients with medically refractory heart failure with ejection fraction between 25% to 45%**
Age and sex	Mean 63 years; 76% (122/160) male
Patient selection criteria	Patients with New York Heart Association (NYHA) functional class III or ambulatory class IV heart failure despite optimal medical therapy, an ejection fraction ranging from 25% to 45% as determined by an echocardiographic core laboratory, and normal sinus rhythm with QRS duration <130 ms. Unless there were extenuating circumstances, patients with ejection fraction 35% or less were required to have an implantable cardiac-defibrillator (ICD).
Technique	Device: OPTIMIZER system (Impulse Dynamics, US). The device was programmed to deliver CCM signals for 5 1-hour periods spaced equally throughout the 24 hours of the day.
Follow-up	**24 weeks**
Conflict of interest/source of funding	The study was supported by research grants from Impulse Dynamics. One author is an employee of Impulse Dynamics and 5 authors have served as consultants to the company.

Analysis

Follow-up issues: Of the 74 patients assigned to the CCM treatment group, 68 (92%) had a device implanted. Reasons why patients did not have an implant included: 1 patient died before device implant, 1 was lost to follow-up, 1 was deemed ineligible (NYHA class II) and withdrawn after randomisation, 1 was found to have an additional abandoned ICD lead and the implant was cancelled and 2 decided not to have the procedure. Follow-up visits were at 12 and 24 weeks.

Study design issues: Prospective randomised controlled trial, designed to confirm a subgroup analysis of the prior FIX-HF-5 study. Patients were not blinded to their treatment allocation. The primary measure of efficacy was defined as the change in peak rate of oxygen consumption as evaluated by a blinded core laboratory. Secondary efficacy parameters included change in quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) and NYHA classification. Some analyses were done on the per-protocol population of data pooled from the FIX-HF-5 subgroup and this cohort. Bayesian repeated measures linear modelling was used for the primary efficacy endpoint analysis with 30% borrowing from the FIX-HF-5 subgroup. The primary safety endpoint was the proportion of patients who did not have a device- or procedure-related complication by 24 weeks (pre-specified lower bound of 70%).

Study population issues: The baseline characteristics were similar between the 2 treatment groups. Overall, 50% of patients had previous myocardial infarction, 50% had diabetes, ejection fraction averaged 32%, peak oxygen consumption was about 15 ml O_2/kg/min, MLWHFQ was 57 points, 6-minute walk test distance was 325 metres, and 90% were in NYHA functional class III.

Other issues: the study reports some results for the FIX-HF-5C cohort, some for the FIX-HF-5 cohort and some pooled results. In the table below, the results from the FIX-HF-5C cohort are presented unless otherwise stated.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **160 (74 versus 86)** **Peak oxygen consumption at 24 weeks (n=142; 68 versus 74) – pooled results** Model-based estimated mean difference in peak oxygen consumption between CCM treatment and control groups was 0.84 ml O_2/kg/min (95% Bayesian credible interval 0.12 to 1.55). Probability that CCM treatment is superior to control=0.989, which exceeds the 0.975 criteria for statistical significance for the primary endpoint. *FIX-HF-5 study only* Model-based estimated mean difference in peak oxygen consumption between CCM treatment and control groups was 1.08 ml O_2/kg/min (95% confidence interval [CI] 0.41 to 1.76). *FIX-HF-5C study only* Model-based estimated mean difference in peak oxygen consumption between CCM treatment and control groups was 0.79 ml O_2/kg/min (95% CI −0.10 to 1.68). **Minnesota Living with Heart Failure Questionnaire (MLWHFQ)** The model-based mean difference in MLWHFQ at 24 weeks between CCM treatment and control groups for the FIX-HF-5C cohort alone was -11.7 points (95% CI −17.6 to −5.9 points; 1 sided p value <0.001). A negative value indicates improvement. **1 NYHA class improvement or more at 24 weeks** • CCM=81% (n=57) • Control=42% (n=32) The odds of improving by at least 1 NYHA functional class in the CCM group was 5.97 times the odds of improving in the control group (p<0.001). **Increase in 6-minute walk test distance** • CCM=43.0±80.7 metres • Control=9.3±87.4 metres, p=0.0093 The improvement was greater in patients with ejection fraction ≥35%. **Overall survival at 24 weeks** • CCM=98% • Control=95%, p=not significant **Freedom from cardiac death and heart failure hospitalisation – pooled results** • CCM=95.5% • Control=89.8%, p=0.042 (log-rank test) This improvement was mainly driven by a reduction in events for the ejection fraction 25% to 35% cohort (p=0.009)	**Complication-free rate=89.7% (95% CI 79.9% to 95.8%)** **Adverse events** (n=68 patients who had device implanted) • Lead dislodgements, n=5 • Deep vein thrombosis, n=1 • Generator erosion resulting in pocket stimulation that needed pocket revision and replacement of pacemaker leads, n=1 **Deaths** • CCM group, n=2 (1 death happened 2 days before the device was supposed to be implanted, the other happened at 164 days after implantation and was caused by sepsis following a cholecystectomy) • Control group, n=4 (2 were caused by cardiac pump failure on days 4 and 36, 1 death followed a VT ablation procedure on day 70, and 1 was caused by pulmonary complications of a noncardiac procedure on day 117.
Abbreviations used: CCM, cardiac contractility modulation; CI, confidence interval; MLWHFQ, Minnesota living with heart failure questionnaire; NYHA, New York Heart Association	

Study 4 Borggrefe MM (2008)

Details

Study type	**Randomised controlled trial** (**FIX-CHF-4)**
Country	Germany, Italy, France, the Netherlands, Czech republic
Recruitment period	2002 to 2005
Study population and number	**n=164** (80 cardiac contractility modulation [CCM] for 3 months followed by sham treatment for 3 months [group 1] versus 84 sham treatment for 3 months followed by CCM for the second 3 months [group 2]) **Patients with symptomatic heart failure and left ventricular ejection fraction ≤35%**
Age and sex	Mean 59 years; 85% (139/164) male
Patient selection criteria	Patients older than 18 years with symptomatic heart failure (New York Heart Association [NYHA] functional class ≥ II), ischaemic or idiopathic cardiomyopathy, left ventricular ejection fraction ≤35%, and peak oxygen uptake between 10 and 20 ml O_2/min/kg. Patients were required to be on appropriate, stable medical treatments for heart failure, including (unless shown to be intolerant) a diuretic, an angiotensin-converting enzyme inhibitor and/or angiotensin-receptor blocker and a beta-blocker. Patients could have a pre-existing implanted pacemaker or implantable cardioverter defibrillator (ICD) or, if clinically indicated, could have 1 at the same time as the CCM device was implanted. Patients were excluded if they were eligible for cardiac resynchronisation therapy (CRT), or they had atrial fibrillation, recent myocardial infarction (within 3 months), clinically significant angina, were hospitalised for heart failure needing intravenous treatments within 30 days or ≥8,900 premature ventricular contractions per 24 hours on a baseline Holter monitor recording.
Technique	Device: OPTIMIZER system (Impulse Dynamics, US). The device was programmed to deliver signals for 7 1 hour periods spaced equally over the day.
Follow-up	**6 months**
Conflict of interest/source of funding	The study was supported by research grants from Impulse Dynamics, US. One author is an employee of Impulse Dynamics, 1 is a consultant to the company and 4 authors receive honoraria for participating in a speakers bureau for Impulse Dynamics.

Analysis

Follow-up issues: Four patients died during the randomisation phase of the study and 9 withdrew (2 for continuous pocket infection, 3 who had a heart transplant, 1 who developed an indication for CRT and 3 for continued worsening of heart failure). 92% (151/164) of patients completed the 6 month primary follow-up period.

Study design issues: Randomised, double blind, crossover study. Patients were randomly allocated to active treatment or sham treatment (device programmed to off) for 12 weeks. During the subsequent 12 weeks, all patients crossed over to the opposite treatment. Randomisation was done 2 to 4 weeks after the device was implanted, using sealed envelopes. An unblinded site clinical investigator opened the envelope and a technician programmed the device accordingly. The primary efficacy endpoints were the difference in peak oxygen consumption and the Minnesota living with heart failure questionnaire (MLWHFQ). A core lab blinded to the assignment group was used to assess peak oxygen consumption from the cardiopulmonary stress test. Assessment of the primary null hypotheses was based on the intention to treat population. A data safety and monitoring board reviewed serious adverse events on 3 separate occasions during the study and would have advised if there any imbalance in events between the groups to suggest a safety concern.

Study population issues: The baseline characteristics in the 2 groups were similar, but there was a higher proportion of patients with ischaemic cardiomyopathy in group 1. The mean ejection fraction was 29%, peak oxygen consumption 13.9 ml/kg/min and QRS duration 118 milliseconds; 62% of patients had an ICD.

Other issues: study is included in review by Liu X et al., 2017 (study 1).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **164**

Primary and secondary efficacy assessments (mean±standard error); results presented for patients with complete data

	Difference from baseline			
	Phase 1		Phase 2	
	Group 1	Group 2	Group 1	Group 2
Peak oxygen consumption (ml/kg/min)	0.40±0.37	0.37±0.41	-0.46±0.33	0.53±0.45
MLWHFQ	-12.1±1.8	-9.7±2.0	-7.4±2.2	-10.4±2.1
6-minute walk test distance (metres)	16.9±8.9	10.8±8.8	-6.3.±10.4	19.6±9.1

A comparison of values at the end of active treatment periods versus end of sham treatment periods indicates statistically significantly improved peak oxygen consumption and MLWHFQ (p=0.03).

New York Heart Association (NYHA) classification improved similarly in both groups in both phases of the study.

Group 1 – proportion of patients by NYHA class at final follow-up (device turned off)

- Class I=8%
- Class II=46%
- Class III=24%
- Class IV=2%

Group 2 – proportion of patients by NYHA class at final follow-up (device turned off)

- Class I=9%
- Class II=50%
- Class III=23%
- Class IV=2%

Interpretable echocardiograms were obtained at baseline and the end of the study in about half of patients. There were no significant changes in ejection fraction detected in any group at any time point.

Safety

Death

There were 6 deaths during the study, 2 before randomisation, 1 in group 1 during the 'off' period (undetermined cause), 1 in group 2 during the 'off' period and 2 in group 2 during the 'on' period (sudden cardiac death and renal failure).

Serious cardiovascular events after device implantation, number of events (number of patients)

	Implant to randomisation	Active	Sham
Number of patients	166	164	164
Total	20 (20)	22 (20)	26 (22)
CHF decompensation	1 (1)	7 (6)	8 (8)
Atrial fibrillation	-	2 (2)	3 (3)
Bleeding at device site	4 (4)	-	-
Pneumonia	2 (2)	-	3 (3)
VF	-	1 (1)	1 (1)
VT	2 (2)	3 (2)	-
Angina	-	1 (1)	3 (2)
Device pocket infection	1 (1)	1 (1)	3 (2)
ICD sensing defect	4 (4)	1 (1)	-
Renal failure	-	1 (1)	3 (1)
Pulmonary oedema	-	1 (1)	1 (1)
Pericardial effusion	1 (1)	1 (1)	-
Cardiogenic shock	-	1 (1)	-
Lead dislodgement	2 (2)	1 (1)	-

Abbreviations used: CHF, chronic heart failure; ICD, implantable cardioverter defibrillator; MLWHFQ, Minnesota living with heart failure questionnaire; NYHA, New York Heart Association; VF, ventricular fibrillation; VT, ventricular tachycardia

Study 5 Liu M (2016)

Details

Study type	**Non-randomised comparative study**
Country	Hong Kong
Recruitment period	2005 to 2012
Study population and number	**n=82** (41 cardiac contractility modulation [CCM] and optimal medical therapy versus 41 optimal medical therapy only) **Patients with symptomatic heart failure and ejection fraction <40%**
Age and sex	Mean 61 years (CCM group), 64 years (control group); 85% male
Patient selection criteria	Inclusion criteria for study arm: Age >18 years; New York Heart Association (NYHA) class III or IV heart failure with left ventricular ejection fraction ≤40; on a stable medical regimen for heart failure for at least 1 month; QRS <130 milliseconds. Exclusion criteria: permanent atrial fibrillation or atrial flutter; severe symptomatic heart failure appropriate for transplantation; treatment with intravenous inotropic medications within the last 3 weeks; baseline peak oxygen consumption <9 ml/min/kg; clinically significant angina pectoris or an episode of unstable angina or myocardial infarction within 30 days of enrolment, or resting ischaemia by ECG or symptoms of angina; potentially correctible cause of heart failure; ICD firing within 1 month of enrolment; >8,900 premature ventricular contractions per 24 hours by Holter; inability to complete a 6-minute walk test or non-cardiac condition that markedly reduces exercise capacity; scheduled or competed coronary artery bypass grafting or percutaneous coronary intervention within the past 3 months; indication for cardiac resynchronisation therapy; prior cardiac transplant, mechanical tricuspid or aortic valves; inability to provide informed consent; participation in another simultaneous experimental protocol.
Technique	Device: OPTIMIZER system (Impulse Dynamics, US). The device was programmed to deliver signals for 7 1 hour periods spread throughout the day.
Follow-up	**Mean 75 months (CCM group), 69 months (control group)**
Conflict of interest/source of funding	The study was partly supported by a research grant by Impulse Dynamics. One of the authors is the founder of Impulse Dynamics, 2 authors are consultants to the company and 1 author is an employee of Impulse Dynamics.

Analysis

Follow-up issues: Patients were followed up until the end of the study or until a primary endpoint was reached. Of the 41 patients in the CCM group, 3 did not complete the follow-up; 1 patient did not return for testing 3 months after implantation and 2 had the device removed.

Study design issues: Prospective, non-randomised comparative study. The study group consisted of consecutive patients with heart failure treated by CCM at a single hospital and the comparator group consisted of patients with heart failure who were enrolled in the same hospital's heart failure registry over the same time period. Patients were matched by age, gender, medications at baseline, left ventricular ejection fraction at baseline, follow-up duration and aetiology of heart failure. The primary endpoint was all-cause mortality. Secondary endpoints included heart failure hospitalisations, cardiovascular death, and the composite outcome of death or heart failure hospitalisation. The analysis was by intention to treat.

Study population issues: The baseline characteristics in the 2 groups were similar for the matching criteria. There were statistically significant differences in NYHA class (all patients in the CCM group were class III, 54% of patients in the control group were class III and 39% were class IV; the mean NYHA class was about 7% higher in the control group compared with the CCM group, p<0.001). 15% (6/41) of patients in the CCM group had paroxysmal atrial fibrillation at baseline compared with 37% (15/41) of patients in the control group (p=0.02). Only 2 patients had an ICD implanted and both were in the CCM group.

Other issues: study is included in review by Liu X et al., 2017 (study 1).

Key efficacy and safety findings

Efficacy and Safety
Number of patients analysed: **82 (41 versus 41)** **All-cause mortality (primary endpoint) – whole cohort** • CCM group=41% • Control=71%, p=0.001 When stratified by baseline ejection fraction (<25% compared with 25 to 40%), there was only a statistically significant survival benefit in patients with ejection fraction between 25 and 40%. **Heart failure hospitalisation rates (Kaplan Meier analysis) – whole cohort** • CCM group=46% • Control=49%, p=0.11 When stratified by baseline ejection fraction (<25% compared with 25 to 40%), there was a statistically significantly lower rate of heart failure hospitalisations in patients with ejection fraction between 25 and 40% in the CCM group compared with the control group (40% versus 64%, p=0.005). **Composite outcome of all-cause mortality or heart failure hospitalisation – whole cohort** • CCM group=58% • Control=78%, p=0.005 When stratified by baseline ejection fraction (<25% compared with 25 to 40%), there was a statistically significantly lower rate in patients with ejection fraction between 25 and 40% in the CCM group compared with the control group (52% versus 88%, p=0.001). **Cardiovascular mortality – whole cohort** • CCM group=34% • Control=51%, p=0.02 When stratified by baseline ejection fraction (<25% compared with 25 to 40%), there was only a statistically significant survival benefit in patients with ejection fraction between 25 and 40%. **Adverse events** 2 patients had a wound infection and the CCM device was removed (1 after 5 months and 1 after 2 months).
Abbreviations used: CCM, cardiac contractility modulation

Study 6 Müller D (2017)

Details

Study type	**Case series (registry)**
Country	Germany (multicentre)
Recruitment period	2010 to 2015
Study population and number	**n=143** **Patients with heart failure and reduced ejection fraction (<45%)**
Age and sex	Mean 62 years; 76% (109/143) male
Patient selection criteria	Patients aged over 18 years with an Optimizer device implanted for clinical heart failure and left ventricular ejection fraction <45%. Only patients who had been taking stable doses of guideline directed medical therapy for at least 30 days were enrolled. There were no exclusion criteria.
Technique	Device: OPTIMIZER system (Impulse Dynamics, US). Devices were programmed to be active for an average of 7 hours a day.
Follow-up	**24 months**
Conflict of interest/source of funding	Support for the study was provided by Impulse Dynamics. One author is an employee of Impulse Dynamics and 2 authors are consultants for the company.

Analysis

Follow-up issues: 74% (106/143) of patients completed the follow-up; 9 patients withdrew their consent or were lost to follow-up, 10 were withdrawn because of serious adverse events, and 18 patients died.

Study design issues: Prospective, observational study. The focus for efficacy data was on New York Heart Association (NYHA), Minnesota living with heart failure questionnaire (MLWHFQ) and left ventricular ejection fraction. Safety parameters included all-cause mortality (primary safety endpoint), cardiac mortality and rate and severity of related serious adverse events. Follow-up testing was done only if there were clinical indications, so a limited number of patients completed exercise testing throughout the study.

Study population issues: Most (72%) patients had NYHA class III heart failure, 20% had class II and 8% had class IV. At the start of the study 10% (14/143) of patients had a cardiac resynchronisation therapy device. This was turned off when the CCM device was implanted.

Other issues: there may be some patient overlap with the case series described in study 7 (Kloppe et al., 2016).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **143**

Impact of CCM on NYHA, MLWHFQ and left ventricular EF over time and by EF class (mean±standard deviation)

Follow-up	EF group	NYHA	MLWHFQ		Left ventricular ejection fraction	
		Mean (n)	value	Change from baseline	% (n)	Change from baseline
Baseline	EF <35%	2.9±0.5 (114)	45.4±19.6 (104)	-	26.1±5.0 (114)	-
	EF ≥35%	2.8±0.4 (28)	44.6±17.3 (25)	-	37.3±3.1 (28)	-
	Total	2.9±0.5 (143)	45.0±19.2 (130)	-	28.3±6.4 (142)	-
6 months	EF <35%	2.3±0.8 (87)*	30.0±19.8 (66)	-16.4±20.8*	28.2±8.3 (68)	2.6±7.2*
	EF ≥35%	1.9±0.8 (21)*	37.3±18.8 (18)	-9.7±17.9	40.5±6.2 (15)	3.2±6.6
	Total	2.2±0.8 (109)*	31.4±19.7 (22)	-15.1±20.3*	30.5±9.2 (83)	2.7±7.1*
12 months	EF <35%	2.2±0.8 (79)*	32.2±21.9 (61)	-12.3±22.8*	28.9±8.8 (62)	3.3±7.8*
	EF ≥35%	2.4±0.8 (19)*	35.3±14.5 (15)	-8.9±9.9	39.1±4.3 (17)	2.4±4.7
	Total	2.2±0.8 (99)*	32.8±20.6 (76)	-11.6±20.9*	31.7±13.1 (79)	3.1±7.3*
18 months	EF <35%	2.2±0.7 (70)*	32.5±24.3 (59)	-13.0±25.6*	31.1±10.3 (55)	5.3±9.8*
	EF ≥35%	2.1±0.6 (15)*	35.0±16.0 (11)	-4.8±15.9	39.3±4.9 (11)	2.4±5.7
	Total	2.2±0.7 (86)*	32.9±23.1 (70)	-11.7±24.5*	32.0±10.5 (66)	4.8±9.3*
24 months	EF <35%	2.2±0.9 (52)*	30.8±23.6 (44)	-15.0±21.6*	33.0±9.1 (37)	7.5±9.3*
	EF ≥35%	2.3±0.7 (15)*	34.5±18.7 (14)	-9.4±18	40.2±5.6 (13)	3.5±6.0
	Total	2.2±0.8 (68)*	31.2±22.5 (59)	-13.6±20.6*	34.9±8.8 (51)	6.5±8.7*

* $p<0.05$ for comparison with baseline

Improvement in functional and symptomatic parameters was not dependant on whether the heart failure was idiopathic or of ischaemic aetiology.

Survival (Kaplan-Meier analysis)

- 1 year=94.2% (95% CI 88.8 to 97.1)
- 2 years=86.4% (95% CI 79.3 to 91.2)

No statistically significant improvements were seen in the 6-minute walk distance test or peak oxygen consumption during follow-up, but data were only available for 41 and 7 patients respectively.

Most patients (>80%) maintained the same medical therapy regimen throughout the study.

Safety

All-cause mortality at 24 month follow-up=7.4% (18/143)

7 deaths were classified as cardiovascular. None of the deaths were classified by investigators as being related to the device or the procedure.

Serious adverse events

Category	All patients (n=143)		EF≥35% (n=29)		EF <35% (n=113)	
	Events	Patients (%)	Events	Patients (%)	Events	Patients (%)
Arrhythmia	20	14 (10)	3	3 (10)	17	13 (12)
General cardiopulmonary	30	23 (16)	3	23 (10)	27	20 (17)
Worsening heart failure	55	37 (26)	11	6 (21)	44	33 (29)
Infection	16	14 (10)	3	3 (10)	13	11 (10)
Bleeding	5	4 (3)	1	1 (3)	4	3 (3)
ICD related	5	5 (3)	1	1 (3)	4	4 (4)
Optimizer IPG malfunction	5	5 (3)	2	2 (7)	3	3 (3)
Lead migration or revision	12	10 (7)	4	3 (10)	8	7 (6)
General medical	41	28 (20)	6	5 (17)	35	23 (20)
Death – unknown cause	4	4 (3)	-	-	4	4 (4)
Serious adverse event probably or possibly related to device	32	25 (17)	6	5 (17)	26	20 (18)
Total	193	91 (64)	34	17 (59)	159	74 (65)

Abbreviations used: CCM, cardiac contractility modulation; CI, confidence interval; EF, ejection fraction; ICD, implantable cardioverter defibrillator; IPG, implantable pulse generator; MLWHFQ, Minnesota living with heart failure questionnaire; NYHA, New York Heart Association

Study 7 Kloppe A (2016)

Details

Study type	**Case series**
Country	Germany (2 centres)
Recruitment period	2002 to 2013
Study population and number	**n=68** **Patients with symptomatic heart failure (New York Heart Association [NYHA] II or III) and normal QRS duration**
Age and sex	Mean 61 years; 88% male
Patient selection criteria	Patients with NYHA II or III symptoms on a guideline-appropriate stable medical treatment for heart failure and with a QRS width ≤130 milliseconds. Patients were offered cardiac contractility modulation (CCM) if they had no recent myocardial infarction (within 3 months), clinically significant angina, or hospitalisation for heart failure needing intravenous treatments within 30 days.
Technique	Device: OPTIMIZER system (Impulse Dynamics, US). The device was programmed to deliver impulses for 7 hours per day, intermittently, by 1 hour of CCM activity about every 3 hours.
Follow-up	**Mean 4.5 years (range 0.25 to 10.3 years)**
Conflict of interest/source of funding	Three authors received honoraria from Impulse Dynamics for giving a talk at a conference.

Analysis

Follow-up issues: patients were routinely followed up every 6 months.

Study design issues: Retrospective observational study. The Seattle Heart Failure Model (SHFM) was used to calculate the projected survival rates. The SHFM was calculated from baseline characteristics of each patient before implant and mean SHFM scores provided the predicted probability of survival at 1, 2 and 5 years. The predicted survival was compared with actual survival (Kaplan-Meier analysis). Medication compliance was not assessed throughout the follow-up.

Study population issues: Baseline characteristics were similar to those in the FIX-CHF-4 study (Borggrefe MM et al., 2008; study 4). Most patients (85%) had NYHA class III heart failure, the mean ejection fraction at baseline was 26.3% and peak oxygen consumption ≥10 ml/min/kg. 68% of patients had ischaemic heart disease and 78% had an implantable cardioverter defibrillator.

Other issues: there may be some patient overlap with the registry data described in study 6 (Müller et al., 2017).

Key efficacy and safety findings

Number of patients analysed: **68**

There were 16 deaths (23.5%) during the follow-up period (6 cardiovascular related).

In 2 patients the CCM therapy was stopped (1 after 6 months because the patient needed a left ventricular assist device and the other after 9 months because of a lack of improvement). Data for these patients were censored at these timepoints.

Predicted mortality (Seattle Heart Failure Model)

- 1 year=6.1%
- 2 years=11.8%
- 5 years=27.7%

Observed mortality (Kaplan-Meier analysis)

- 1 year=0%
- 2 years=3.5%
- 5 years=14.2%

Observed mortality was statistically significantly lower than predicted mortality (p=0.007)

Abbreviations used: CCM, cardiac contractility modulation

Study 8 Anker SD (2019)

Details

Study type	**Case series (registry - CCM-REG)**
Country	Germany (31 sites)
Recruitment period	2013 to 2017
Study population and number	**n=140** **Patients with New York Heart Association (NYHA) class III or IV symptoms, QRS <130 milliseconds and left ventricular ejection fraction between 25% and 45%**
Age and sex	Mean 66 years; 79% male
Patient selection criteria	Patients with symptomatic heart failure NYHA class III or IV, QRS duration <130 milliseconds and left ventricular ejection fraction between 25% and 45%. Patients were only enrolled if data needed to calculate the Seattle Heart Failure Model (SHFM) and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) scores within 3 months of OPTIMIZER implantation were available.
Technique	Device: OPTIMIZER system (Impulse Dynamics, US). The device was programmed to be active for 5 to 7 hours per day.
Follow-up	**3 years**
Conflict of interest/source of funding	7 of the authors received support from Impulse Dynamics for the registry study as part of a clinical trials agreement between their institution and Impulse Dynamics. One author is a paid adviser for Impulse Dynamics and a member of a scientific steering committee. Two authors are paid consultants to Impulse Dynamics. Impulse Dynamics provides support to the Medical College of Wisconsin for the consulting services 1 author.

Analysis

Follow-up issues: Patients were routinely followed up every 6 months.

Study design issues: Prospective, multicentre observational registry study. All patients implanted with an Optimizer device at participating centres were offered participation and 72% of patients provided informed consent. Data collection included assessment of NYHA classification and Minnesota living with heart failure questionnaire (MLWHFQ) score. Left ventricular ejection fraction was obtained only if ordered as part of routine clinical care. The primary endpoint was a comparison of observed survival (based on Kaplan-Meier analysis) to that predicted by the Seattle Heart Failure Model (SHFM) through 3 years of follow up.

Study population issues: 41% (57/140) of patients had an ejection fraction between 35% and 45%, and 59% (83/140) had an ejection fraction between 25% and 34%. At the time of enrolment, 97 patients had an implantable cardioverter defibrillator and 5 had a cardiac resynchronisation therapy device. The heart failure was of ischaemic aetiology in 69% of patients.

Other issues: there may be some patient overlap with Müller D et al. (2017)

Key efficacy and safety findings

Efficacy

Number of patients analysed: 140

Comparison of survival observed after cardiac contractility modulation device implantation to that predicted by the Seattle Heart Failure Model

	Number at risk	Observed	Predicted	p
Ejection fraction between 25% and 45% (n=140)				
1 year	104	91.6% (85.3% to 95.3%)	91.3%	0.1644
2 years	71	86.2% (78.2% to 91.4%)	83.7%	
3 years	29	82.8% (73.4% to 89.1%)	76.7%	
Ejection fraction between 35% and 45% (n=57)				
1 year	43	94.5% (83.9% to 98.2%)	90.4%	0.0463
2 years	30	91.7% (79.0% to 96.9%)	82.2%	
3 years	12	88.0% (72.5% to 95.1%)	74.7%	
Ejection fraction between 25% and 34% (n=83)				
1 year	61	89.6% (80.2% to 94.6%)	91.8%	0.8072
2 years	41	82.5% (70.9% to 89.8%)	84.6%	
3 years	17	79.4% (66.3% to 87.9%)	78.0%	

Rate of hospitalisations for heart failure and other cardiovascular causes in the 2 years after CCM activation compared with 1 year before

Category	1 year before enrolment		2 years after CCM activation		P
	Events	Event rate	Events	Event rate	
Ejection fraction between 25% and 45%					
All	195	1.39	162	0.58	<0.0001
HF	134	0.96	73	0.26	<0.0001
CV not HF	34	0.24	24	0.09	<0.0001
Ejection fraction between 35% and 45%					
All	83	1.46	51	0.45	<0.0001
HF	47	0.82	18	0.16	<0.0001
CV not HF	23	0.4	9	0.08	<0.0001
Ejection fraction between 25% and 34%					
All	112	1.35	111	0.67	<0.0001
HF	87	1.05	55	0.33	<0.0001
CV not HF	11	0.13	15	0.09	0.3309

Improvement in MLWHFQ score (points decrease)

Ejection fraction between 25% and 45%

- 6 months=11.7
- 12 months=11.8
- 18 months=11.4

Safety

Death

There were 18 deaths (12.9%) in the whole cohort (11 cardiac, 5 non-cardiac and 2 unknown); 13 deaths were in the group of patients with ejection fraction between 25% and 34% (8 cardiac related, 3 non-cardiac and 2 unknown).

Serious adverse events – whole cohort

Category	Number of events	Number of patients	%
Lead fracture or failure	1	1	0.7
Device related - other	9	9	6.4
Bleeding (clinically significant)	2	2	1.4
Infection (other than device pocket)	13	10	7.1
ICD related	2	2	1.4
Arrhythmia	10	9	6.4
Worsening HF	61	32	22.9
Cardiac – other	12	9	6.4
General cardiopulmonary	35	24	17.1
Sepsis	1	1	0.7
Transient ischaemic attack or stroke	3	2	1.4
Thromboembolism (non-neurological)	1	1	0.7
General medical	51	35	25.0
Total	201	82	58.6

• 24 months=17.1 p<0.001 at each timepoint *Ejection fraction between 25% and 34%* • 6 months=10.4 • 12 months=7.3 • 18 months=7.9 • 24 months=12.5 p≤0.005 at each timepoint *Ejection fraction between 35% and 45%* • 6 months=13.6 • 12 months=18.4 • 18 months=16.3 • 24 months=25.3 p≤0.001 at each timepoint **Reductions in NYHA class** *Ejection fraction between 25% and 45%* • 6 months=0.6 • 12 months=0.7 • 18 months=0.7 • 24 months=0.8 p<0.001 at each timepoint Similar sustained improvements were seen in the 2 subgroups. **Increases in LVEF at 6 months** • Whole cohort=LVEF increased from 32.8±4.9 at baseline to 35.8±8.2 (n=51, p=0.003)	
Abbreviations used: CCM, cardiac contractility modulation; CV, cardiovascular; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MLWHFQ, Minnesota living with heart failure questionnaire; NYHA, New York Heart Association	

Validity and generalisability of the studies

- There were no data from the UK.
- Most studies only included patients with an ejection fraction below 35% but some studies had a higher limit of 45%.
- There are some outcomes from follow-up at 24 months and beyond.
- Most studies only included patients with NHYA class III or IV heart failure, but some studies included a proportion of patients with NYHA class II heart failure.[4,6,7]
- The largest randomised controlled trial did not blind patients to their treatment allocation, creating the risk of an unbalanced placebo effect in the CCM treatment arm.[2] The primary efficacy endpoint in this study was ventilatory anaerobic threshold, which is more objective than other efficacy outcome measures. This was a requirement of the US Food and Drug Administration.
- The randomised, double-blind crossover study noted improvements in efficacy outcomes in both treatment and control groups in the first 3 months, suggesting a placebo effect.[4]
- The evidence included some patients whose symptoms had not responded to cardiac resynchronisation therapy.
- The proportion of patients with an implantable cardioverter defibrillator at baseline varied between studies.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Subcutaneous implantable cardioverter defibrillator insertion for preventing sudden cardiac death. NICE interventional procedures guidance 603 (2017). Available from http://www.nice.org.uk/guidance/IPG603
- Artificial heart implantation as a bridge to transplantation for end-stage refractory biventricular heart. NICE interventional procedures guidance 602 (2017). Available from http://www.nice.org.uk/guidance/IPG602
- Implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation. NICE interventional procedures guidance 516 (2015). Available from http://www.nice.org.uk/guidance/IPG516
- Insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure. NICE interventional procedures guidance 463 (2013). Available from http://www.nice.org.uk/guidance/IPG463
- Short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery. NICE interventional procedures guidance 177 (2006). Available from http://www.nice.org.uk/guidance/IPG177

Medical technologies

- ENDURALIFE powered CRT-D devices for treating heart failure. Medical technologies guidance 33 (2017). Available from https://www.nice.org.uk/guidance/mtg33

Technology appraisals

- Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. NICE technology appraisal 388 (2016). Available from http://www.nice.org.uk/guidance/TA388
- Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure. NICE technology appraisal 314 (2014). Available from http://www.nice.org.uk/guidance/TA314

- Ivabradine for treating chronic heart failure. NICE technology appraisal 267 (2012). Available from http://www.nice.org.uk/guidance/TA267

NICE guidelines

- Chronic heart failure in adults: diagnosis and management. NICE guideline 106 (2018). Available from http://www.nice.org.uk/guidance/NG106

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by specialist advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Specialist Adviser Questionnaires for cardiac contractility modulation device implantation for heart failure were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 1 company who manufactures a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trials:

- Evaluation of the Safety and Efficacy of the 2-lead OPTIMIZER® Smart System (FIX-HF-5C2) (NCT03339310); single group assignment; US and Germany; estimated enrolment 60; estimated study completion date October 2019.
- Continued Access Protocol for the Evaluation of the OPTIMIZER Smart System (FIX-HF-5CA) (NCT03102437); single group assignment; US; estimated enrolment 250; estimated study completion date August 2018.
- CCM in Heart Failure With Preserved Ejection Fraction (NCT03240237); single group assignment; Germany and Sweden; estimated enrolment 50; estimated study completion date March 2019.

References

1. Liu X, Yang HJ, Ping HQ, et al. (2017) The safety and efficacy of cardiac contractility modulation in heart failure: A meta-analysis of clinical trials. Herz 42: 766–75
2. Kadish A, Nademanee K, Volosin K, et al. (2011) A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. American Heart Journal 161: 329–37
3. Abraham WT, Kuck KH, Goldsmith RL, et al. (2018) A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation. JACC Heart Failure 6: 874–83
4. Borggrefe MM, Lawo T, Butter C, et al. (2008) Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure. European Heart Journal 29: 1019–28
5. Liu M, Fang F, Luo XX, et al. (2016) Improvement of long-term survival by cardiac contractility modulation in heart failure patients: A case-control study. International Journal of Cardiology 206: 122–26
6. Muller D, Remppis A, Schauerte P, et al. (2017) Clinical effects of long-term cardiac contractility modulation (CCM) in subjects with heart failure caused by left ventricular systolic dysfunction. Clinical Research in Cardiology 106: 893–904
7. Kloppe A, Lawo T, Mijic D, et al. (2016) Long-term survival with Cardiac Contractility Modulation in patients with NYHA II or III symptoms and normal QRS duration. International Journal of Cardiology 209: 291–5
8. Anker SD, Borggrefe M, Neuser H et al. (2019) Cardiac contractility modulation improves long-term survival and hospitalizations in heart failure with reduced ejection fraction. European Journal of Heart Failure doi:10.1002/ejhf.1374

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	03/10/18	2018, Issue 10
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	03/10/18	2018, Issue 10
HTA database (CRD website)	03/10/18	-
MEDLINE (Ovid)	02/10/18	1946 to October 01, 2018
MEDLINE In-Process (Ovid) & MEDLINE ePubs ahead of print (Ovid)	02/10/18	October 01, 2018
EMBASE (Ovid)	02/10/2018	1974 to 2018 Week 40
BLIC		n/a

Trial sources searched 11/07/2018

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched 11/07/2018

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	exp heart failure/
2	cardiomyopathy, dilated/
3	shock, cardiogenic/
4	((dilated or congestiv* or shock*) adj4 cardio*).tw.
5	exp ventricular dysfunction/
6	cardiac output, low/
7	((heart or cardi* or myocard*) adj4 (fail* or decompensat* or dysfunct* or insufficien*)).tw.

8	((ventricul* or ventricle*) adj4 (fail* or decompensat* or insufficien* or dysfunction*)).tw.
9	(("left ventricular" or "left ventricle") adj4 (fail* or decompensat* or insufficien* or dysfunction*)).tw.
10	LVSD.tw.
11	or/1-10
12	(cardiac* adj4 contract* adj4 modulat*).tw.
13	(optimizer iv* or optimizer 4).tw.
14	(optimizer II or optimizer 2 or optimizer III or optimizer 3).tw.
15	(optimizer* adj4 (system* or smart)).tw.
16	CCM.tw.
17	Implant* pulse generat*.tw.
18	impulse dynamics.tw.
19	Electric Stimulation Therapy/mt [Methods]
20	Elect* stimulat* therap*.tw.
21	or/12-20
22	11 and 21
23	animals/ not humans/
24	22 not 23

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Case reports were excluded unless they described a unique safety event.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Abi-Samra F and Gutterman D (2016) Cardiac contractility modulation: a novel approach for the treatment of heart failure Heart Failure Reviews 21: 645-660	Review	The technology is used commercially in Europe with nearly 3000 patients implanted worldwide. Indications include patients with reduced EF and normal or slightly prolonged QRS duration, thus filling an important therapeutic gap among the 2/3 of patients with heart failure who do not meet criteria for CRT.	A more recent review is included (Liu X et al., 2017; study 1).
Abraham WT, Nademanee K, Volosin K et al. (2011) Subgroup analysis of a randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure Journal of Cardiac Failure 17: 710–17	RCT n=206 (109 versus 97) FU=50 weeks	The results of this retrospective hypothesis-generating analysis indicate that CCM significantly improves objective parameters of exercise tolerance in a subgroup of patients characterised by normal QRS duration, NYHA functional class III symptoms, and EF >25%.	Subgroup analysis of RCT included in table 2.
Augello G, Santinelli V, Vicedomini G, et al. (2004) Cardiac contractility modulation by non-excitatory electrical currents. The new frontier for electrical therapy of heart failure Italian Heart Journal: Official Journal of the Italian Federation of Cardiology 5 Suppl 6: 68S-75S	Case series n=13	If further studies provide evidence of long-term safety and reliability, CCM could become useful to symptomatic drug refractory HF patients or to patients not tolerating symptomatic and functional effects of standard medical therapy.	More recent studies with more patients or longer follow-up are included.
Borggrefe M and Burkhoff D (2012) Clinical effects of cardiac contractility modulation (CCM) as a treatment for chronic heart failure European Journal of Heart Failure 14: 703-12	Review	Clinical studies have primarily focused on patients with normal QRS durations in view of the fact that cardiac resynchronisation (CRT) is a viable option for patients with prolonged QRS duration. These studies show that CCM improves exercise tolerance as indexed by peak oxygen consumption and quality of life indexed by the Minnesota Living with Heart Failure Questionnaire.	A more recent systematic review is included (Liu X et al., 2017; study 1).
Burkhoff D (2011) Does contractility modulation have a role in the treatment of heart	review	Results of 2 randomised controlled trials show the	A more recent systematic review is

failure? Current Heart Failure Reports 8: 260-5		procedure improves exercise tolerance and quality of life.	included (Liu X et al., 2017; study 1).
Burri H and Bordachar P (2013) Cardiac contractility modulation for treatment of heart failure Kardiovaskulare Medizin 16: 259-262	Review	Further data from largescale randomised studies with long-term follow-up are required before this therapy may one day be recognised as valid treatment in international guidelines.	A more recent systematic review is included (Liu X et al., 2017; study 1).
Butter C, Wellnhofer E, Schlegl M, et al. (2007) Enhanced inotropic state of the failing left ventricle by cardiac contractility modulation electrical signals is not associated with increased myocardial oxygen consumption Journal of Cardiac Failure 13: 137-42	Case series n=9	The study results suggest that unlike cAMP-dependent positive inotropic drugs, the increase in left ventricular function during CCM therapy is elicited without increasing myocardial oxygen consumption.	More recent studies with more patients or longer follow-up are included.
Choudhury AK, Paul GK and Rahman MZ (2012) Cardiac contractility modulation device-new hope for refractory heart failure patients Mymensingh Medical Journal: MMJ 21: 580-2	Review	Application of CCM signals to the failing heart is associated with improved gene expression which ultimately causes LV global, cellular and biochemical remodelling as a result improved LV systolic function.	A more recent systematic review is included (Liu X et al., 2017; study 1).
Giallauria F, Vigorito C, Piepoli MF, et al. (2014) Effects of cardiac contractility modulation by non-excitatory electrical stimulation on exercise capacity and quality of life: an individual patient's data meta-analysis of randomized controlled trials International Journal of Cardiology 175: 352–57	Systematic review and meta-analysis n=641 (3 studies)	Pooled analysis showed that, compared to control, CCM significantly improved peak oxygen consumption (mean difference +0.71, 95% CI 0.20 to 1.21 mL/kg/min, p=0.006), 6-minute walk test distance (mean difference +13.92, 95% CI -0.08 to 27.91 m, p=0.05) and quality of life measured by Minnesota Living With Heart Failure Questionnaire (mean difference -7.17, 95% CI -10.38 to -3.96, p<0.0001).	A more recent review is included (Liu X et al., 2017; study 1).
Goliasch G, Khorsand A, Schutz M, et al. (2012) The effect of device-based cardiac contractility modulation therapy on myocardial efficiency and oxidative metabolism in patients with heart failure European Journal of Nuclear Medicine & Molecular Imaging 39: 408-15	Case series n=21	The results indicate that CCM does not induce increased myocardial oxygen consumption, even under stress conditions.	Studies with more patients or longer follow-up are included.
Kahwash R, Burkhoff D and Abraham WT (2013) Cardiac contractility modulation in patients with advanced heart failure Expert Review of Cardiovascular Therapy 11: 635-45	Review	Clinical trials show that CCM improves exercise tolerance, as measured by peak oxygen consumption and quality of life, assessed by the Minnesota Living with Heart Failure Questionnaire. The device is currently available for the treatment of heart failure in Europe.	A more recent review is included (Liu X et al., 2017; study 1).

Kloppe A, Mijic D, Schiedat F, et al. (2016) A randomized comparison of 5 versus 12 hours per day of cardiac contractility modulation treatment for heart failure patients: a preliminary report Cardiology journal 23: 114-119	RCT n=19 FU=24 weeks	Together with previously reported experience with CCM, delivery of CCM therapy is equally safe and appears similarly effective over the range of shorter (5 h) to longer (12 h) daily periods of application. Given the small sample size, further studies are warranted.	Small study comparing periods of application.
Kuschyk J, Nägele H, Heinz-Kuck K et al. (2018) Cardiac contractility modulation treatment in patients with symptomatic heart failure despite optimal medical therapy and cardiac resynchronisation therapy (CRT). International Journal of Cardiology https://doi.org/10.1016/j.ijcard.2018.10.086	Case series n=17 FU=6 months	Patients with heart failure and reduced ejection fraction who remain moderately to severely symptomatic despite use of cardiac resynchronisation therapy, may benefit from CCM therapy with improvement in quality of life and exercise tolerance. A larger prospective study in this population is warrented.	Studies with more patients or longer follow-up are included.
Kuschyk J, Roeger S, Schneider R, et al. (2015) Efficacy and survival in patients with cardiac contractility modulation: long-term single center experience in 81 patients International Journal of Cardiology 183: 76-81	Case series n=81 FU=mean 24 months	CCM therapy improved quality of life, exercise capacity, NYHA class, EF and NT-proBNP levels during long-term follow up. Mortality rates appeared to be lower than estimated from the MAGGIC score.	Studies with more patients or longer follow-up are included.
Kwong JSW, Sanderson JE, Yu C-M (2012) Cardiac contractility modulation for heart failure: a meta-analysis of randomized controlled trials. PACE 35: 1111–18	Systematic review and meta-analysis 3 studies (n=641)	There were no statistically significant differences in all-cause mortality or all-cause hospitalisation. There was no increase in adverse effects with cardiac contractility modulation. Large, well-designed trials are needed to confirm its role.	A more recent review is included.
Lyon AR, Samara MA and Feldman DS (2013) Cardiac contractility modulation therapy in advanced systolic heart failure Nature Reviews Cardiology 10: 584-98	Review	Long-term application of CCM seems to improve patients' exercise tolerance and quality of life. These benefits are apparently accomplished with an acceptable safety profile; however, to date, no data have demonstrated reductions in hospitalisations for heart failure or mortality. CCM is currently available in Europe and ongoing studies are attempting to identify the ideal target population and accumulate additional outcome data.	A more recent review is included.
Nagele H, Behrens S and Eisermann C (2008) Cardiac contractility modulation in non-responders to cardiac resynchronization therapy Europace 10: 1375-1380	Case series n=16 FU=mean 147 days	The CCM method is feasible and could be applied with calculated risks as a possible useful adjunct in CRT-Non Responders when no other options are available; however, mortality and event rates are high in this very sick population.	Studies with more patients or longer follow-up are included.

Neelagaru SB, Sanchez JE, Lau SK, et al. (2006) Nonexcitatory, cardiac contractility modulation electrical impulses: Feasibility study for advanced heart failure in patients with normal QRS duration Heart Rhythm 3: 1140-1147	RCT n=49 FU=6 months	Despite a sicker population in the treatment group, no specific safety concerns emerged with chronic cardiac contractility modulation signal administration. Further study is required to definitively define the safety and efficacy of cardiac contractility modulation signals.	Larger or more recent studies are included. This study is included in the review by Liu X et al., 2017 (study 1).
Pappone C, Augello G, Rosanio S, et al. (2004) First human chronic experience with cardiac contractility modulation by nonexcitatory electrical currents for treating systolic heart failure: mid-term safety and efficacy results from a multicenter study Journal of Cardiovascular Electrophysiology 15: 418–27	Case series n=13 FU=9 months	CCM therapy appears to be safe and feasible. Proarrhythmic effects of this novel therapy seem unlikely. Preliminary data indicate that CCM gradually and significantly improves systolic performance, symptoms, and functional status. CCM therapy for 7 hours per day is associated with greater dispersion near the mean, emphasising the need to individually tailor CCM delivery duration.	Studies with more patients or longer follow-up are included.
Pappone C, Rosanio S, Burkhoff D, et al. (2002) Cardiac contractility modulation by electric currents applied during the refractory period in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy American Journal of Cardiology 90: 1307–13	Case series n=18	CCM stimulation in patients with heart failure enhanced regional and global measures of left ventricular systolic function, regardless of the varied delivery chamber or whether modulation was performed during right ventricular pacing or biventricular pacing.	Studies with more patients or longer follow-up are included.
Pappone C, Vicedomini G, Salvati A, et al. (2001) Electrical modulation of cardiac contractility: clinical aspects in congestive heart failure Heart Failure Reviews 6: 55-60	Case series n=15	The study suggests that unlike modified pacing techniques, delivery of the signal to the left ventricle during the refractory period resulted in a rapid increase in myocardial contractility and improved hemodynamic performance. The near instantaneous contractility improvement achieved by this type of stimulus was shown to be safe and effective independently of the primary cause of heart failure or the function of the conduction system.	Studies with more patients or longer follow-up are included.
Radlberger Mag P, Adlbrecht C and Mittermayr T (2011) Cardiac contractility modulation in patients with heart failure refractory to drug treatment Experimental and Clinical Cardiology 16: 43-46	Systematic review n=251 (4 studies)	The overall strength of evidence for effectiveness and safety of CCM in patients suffering heart failure refractory to drug treatment is low. Public reimbursement is currently not recommended. Existing evidence is not sufficient to assess the net benefit of the intervention in evaluation.	A more recent systematic review is included (Liu X et al., 2017; study 1).
Roger S, Michels J, Heggemann F et al. (2014) Long term impact of	Case series n=70	CCM prevents chronic ventricular depolarisation delay that occurs	Studies with more patients

cardiac contractility modulation on QRS duration. Journal of Electrocardiology 47: 936–40	FU=mean 2.8 years	in heart failure and that is associated with poorer outcomes. This supports the safety of long-term CCM therapy and suggests a possible long-term benefit in maintaining QRS duration.	or longer follow-up are included.
Roger S, Rudic B, Akin I, et al. (2018) Long-term results of combined cardiac contractility modulation and subcutaneous defibrillator therapy in patients with heart failure and reduced ejection fraction Clinical Cardiology 41: 518-524	Case series n=20 FU=mean 34 months	CCM and subcutaneous implantable cardioverter-defibrillator (S-ICD) can be successfully combined in patients with heart failure with reduced ejection fraction. S-ICD and CCM remain efficacious when used together, with no interference affecting their function.	Small case series focusing on the combination of CCM and ICD.
Roger S, Said S, Kloppe A, et al. (2017) Cardiac contractility modulation in heart failure patients: Randomized comparison of signal delivery through one vs. two ventricular leads Journal of Cardiology 69: 326-332	RCT n=48 FU=6 months	The efficacy and safety of CCM in this study were similar when the signal was delivered through either 1 or 2 ventricular leads. These results support the potential use of a single ventricular lead for delivery of CCM.	Small RCT comparing 1 and 2 ventricular leads.
Roger S, Schneider R, Rudic B, et al. (2014) Cardiac contractility modulation: First experience in heart failure patients with reduced ejection fraction and permanent atrial fibrillation Europace 16: 1205-1209	Case series n=5 FU=40 months	CCM signal delivery is feasible in heart failure patients with permanent atrial fibrillation by sequential atrial-ventricular pacing, so that the atrial pacing spike is interpreted as a p wave by the CCM signal delivery algorithm.	Small case series of patients with permanent atrial fibrillation.
Sabbah HN, Gupta RC, Rastogi S, et al. (2006) Treating heart failure with cardiac contractility modulation electrical signals Current Heart Failure Reports 3: 21-4	Review	Treatment of patients with heart failure using CCM electrical signals is at present an investigational form of therapy.	A more recent systematic review is included (Liu X et al., 2017; study 1).
Schau T, Seifert M, Meyhfer J, et al. (2011) Long-term outcome of cardiac contractility modulation in patients with severe congestive heart failure Europace 13 (10): 1436-1444.	Case series n=54 FU=21 months	Cardiac contractility modulation appears to be a safe therapeutic option for advanced heart failure patients who have no other therapeutic options. Symptomatic improvement by CCM has been shown in earlier studies but this observational study suggests, for the first time, that there is no adverse effect of CCM on long-term survival.	Studies with more patients or longer follow-up are included.
Stix G, Borggrefe M, Wolpert C, et al. (2004) Chronic electrical stimulation during the absolute refractory period of the myocardium improves severe heart failure European Heart Journal 25: 650-5	Case series n=25 FU=8 weeks	These preliminary data indicate that CCM by delivery of intermittent nonexcitatory electrical stimuli is a promising technique for improving ventricular systolic function and symptoms in patients with drug-refractory NYHA class III heart failure.	Studies with more patients or longer follow-up are included.

Tschöpe C, Kherad B, Klein O et al. (2018) Cardiac Contractility Modulation: Mechanisms of action in heart failure with reduced ejection fraction and beyond. European Journal of Heart Failure (accepted for publication)	Review	Clinical studies show trends for greater improvements in exercise tolerance, quality of life and functional status in patients with ejection fraction (EF) 35-45% versus those with lower EFs, a finding that was reproduced in separate studies. Whether the mechanisms also apply to patients with preserved EF needs to be investigated. Therefore, a prospective, multi-centre, single arm open label 24-week exploratory study evaluating CCM therapy in patients who are symptomatic despite optimal medical therapy is planned: Cardiac Contractility Modulation (CCM™) Therapy in Subjects with Heart Failure with preserved Ejection Fraction, in brief CCM-HFpEF (EUDAMED; number CIV1612017844).	Review focuses on mechanism of action.
Winter J, Brack KE and Ng GA (2011) Cardiac contractility modulation in the treatment of heart failure: initial results and unanswered questions European Journal of Heart Failure 13: 700-10	Review	The results of the ongoing clinical trials in patients with advanced heart failure (HF) are promising and have demonstrated beneficial effects on cardiac structural and molecular remodelling as well as measured patient clinical outcomes. However, much larger population numbers are needed to confirm the role of CCM therapy in the treatment of systolic HF.	A more recent systematic review is included (Liu X et al., 2017; study 1).
Yu CM, Chan JY, Zhang Q, et al. (2009) Impact of cardiac contractility modulation on left ventricular global and regional function and remodeling Jacc: Cardiovascular Imaging 2: 1341-9	Case series n=30 FU=3 months	CCM improves both global and regional left ventricular (LV) contractility, including regions remote from the impulse delivery, and may contribute to LV reverse remodelling and gain in systolic function. Such improvement is unrelated to diastolic function or mechanical dyssynchrony.	Studies with more patients or longer follow-up are included.
Zhang Q, Chan YS, Liang YJ, et al. (2013) Comparison of left ventricular reverse remodeling induced by cardiac contractility modulation and cardiac resynchronization therapy in heart failure patients with different QRS durations International Journal of Cardiology 167: 889-93	Case series n=132 FU=3 months	CCM exhibited a similar left ventricular reverse remodelling response to CRT for patients with a mildly prolonged QRS, though the effect was less strong when compared to CRT for patients with a very wide QRS.	Studies with longer follow-up are included.