ORIGINAL RESEARCH ARTICLE

A comprehensive individual patient data meta-analysis of the effects of cardiac contractility modulation on functional capacity and heart failure-related quality of life

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Abstract

Aims   Cardiac contractility modulation, also referred to as CCM™, has emerged as a promising device treatment for heart failure (HF) in patients not indicated for cardiac resynchronization therapy. We performed a comprehensive individual patient data meta-analysis of all non-confounded prospective randomized controlled trials of CCM vs. control that have measured functional capacity and/or quality of life questionnaires in patients with HF.

Methods and results   The Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE were searched in January 2020 to identify eligible randomized controlled trials. We also asked the sole manufacturer of the device for their list of known trials. Primary outcomes of interest were peak oxygen consumption (peak VO_2), 6 min walk test distance, and quality of life measured by Minnesota Living with Heart Failure Questionnaire (MLWHFQ), and all data were received as individual patient and individual time point data-points. Mean differences and 95% confidence intervals (CIs) were calculated for continuous data using a fixed-effects model. Five trials were identified, four randomized studies enrolling 801 participants for all endpoints of interest, and for peak VO_2 alone ($n = 60$), there was an additional single arm non-randomized trial (FIX-HF-5C2) with a prospective comparison of its 24 week peak VO_2 data compared with the control group of the FIX-HF-5C control patients. Pooled analysis showed that, compared with control, CCM significantly improved peak VO_2 (mean difference +0.93, 95% CI 0.56 to 1.30 mL/kg/min, $P < 0.00001$), 6 min walk test distance (mean difference +17.97, 95% CI 5.48 to 30.46 m, $P = 0.005$), and quality of life measured by MLWHFQ (mean difference −7.85, 95% CI −10.76 to −4.94, $P < 0.00001$). As a sensitivity analysis, we excluded the FIX-HF-5C2 trial (only relevant for peak VO_2), and the result was similar, mean difference +0.65, 95% CI 0.21 to 1.08 mL/kg/min, $P = 0.004$.

Conclusions   This comprehensive meta-analysis of individual patient data from all known randomized trials has shown that CCM provides statistically significant and clinically meaningful benefits in measures of functional capacity and HF-related quality of life.

Keywords   Cardiac contractility modulation; OPTIMIZER™ device; Peak oxygen consumption; 6 min walk test; Minnesota Living with Heart Failure Questionnaire; Individual patient data meta-analysis

Introduction

In the management of heart failure (HF), therapeutic strategies commonly aim for improved outcomes in terms of reduced mortality and fewer unplanned hospitalizations for HF. Clinical trials powered to show improvements in such outcomes need to include a large number of patients and span many years. Drug and device treatments are thus usually studied in smaller trials first, providing proof of concept based on intermediate endpoints. These endpoints, sometimes call surrogate endpoints, include estimations of functional capacity, haemodynamic measurements, biomarkers, or patient-reported outcomes (PROs). Of these, PROs (if derived from validated HF-related quality of life instruments) and objective patient relevant measures of functional limitation [such as peak oxygen consumption (peak VO_2) or 6 min corridor walk test distance] are considered potentially approvable, whereas haemodynamic and biomarker endpoints are not. Despite this, few of the established HF therapies have been shown to improve either PROs or functional capacity.[1–3]

Over the last two decades, device-based therapies such as left ventricular assist devices and cardiac resynchronization (CRT) have become established therapies for selected HF patients. Left ventricular assist device therapy remains restricted to a very small minority of severely affected advanced HF patients. CRT has been shown to improve clinical status, left ventricular function, quality of life, and functional capacity[4–7] as well as hospitalization rates and survival,[8–11] yet it remains recommended in only a minority of HF patients. Current guidelines only recommend CRT if QRS duration shows a left bundle branch block pattern with a duration greater than 150 ms, although it may be considered down to a QRS duration of 130 ms,[12] whereas it is harmful with QRS durations below 130 ms.[13] Thus, it is estimated that CRT is indicated for only 15–20% of HF with reduced ejection fraction (HFrEF) patients. Even then, approximately 30% of patients receiving CRT are considered non-responders.[14,15] Despite significant improvements in therapies (drugs and devices) for HFrEF achieved during the last several decades, the 5 year survival rate has remained substantially unchanged at about 50%.[16,17] Thus, the development of new innovative device-based therapies for patients with persistent symptoms despite optimal medical therapy (OMT) remains an important goal. Cardiac contractility modulation (CCM), if proven to be clinically beneficial, could fulfil a significant unmet medical need.[18] Another alternative, His bundle pacing, may be suitable for selected patients ineligible for CRT, as it provides a more physiological simultaneous electrical activation of the ventricles via the His–Purkinje system with the possibility to improve QRS duration in both left and right bundle branch block patients.[19]

Cardiac contractility modulation is an electrical technique that consists of biphasic pulses of relatively high voltage being delivered to the right ventricular septum during the absolute refractory period of the myocardium.[20,21] CCM therapy is delivered via a small implantable pulse generator inserted like a pacemaker in a minimally invasive procedure.[22] It has been shown to improve calcium handling, to reverse the foetal myocyte gene programme associated with HF, and to facilitate reverse remodelling.[23] CCM has been studied in patients with symptomatic HF on OMT, and with a QRS duration <130 ms and ejection fraction (EF) <45%, and as such has been investigated in patients ineligible for CRT.[24,25] In such patients, CCM has been shown, in three studies of small to medium size, to improve quality of life, left ventricular EF (LVEF), indexes of diastolic function, New York Heart Association (NYHA) classification, 6 min walk test (6MWT) distance, and peak VO_2 during cardiopulmonary stress testing.[26–28] These findings have recently been confirmed in the Bayesian designed randomized FIX-HF-5C study,[29] an approved trial design under the Expedited Access Pathway of the US Food and Drug Administration (FDA).[30] This trial result thus led to the subsequent approval of CCM by the FDA to improve 6 min hall walk distance, quality of life, and functional status of NYHA class III HF patients who remain symptomatic, despite guideline-directed medical therapy, who are in normal sinus rhythm, are not indicated for CRT, and have an LVEF ranging from 25% to 45%.[31] This trial, although not powered as a mortality and morbidity trial, also showed a nominally but borderline significant reduction in the 6 month composite rate of cardiac mortality and HF hospitalizations, with the composite of cardiovascular death and HF hospitalizations being reduced from 10.8% to 2.9% (P = 0.048). Based on the first three trials, HF treatment guidelines had already suggested that CCM could be considered in patients with symptomatic HF despite OMT and with normal or mildly prolonged QRS duration and a reduced LVEF.[12] Because interventions targeted at ameliorating exercise intolerance in HFrEF are becoming increasingly important in advanced HF, we performed an updated individual patient meta-analysis systematically to review the efficacy of CCM with a focus on functional capacity and quality of life instruments in HFrEF patients.

Methods

Search strategy

The Cochrane Database, MEDLINE, and EMBASE were searched in January 2020 to identify eligible human studies using the keyword: 'cardiac contractility modulation'. No language restrictions were applied. Reference lists of retrieved records were screened for further relevant studies. All review articles with a subject of 'cardiac contractility modulation' and their reference lists were also searched. Clinical trials registers (http://www.clinicaltrials.gov, http://www.controlled-trials.com) were searched for ongoing studies. The sole manufacturer of the device, Impulse Dynamics, was also asked

and provided lists of all trials they were aware of that had evaluated CCM. The results of study selection are presented in a flow diagram as depicted by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (*Figure 1*).

Study selection

For inclusion in the present analysis, studies had to meet the following criteria: (i) it was a randomized clinical trial (but see also note below concerning FIX-HF-5C2); (ii) it included adult patients (≥18 years) with documented HF (NYHA functional classification ≥II); (iii) the intervention group had to be allocated to CCM; and (iv) the control group was allocated to either sham treatment or OMT. Concomitant medical therapy was given in both groups (intervention and control). A total of 251 potentially relevant records were screened, and five studies were identified (www.clinicaltrials.gov). After screening, four studies were initially selected for analysis. A fifth trial was later identified by direct enquiry of investigators and the sponsor, so it was included, despite the fact that it was published in full paper form only in April 2020. This trial was a single arm non-randomized trial (FIX-HF-5C2) with a prospective comparison of its 24 week peak VO_2 data compared with the control group of the FIX-HF-5C control patients, and which reported data only on one of our primary outcomes, peak VO_2 (mL/kg/min), and not 6MWT distance (m), or quality of life measured by Minnesota Living with Heart Failure Questionnaire (MLWHFQ).[32] We included the FIX-HF-5C2 trial only for the endpoint of peak VO_2, and also as a sensitivity analysis, we recalculated all results with FIX-HF-5C2 excluded. All patients were on OMT. Two authors selected studies independently (F. G. and A. J. S. C.), and disagreements were resolved by consensus.

Figure 1 Study selection presented in a flow diagram as depicted by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.
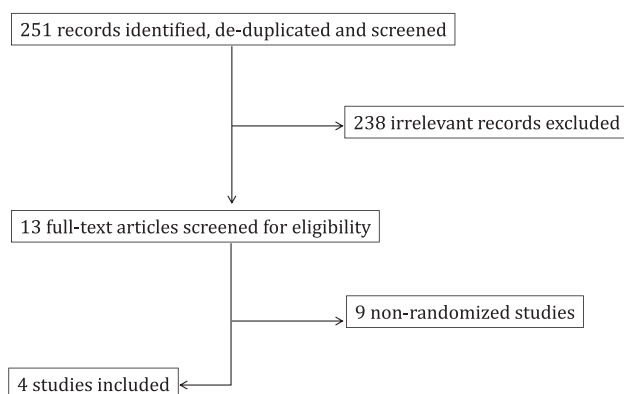
Outcome measures

Primary outcomes were (i) peak VO_2 (mL/kg/min), (ii) 6MWT distance (m), and (iii) quality of life measured by MLWHFQ. Peak VO_2, as evaluated by cardiopulmonary exercise testing, is a measure of peak aerobic capacity and has consistently demonstrated its prognostic value in HF patients. Together with other typically more invasive evaluation techniques, peak VO_2 is used to prognosticate survival and the need for heart transplantation. Six minutes of walk distance is the number of metres covered over 6 min of maximal self-paced walking. A lower score (reflecting less distance covered in 6 min) indicates worse exercise tolerance. The MLWHFQ was used to assess the patients' perception of the impact of HF on physical, socio-economic, and psychological aspects of their life. Patients respond to 21 items using a 6-point Likert scale (0–5); the higher the score, the worse the quality of life. We received all data as individual patient data and individual time point data-points, from the trial leaders or the sole sponsor of CCM.

Study quality assessment

The Cochrane Collaboration's tool for assessing risk of bias was used to assess quality of included trials on the following domains: (i) random sequence generation; (ii) allocation concealment; (iii) blinding; (iv) incomplete outcome data; and (v) selective reporting. Categories of 'low risk', 'high risk', or 'unclear risk' were used as judgements against the criteria stated by the assessment tool (see Supporting Information, Appendix).

Statistical analysis

RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, DK) was used to conduct meta-analyses for outcome measures. Data used were continuous and were reported as mean and standard deviation (SD). Results were presented as weighted mean differences for continuous data, along with the 95% confidence intervals (CIs). A Mantel–Haenszel random-effects model was adopted taking into account potential heterogeneity across studies. The I^2 statistic was used to explore statistical heterogeneity. P values ≤0.05 for two-sided tests were considered to be statistically significant. An Egger plot was produced to identify sources of publication bias. Subgroup analyses (not pre-specified in each of the parent trials) were conducted by subdividing the study population according to age (<60 vs. >60 years old), gender (male vs. female), LVEF (≤25% vs. >25%), and HF aetiology (ischaemic vs. non-ischaemic). These reflect common questions asked of effective HF therapies that are commonly thought to affect treatment response.

Table 1 Characteristics of included studies

	FIX-HF-5 pilot		FIX-CHF-4		FIX-HF-5		FIX-HF-5C		FIX-HF-5C2	
First author	Neelagaru SB[26]		Borggrefe MM[27]		Kadish A[28]		Abraham WT[29]		Wiegn P[32]	
Year of publication	2006		2008		2011		2018		2020	
Total study cohort sample size (N)	49		164		428		160		60	
Randomized	Yes		Yes		Yes		Yes		No	
Double blinded	No		Yes		Yes		No		No	
	CCM	Control	CCM	Control	CCM	Control	CCM	Control[c]	CCM	Control[c]
Age (years)	52 ± 15	60 ± 12	59 ± 10	60 ± 10	58 ± 13	59 ± 12	63 ± 11	63 ± 11	66 ± 9	63 ± 11
Male (%)	68	71	89	81	73	71	73	79	88	79
Ischaemic CHF (%)	64	67	64	56	65	67	62	59	68	59
EF (%)[a]	24.9 ± 6.5	31.4 ± 7.4	29.3 ± 6.6	29.8 ± 7.8	25.7 ± 6.6	26.1 ± 6.5	33 ± 6	33 ± 5	34 ± 6	33 ± 5
NYHA class III (%)	100	96	72	80	91	86	86	91	98	91
Peak VO_2 (mL/kg/min)	14.3 ± 2.8	16.0 ± 2.9	14.1 ± 3.0	13.6 ± 2.7	14.7 ± 3.0	14.7 ± 2.9	15.5 ± 2.6	15.4 ± 2.8	15.0 ± 2.9	15.4 ± 2.8
6MWT (m)	321 ± 82	352 ± 95	386 ± 103	394 ± 102	326 ± 82	324 ± 92	317 ± 88	324 ± 90	NA	324 ± 90
MLWHFQ score	56.4 ± 24.8	52.1 ± 21.4	38.9 ± 27.4	36.5 ± 27.1	60.5 ± 23.0	57.4 ± 22.6	56 ± 23	57 ± 23	NA	57 ± 23
Interventions	CCM (OPTIMIZER™ system) signals on; control; signals off		CCM (OPTIMIZER™ system) allocated to on/off (Group 1: on to off; Group 2: off to on)		CCM (OPTIMIZER™ system) and optimal medical therapy[b] vs. optimal medical therapy alone (control)		CCM (OPTIMIZER™ system) and optimal medical therapy vs. optimal medical therapy alone (control)		The OPTIMIZER™ Smart system with 2-lead	
Outcomes	Peak VO_2, 6MWT, MLWHFQ Others: NYHA classification, Holter monitoring		Peak VO_2, 6MWT, MLWHFQ Others: NYHA classification, LV function		Peak VO_2, 6MWT, MLWHFQ Others: NYHA classification, LVEF, LV end-diastolic dimension, VAT, composite of all-cause mortality and all-cause hospitalizations		Peak VO_2, 6MWT, MLWHFQ Others: safety		Peak VO_2 Others: NYHA. safety	
Follow-up visits	12, 24 weeks		Phase I: 12 weeks; Phase II: 24 weeks		12, 24, 50 weeks		12, 24 weeks		12, 24 weeks	

6MWT, 6 min walk test; CCM, cardiac contractility modulation; CHF, chronic heart failure; EF, ejection fraction; LV, left ventricular; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; NA, not available; NYHA, New York Heart Association; peak VO_2, peak oxygen consumption; VAT, ventilatory anaerobic threshold.
[a]Values are mean ± standard deviation.
[b]Optimal medical therapy included angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (91%) and beta-blockers (93%).
[c]Results from the prior FIX-HF-5C study[29] were used as basis for assessment of the 2-lead OPTIMIZER system performance (compared with FIX-HF-5C Optimizer group) and clinical effects (compared with FIX-HF-5C control group).

Results

Description of studies

The four fully randomized clinical trials included in this review had an aggregate of 801 subjects. The trials included were the FIX-HF-5 pilot study,[26] the FIX-CHF-4 study,[27] the FIX-HF-5 study,[28] and the FIX-HF-5C study.[29] With the addition of peak VO_2 data ($n = 60$) from the FIX-HF-5C2 (the 2-lead version of the OPTIMIZER system), a treatment-only extension of the FIX-HF-5C study whose data were prospectively compared with the FIX-HF-5C control group for FDA submission and publication, we had 861 patients. The baseline characteristics of all 861 patients were similar: the most common aetiology of HF was ischaemic, and the majority of the participants were of NYHA classification III (*Table 1*). All studies used the OPTIMIZER™ system as the intervention on a background of optimal guideline-directed medical therapy and control groups consisted of either sham treatment (FIX-HF-5 pilot and FIX-CHF-4) or guideline-directed medical therapy alone (FIX-HF-5 and FIX-HF-5C). All studies were multicentre studies. Withdrawals and associated reasons were described in each trial, and there was no evidence of selective outcome reporting.
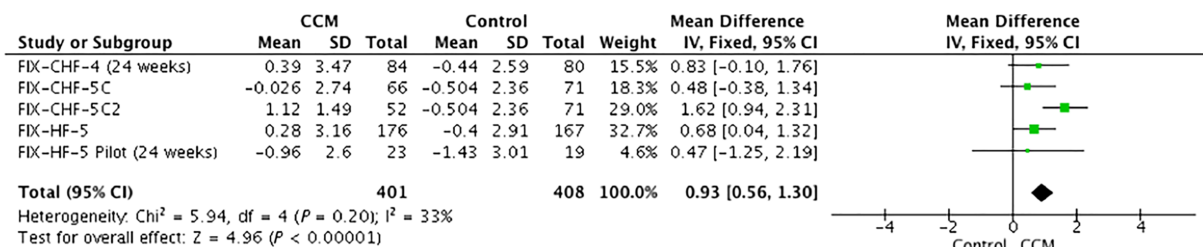
Data analyses

Peak VO_2

Data showed a significant increase in peak VO_2 in the CCM group ($n = 401$) compared with controls ($n = 408$) (mean difference +0.93 mL/kg/min, 95% CI 0.56 to 1.30, $P < 0.00001$) (*Figure 2*, panel A).
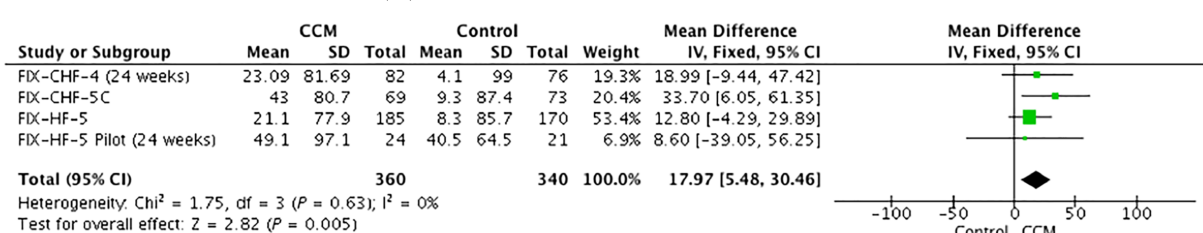
In the FIX-HF-5 pilot study, both groups showed a slight decline in peak VO_2 from baseline over the 24 week period, although this was more evident among the controls (-1.43 ± 3.01 mL/kg/min vs. -0.96 ± 2.6, $P = 0.29$). In the FIX-CHF-4 trial, which employed a cross-over design, during the first 3 months of the study (phase I), peak VO_2 increased similarly in both groups by ~0.4 mL/kg/min, independent of whether the device was turned on or off; however, in the second 3 months of the study (phase II), peak VO_2 remained

Figure 2 Forest plots for changes in peak oxygen consumption (peak VO_2) (mL/kg/min) (panel A); in 6 min walk test (6MWT) distance (panel B); and in Minnesota Living with Heart Failure Questionnaire (MLWHFQ) score (panel C). CCM, cardiac contractility modulation; CI, confidence interval; SD, standard deviation.
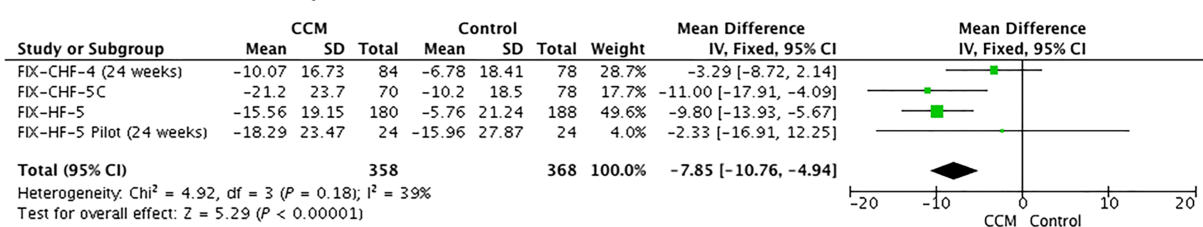
Panel A. Peak VO_2 (ml/kg/min)

Study or Subgroup	CCM Mean	CCM SD	CCM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
FIX-CHF-4 (24 weeks)	0.39	3.47	84	-0.44	2.59	80	15.5%	0.83 [-0.10, 1.76]
FIX-CHF-5C	-0.026	2.74	66	-0.504	2.36	71	18.3%	0.48 [-0.38, 1.34]
FIX-CHF-5C2	1.12	1.49	52	-0.504	2.36	71	29.0%	1.62 [0.94, 2.31]
FIX-HF-5	0.28	3.16	176	-0.4	2.91	167	32.7%	0.68 [0.04, 1.32]
FIX-HF-5 Pilot (24 weeks)	-0.96	2.6	23	-1.43	3.01	19	4.6%	0.47 [-1.25, 2.19]
Total (95% CI)			**401**			**408**	**100.0%**	**0.93 [0.56, 1.30]**

Heterogeneity: Chi² = 5.94, df = 4 (P = 0.20); I² = 33%
Test for overall effect: Z = 4.96 (P < 0.00001)

Panel B. 6MWT distance (m)

Study or Subgroup	CCM Mean	CCM SD	CCM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
FIX-CHF-4 (24 weeks)	23.09	81.69	82	4.1	99	76	19.3%	18.99 [-9.44, 47.42]
FIX-CHF-5C	43	80.7	69	9.3	87.4	73	20.4%	33.70 [6.05, 61.35]
FIX-HF-5	21.1	77.9	185	8.3	85.7	170	53.4%	12.80 [-4.29, 29.89]
FIX-HF-5 Pilot (24 weeks)	49.1	97.1	24	40.5	64.5	21	6.9%	8.60 [-39.05, 56.25]
Total (95% CI)			**360**			**340**	**100.0%**	**17.97 [5.48, 30.46]**

Heterogeneity: Chi² = 1.75, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.82 (P = 0.005)

Panel C. MLWHFQ

Study or Subgroup	CCM Mean	CCM SD	CCM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
FIX-CHF-4 (24 weeks)	-10.07	16.73	84	-6.78	18.41	78	28.7%	-3.29 [-8.72, 2.14]
FIX-CHF-5C	-21.2	23.7	70	-10.2	18.5	78	17.7%	-11.00 [-17.91, -4.09]
FIX-HF-5	-15.56	19.15	180	-5.76	21.24	188	49.6%	-9.80 [-13.93, -5.67]
FIX-HF-5 Pilot (24 weeks)	-18.29	23.47	24	-15.96	27.87	24	4.0%	-2.33 [-16.91, 12.25]
Total (95% CI)			**358**			**368**	**100.0%**	**-7.85 [-10.76, -4.94]**

Heterogeneity: Chi² = 4.92, df = 3 (P = 0.18); I² = 39%
Test for overall effect: Z = 5.29 (P < 0.00001)

increased in subjects who crossed over from sham to active treatment, whereas peak VO_2 decreased by ~0.8 mL/min/kg in subjects who crossed from active treatment to sham. Over the entire 24 week study period, peak VO_2 significantly increased in the 'sham-to-CCM' group (+0.39 ± 3.47 mL/kg/min) compared with the 'CCM-to-sham' group (−0.44 ± 2.59 mL/kg/min) for net treatment effect of ~0.8 mL/min/kg (Figure 2, panel A). The FIX-HF-5 study showed an improvement in peak VO_2 in the CCM group (+0.28 ± 3.16 mL/kg/min) compared with the OMT group (−0.40 ± 2.91 mL/kg/min) (Figure 2, panel A). In the FIX-HF-5C study, both groups showed an initial decline in peak VO_2 that was, however, less marked in the CCM group (−0.02 ± 2.74 mL/kg/min) compared with the control group (−0.50 ± 2.36 mL/kg/min, P = 0.28) (Figure 2, panel A). The FIX-HF-5C2 data showed a significant improvement in peak VO_2 in the CCM group (+1.12 ± 1.49 mL/kg/min) compared with the OMT group (−0.50 ± 2.36 mL/kg/min) (Figure 2, panel A). In the FIX-HF-5C2 study, the change of peak VO_2 from baseline to 24 weeks was 1.72 (95% Bayesian credible interval, 1.02–2.42) mL/kg/min greater in the 2-lead device group compared with controls (Figure 2, panel A).

A subgroup analysis showed that CCM significantly improved peak VO_2 in both age cohorts (≤60 vs. >60 years) (test for the overall effect: Z = 2.22, P = 0.03; test for subgroup differences: χ^2 = 9.78, P = 0.37) and in both gender cohorts (test for the overall effect: Z = 3.52, P = 0.0004; test for subgroup differences: χ^2 = 0.00, P = 0.98). Finally, subgroup analysis showed that CCM significantly improved peak VO_2 in patients with LVEF ≤25% (mean difference 0.73, 95% CI 0.08 to 1.38 mL/kg/min, P = 0.03) or with LVEF >25% (mean difference 0.94, 95% CI 0.55 to 1.33 mL/kg/min, P < 0.00001) (test for the overall effect: Z = 5.23, P < 0.00001; test for subgroup differences: χ^2 = 0.29, P = 0.59) (see Supporting Information, Tables S1-S4). It is interesting to note this larger effect on peak VO_2 in patients with LVEF ranging from 25% to 45% as these subjects may have more residual left ventricular muscle able to respond to the CCM stimulus. And of course, this is of significance because it is this group specifically mentioned in the FDA label for use in the USA. As an additional sensitivity analysis, we excluded the FIX-HF-5C2 trial (only relevant for peak VO_2), and the result was similar, mean difference +0.65, 95% CI 0.21 to 1.08 mL/kg/min, P = 0.004.

Distance on the 6 min walk test

The available data showed significant improvements in 6MWT distance in the CCM group (n = 360) (mean difference +17.97 m, 95% CI 5.48 to 30.46, P = 0.005) (Figure 2, panel B).

In the FIX-HF-5 pilot study, similar improvements in both groups at 12 weeks from baseline were observed, with a further increase of ~13 m in the CCM group at 24 weeks. The FIX-CHF-4 study also showed a similar increase in both groups during the first 12 weeks (+16.9 ± 79.6 and 10.8 ± 8.8 m), with a further increase in the 'sham-to-CCM' group (+19.6 ± 83.4 m)

and a decline in the 'CCM-to-sham' group (−6.3 ± 93.0 m) during the second phase. Over the 24 week period, 6MWT distance significantly increased in the 'sham-to-CCM' group (+23.09 ± 81.69 m) compared with the 'CCM-to-sham' group (+4.1 ± 99.0 m). In FIX-HF-5, the observed increase in 6MWT distance (10 m) in the CCM group was not statistically significant compared with controls (P = 0.108). In the FIX-HF-5C study, the CCM group showed a significant improvement in 6MWT distance (+43 ± 80.7 m) compared with controls (+9.3 ± 87.4 m, P = 0.009).

Stratification analysis by gender showed significant improvements in 6MWT distance in men in the CCM group (n = 268) (mean difference 21.12, 95% CI 7.39 to 34.84 m, P = 0.003), whereas no significant changes were observed among the women of the CCM group (n = 120) (mean difference 1.05, 95% CI −21.22 to 23.22 m, P = 0.57) (test for the overall effect: Z = 0.09, P = 0.93; test for subgroup differences: χ^2 = 2.26, P = 0.13). In the CCM group with an ischaemic aetiology (n = 232), data showed a significant improvement in 6MWT distance (mean difference 21.32, 95% CI 8.13 to 34.51 m, P = 0.002), whereas no significant changes in 6MWT distance were observed among the CCM patients of non-ischaemic aetiology (n = 134) (mean difference 4.87, 95% CI −16.55 to 26.3 m, P = 0.66) (test for the overall effect: Z = 2.93, P = 0.003; test for subgroup differences: χ^2 = 1.64, P = 0.20). CCM significantly improved 6MWT distance in patients with LVEF >25% (n = 287) (mean difference 15.84, 95% CI 3.16 to 28.52 m, P = 0.01) compared with patients with LVEF ≤25% (n = 144) (mean difference 9.08, 95% CI −11.12 to 29.67 m, P = 0.37) (test for the overall effect: Z = 2.55, P = 0.01; test for subgroup differences: χ^2 = 0.29, P = 0.59) (see Supporting Information, Tables S5-S8).

Quality of life

Data showed significant improvements in the MLWHFQ score in the CCM group (n = 358) (mean difference −7.85, 95% CI −10.76 to −4.94, P < 0.00001) compared with controls (n = 368) (Figure 2, panel C). In the FIX-HF-5 pilot study,[26] MLWHFQ score changed similarly in both treatment and control groups. In the FIX-CHF-4 study, mean (±SD) values of MLWHFQ score improved significantly while on active therapy compared with sham therapy by −3.29 (95% CI −8.72 to 2.14). FIX-HF-5 reported a significant improvement in MLWHFQ from baseline in the CCM group compared with control (−9.8 points, 95% CI −13.93 to 12.25). In the FIX-HF-5C study, mean (±SD) values of MLWHFQ score significantly improved while on CCM active therapy compared with controls by −11 (95% CI −17.9 to 4.1).

Subgroup analyses showed significant changes in quality of life measured by MLWHFQ both in patients ≤60 years old (mean difference −6.31, 95% CI −10.03 to −2.59, P = 0.0009) and in patients >60 years old (mean difference −6.28, 95% CI −10.61 to −1.86, P = 0.005) (test for the overall effect: Z = 4.34, P < 0.0001; test for subgroup

differences: χ^2 = 0.00, P = 0.98). Gender subgroup analysis showed significant improvements in MLWHFQ score in both men (n = 268) (mean difference −7.76, 95% CI −11.13 to −4.39, P < 0.00001) and women (n = 123) (mean difference −5.94, 95% CI −11.63 to −0.24, P = 0.04) (test for the over-all effect: Z = 4.93, P < 0.00001; test for subgroup differ-ences: χ^2 = 0.29, P = 0.59). Moreover, subgroup analysis showed significant changes in MLWHFQ score both with CCM in the group with LVEF ≤25% (n = 203) (mean differ-ence −6.56, 95% CI −10.31% to −2.80%, P = 0.0006) and among CCM randomized patients with LVEF >25% (n = 152) (mean difference −5.88, 95% CI −10.05% to −1.71%, P = 0.006) (test for the overall effect: Z = 4.39, P < 0.0001; test for subgroup differences: χ^2 = 0.06, P = 0.81). Finally, data showed significant changes in quality of life measured by MLWHFQ in patients with an ischaemic aetiology (n = 233) (mean difference −9.14, 95% CI −12.56 to −5.72, P < 0.00001), whereas no significant changes were observed in patients with a non-ischaemic aetiology (n = 137) (mean difference −3.10, 95% CI −7.71 to 1.52, P = 0.19) (test for the overall effect: Z = 4.99, P < 0.00001; test for subgroup differences: χ^2 = 4.25, P = 0.04) (see Supporting Information, Tables S9-S12).

Discussion

This individual patient meta-analysis including data from all four randomized controlled trials (RCTs), and a single arm ex-tension trial, in total enrolling a total of 861 participants, showed that CCM significantly improves functional capacity (as measured by peak VO_2 and 6MWT distance) and quality of life (as measured by MLWHFQ score) in HF patients. CCM was safe with no adverse effect on hospitalizations or mortal-ity in any of the trials or overall. Relatively consistent effects were seen on peak VO_2, 6MWT, and MLWHFQ in all the trials analysed. A post hoc analysis of participants from FIX-HF-5 with EF ≥25% and NYHA class III (n = 206, about half of the original FIX-HF-5 population) had earlier showed that CCM significantly improved peak VO_2 (+1.31 mL/kg/min, P = 0.001), ventilatory anaerobic threshold (+0.64 mL/kg/min, P = 0.03), and MLWHFQ score (10.8 points, P = 0.003). Although pre-specified in the protocol, these analyses were considered retrospective and only viewed as hypothesis gen-erating, despite demonstrating a potentially higher benefit from the use of CCM in the less clinically compromised HF population. The subsequent FDA-approved design FIX-HF-5C trial confirmed these results through its prospective Bayesian analysis. Thus, CCM is seen as a potential therapy for HF that extends beyond those eligible for CRT. With an FDA approval for 25–45% LVEF in those without a prolonged QRS, it may be suitable for 20–25% of the HFrEF population. This may be larger than another alternative, His bundle pacing, because

the latter has not been established as safe in subjects with a narrow QRS, although it may offer some advantages of those with a wide QRS particularly of the RBBB type.

The results of this individual patient data meta-analysis confirm and extend the results of a previous meta-analysis of three studies, which included a total of 641 participants and which showed that, compared with control, CCM signifi-cantly improved peak VO_2 (+0.71, 95% CI 0.20 to 1.21 mL/kg/min, P = 0.006), 6MWT distance (+13.92 m, 95% CI −0.08 to 27.91 m, P = 0.05), and MLWHFQ (−7.17, 95% CI −0.38 to −3.96, P < 0.0001).[33] One other meta-analysis of CCM has also recently been published, with discrepant results.[34] The authors of this report, however, did not perform an individual patient data analysis (the preferred mode of meta-analysis) and also did not report peak VO_2 data, the most reliable and most objective measure of functional capacity in HF. This report also contained some significant errors, calling into question its reliability. For the FIX-HF-5 pilot study, it errone-ously classified it as a single centre study, quoted inaccurate inclusion/exclusion and main study outcomes, and ignored its 6MWT distance results. For the FIX-CHF-4 trial, this report also erroneously classified it as a single centre study, quoted inaccurate inclusion/exclusion and main study outcomes, plotted incorrect 6MWT distance results, and counted one patient with VT twice. For the FIX-HF-5 trial, this meta-analysis incorrectly estimated hospitalizations by in-cluding fatal events and misleadingly counted total arrhyth-mia events rather than the numbers of patients with an arrhythmia as is needed when composing a meta-analysis of trials of different durations. Finally, for the FIX-HF-5C trial, this meta-analysis presented data on hospitalizations that were not reported in either the trial paper or the online ap-pendices, and which cannot therefore be verified, and which appear highly unlikely.

The present updated meta-analysis including 861 patients showed a more consistent improvement in peak VO_2 (+0.93, 95% CI 0.56 to 1.30 mL/kg/min, P < 0.00001), 6MWT distance (+17.97, 95% CI 5.48 to 30.46 m, P = 0.005), and quality of life measured by MLWHFQ (−7.85, 95% CI −10.76 to −4.94, P < 0.00001) compared with the earlier meta-analysis and allowed more detailed patient subgroup analysis.

The overall impact of CCM on functional capacity and qual-ity of life is similar to that reported in prior studies of CRT in patients with a prolonged QRS duration (MUSTIC, MIRACLE, CONTAK-CD, and MIRACLE ICD trials). In a meta-analysis of six studies of CRT, the 95% CIs for the improvement in peak VO_2 with CRT went from 0.32 to 3.22 mL/kg/min, with bor-derline significance, P = 0.017,[35] compared with the narrower CI, and more highly significant effect seen here: 95% CIs for the improvement in peak VO_2 with CCM between 0.56 and 1.30 mL/kg/min, P < 0.00001, giving a considerably more precise estimate of efficacy and of increased statistical signif-icance. Also, another meta-analysis of 15 studies of CRT showed a significant increase in 6MWT distance with CRT of

17.50 m (95% CI 7.05 to 27.94), almost identical to this meta-analysis of the CCM trials, where the improvement was +17.97, 95% CI 5.48 to 30.46 m, $P = 0.005$.[36] The present meta-analysis also showed a clinically significant improvement of quality of life measured by MLWHFQ (−7.85 points). It is well known that all domains of the MLHFQ and other tools have a good sensitivity to change in the population studied.[37,38] A previous study on MLWHFQ showed that the minimal clinically important difference based on patients whose response to the anchor question was 'somewhat better' ranged from 3.59 to 19.14 points, confirming the clinical relevance of our findings (−7.85 points, 95% CI −10.76 to −4.94, $P < 0.00001$). Other HFrEF therapies associated with such improvements in functional capacity and PROs include exercise training and cardiac rehabilitation.[39–41]

Thus, although in a different cohort of patients, these findings show CCM to be of comparable impact on functional capacity and exercise tolerance as CRT. The efficacy of CCM raises the tantalizing suggestion that CCM type stimulation could in future be tested in CRT non-responders when no other options are available.[42–44]

The trials reviewed provided insufficient patient years of exposure for meaningful calculations regarding effects on hospitalization or mortality rates in a meta-analysis. There were 24 post-randomization hospitalizations in the FIX-HF-5 pilot study,[33] 18 in control, compared with 6 in the treatment group. The point estimates of hospitalization-free survival at 6 months were 62% in the control group compared with ~84% in the treatment group. The hazard ratio (treatment/control) is 0.47 (95% CI 0.16–1.40) so that the risk reduction for subjects receiving treatment is 53% compared with controls ($P = 0.17$).[26] In the FIX-CHF-4 trial,[27] there were six deaths during the study, two prior to randomization (ventricular fibrillation and worsening HF), one in Group 1 during the OFF period (undetermined cause), one in Group 2 during the OFF period, and two in Group 2 during the ON period (sudden cardiac death and renal failure). There were 46 hospitalizations in 31 patients during CCM OFF periods, compared with 41 hospitalizations in 31 patients during CCM ON periods.[27] In the FIX-HF-5 trial,[28] for the composite safety endpoint of all-cause hospitalizations and all-cause mortality, 4 subjects in the CCM group and 14 subjects in the OMT group were withdrawn from the study before experiencing a safety endpoint and therefore lost to follow-up. Seven (3.3%) of the 213 OMT subjects and 10 (4.9%) of the 203 subjects who received an OPTIMIZER system died during the 50 week follow-up period ($P = 0.47$). With an intent-to-treat analysis, 13 (6.0%) of the 215 subjects randomized to the CCM group died during the 50 week follow-up period ($P = 0.25$ vs. OMT). In the FIX-HF-5C trial,[29] there were six deaths during the study period: four in the control group and two in the CCM group. One CCM patient death occurred 2 days before the scheduled implantation date (patient never received an implant), and the other occurred at 164 days

after implantation and was due to sepsis following a cholecystectomy. The four deaths in the control group included two deaths due to cardiac pump failure (on Days 4 and 36), one death following a VT ablation procedure (on Day 70), and pulmonary complications of a non-cardiac procedure (on Day 117).[29] In the FIX-HF-5C2,[32] no deaths were reported during the 24 week study period in the 2-lead OPTIMIZER subjects; in contrast, there were four deaths in the FIX-HF-5C control subjects during the same period of follow-up.

Limitations

In this meta-analysis, several limitations should be acknowledged. Study cohorts are relatively young and predominantly male; therefore, future data would be needed in older individuals and in more women. Patients with permanent atrial fibrillation 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 nine patients with atrial fibrillation. Furthermore, the 2-lead system has been available and used in patients with atrial fibrillation in EU for 10 years although, as of now, specific reports of the effects of CCM in patients with atrial fibrillation have not been completed. Although no formal statistical heterogeneity was observed, the studies analysed differed in study design limiting our ability to define representative results across different patient subgroups.

In conclusion, this meta-analysis showed statistically significant and clinically worthwhile beneficial effects of CCM in improving functional capacity, exercise tolerance, and quality of life in HF patients. Larger, well-conducted RCTs using a parallel double-blind design are needed in order to determine the effect of CCM on major mortality and morbidity outcomes before CCM can be widely recommended as an effective treatment option for HF patients. However, in those in whom conventional interventions are failing or contraindicated, these results suggest 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. Finally, RCTs including more women and including older individuals would also be valuable.

Conflict of interest

Prof. Coats declares having received honoraria and/or lecture fees from Astra Zeneca, Bayer, Menarini, Novartis, Nutricia, Servier, Vifor, Actimed, Cardiac Dimensions, CVRx, Enopace, Faraday, Gore, Impulse Dynamics, Respicardia, Stealth Peptides, V-Wave, Corvia, Arena, and ESN Cleer. Dr Raval

declares no conflicts relevant to this manuscript. Outside this manuscript, he declares the following: steering committee of the Shore registry, advisor for care DX and steering committee for Post Approval Study for CardioMEMS/Abbott. Prof. Giallauria, Dr Kuschyk, Dr Cuomo, and Dr Parlato have nothing to disclose.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Forest plots for changes in peak VO$_2$ (ml/kg/min) stratified by age.

Table S2. Forest plots for changes in peak VO$_2$ (ml/kg/min) stratified by gender.

Table S3. Forest plots for changes in peak VO$_2$ (ml/kg/min) stratified by aetiology.

Table S4. Forest plots for changes in peak VO$_2$ (ml/kg/min) stratified by left ventricular ejection fraction (≤25% vs. >25%).

Table S5. Forest plots for changes in 6-minute walking distance (m) stratified by age.

Table S6. Forest plots for changes in 6-minute walking distance (m) stratified by gender.

Table S7. Forest plots for changes in 6-minute walking distance (m) stratified by aetiology.

Table S8. Forest plots for changes in 6-minute walking distance (m) stratified by left ventricular ejection fraction (≤25% vs. >25%).

Table S9. Forest plots for changes in Minnesota Living with Heart Failure Questionnaire (MLWHFQ) stratified by age.

Table S10. Forest plots for changes in Minnesota Living with Heart Failure Questionnaire (MLWHFQ) stratified by gender.

Table S11. Forest plots for changes in Minnesota Living with Heart Failure Questionnaire (MLWHFQ) stratified by aetiology.

Table S12. Forest plots for changes in Minnesota Living with Heart Failure Questionnaire (MLWHFQ) stratified by left ventricular ejection fraction (≤25% vs. >25%).

Data S1. Supporting information

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