Cardiac Contractility Modulation for Heart Failure

Abbreviations used throughout the Decision Memorandum for Cardiac Contractility Modulation for Heart Failure Management

Abbreviations

6MWT – Six-Minute Walk Test
ACC – American College of Cardiology Foundation
ACS – Acute Coronary Syndrome
AE – Adverse Events
AF – Atrial Fibrillation
AHA – American Heart Association
AHRQ- Agency for Healthcare Research and Quality
ASC – Ambulatory Surgery Center
ASE – American Society of Echocardiography
CAD – Coronary Artery Disease
CCM – Cardiac Contractility Modulation
CHF – Congestive Heart Failure

CI – Confidence Interval
CKD – Chronic Kidney Disease
CMS – Centers for Medicare & Medicaid Services
CRT – Cardiac Resynchronization Therapy
EF – Ejection Fraction
EU – European Union
FDA – Food and Drug Administration
GDMT – Guideline-Directed Medical Therapy
GFR – Glomerular Filtration Rate
GLS – Global Longitudinal Strain
HF – Heart failure
HFimpEF – Heart Failure, Improved Ejection Fraction
HFmrEF – Heart Failure, Mildly Reduced Ejection Fraction
HFpEF – Heart Failure, Preserved Ejection Fraction
HFrEF – Heart Failure, Reduced Ejection Fraction
HFSA – Heart Failure Society of America
HHS – U.S. Department of Health and Human Services
HRS – Heart Rhythm Society
ICD – Implantable Cardioverter Defibrillator
ICM – Ischemic Cardiomyopathy
IDE – Investigational Device Exemption
IV – Intravenous
KCCQ – Kansas City Cardiomyopathy Questionnaire
KDIGO – Kidney Disease Improving Global Outcomes
NICM – Non-Ischemic Cardiomyopathy
LBBB – Left Bundle Branch Block
LV – Left Ventricle
LVEF – Left Ventricular Ejection Fraction
LVMEE – Left Ventricular Myocardial Mechano-energetic Efficiency
LVGLS – Left Ventricular Global Longitudinal Strain
MA – Meta Analysis
MACs – Medicare Administrative Contractors
MAGGIC – Meta-Analysis Global Group in Chronic [Heart Failure]
MCID – Minimum Clinically Important Difference
MEE – Mechano-Energetic Efficiency
MI – Myocardial infarction
MLWHFQ – Minnesota Living With Heart Failure Questionnaire
MS - millisecond
NA – Not applicable
NCA – National Coverage Analysis
NCD – National Coverage Determination
NR – Not reported
NTproBNP – N-terminal pro-brain natriuretic peptide

NYHA – New York Heart Association
O_2 – Oxygen
OMT – Optimal Medical Therapy
pVO_2 – Peak oxygen consumption
QoL – Quality of Life
RBBB – Right Bundle Branch Block
RCT – Randomized Controlled Trial
RV – Right Ventricle
RWE – Real-World Evidence
SAE – Serious Adverse Event
SCAI – Society for Cardiovascular Angiography and Interventions
SCMR – Society for Cardiovascular Magnetic Resonance
S-ICD – Subcutaneous implantable cardioverter defibrillator
SD – Standard deviation
SDM – Shared Decision-Making
SHFM – Seattle Heart Failure Model
TAPSE – Tricuspid Annular Plane Systolic Excursion
US – United States

Note – GDMT (Guideline-directed medical therapy) and OMT (Optimal Medical Therapy) are used interchangeably throughout this document.

I. Final Decision

A. Decision

Cardiac Contractility Modulation (CCM) for heart failure (HF) management is covered under Coverage with Evidence Development (CED) according to the provisions in sections (B) and (C) below.

B. Coverage Criteria

The implantation of CCM is covered for HF management when furnished according to a Food and Drug Administration (FDA) market-authorized indication and all of the following conditions are met:

1. Patient Criteria

Patients must meet the FDA market-authorized indications for use and remain symptomatic despite at least 3 months of optimized guideline-directed medical therapy (GDMT) as determined by the heart team prior to CCM implantation.

Patients are excluded from coverage if they meet any of the following criteria:

- Meet any of the contraindications in the FDA labeling; or,
- Have had a heart transplant; or,
- Are younger than 18 years old.

2. CED Study Criteria

The CCM and related items and services are furnished in the context of a CMS-approved CED study. CMS-approved CED study protocols must include only those patients who meet the criteria in section B.1 and include all of the following:

a) Primary outcomes of all-cause mortality, HF hospitalizations, or a composite of these, through a minimum of 24 months. Each component of a composite outcome must be individually reported.
b) An active comparator.
c) A care management plan that identifies members, roles, and responsibilities of the clinical team that performs the follow-up CCM patient management.
d) Design sufficient for subgroup analyses by:
    1. Age (Stratify <65, 65-74, 75+);
    2. Other clinically important patient demographic factors;
    3. Ischemic cardiomyopathy versus non-ischemic cardiomyopathy;
    4. No CRT, CRT;
    5. Left ventricular ejection fraction (LVEF) ≥35% versus <35%;
    6. Systolic blood pressure ≥ median versus < median;
    7. Diabetic vs non-diabetic.
e) In addition, CMS-approved CED studies must adhere to the scientific standards (criteria 1-17 below) that have been identified by the Agency for Healthcare Research and Quality (AHRQ) as set forth in Section VI. of CMS' Coverage with Evidence Development Guidance Document, published August 7, 2024 (the "CED Guidance Document").
    1. Sponsor/Investigator: The study is conducted by sponsors/investigators with the resources and skills to complete it successfully.
    2. Milestones: A written plan is in place that describes a detailed schedule for completion of key study milestones, including study initiation, enrollment progress, interim results reporting, and results reporting, to ensure timely completion of the CED process.
    3. Study Protocol: The CED study is registered with ClinicalTrials.gov and a complete final protocol, including the statistical analysis plan, is delivered to CMS prior to study initiation. The published protocol includes sufficient detail to allow a judgment of whether the study is fit-for-purpose and whether reasonable efforts will be taken to minimize the risk of bias. Any changes to approved study protocols should be explained and publicly reported.
    4. Study Context: The rationale for the study is supported by scientific evidence and study results are expected to fill the specified CMS-identified evidence deficiency and provide evidence sufficient to assess health outcomes.
    5. Study Design: The study design is selected to safely and efficiently generate valid evidence of health outcomes. The sponsors/investigators minimize the impact of confounding and biases on inferences through rigorous design and appropriate statistical techniques. If a contemporaneous comparison group is not included, this choice should be justified, and the sponsors/investigators discuss in detail how the design contributes useful information on issues such as durability or adverse event frequency that are not clearly answered in comparative studies.

6. Study Population: The study population reflects the demographic and clinical diversity among the Medicare beneficiaries who are the intended population of the intervention, particularly when there is good clinical or scientific reason to expect that the results observed in premarket studies might not be observed in older adults or subpopulations identified by other clinical or demographic factors.
7. Subgroup Analyses: The study protocol explicitly discusses beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion requirements effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. In the protocol, the sponsors/investigators describe plans for analyzing demographic subpopulations as well as clinically-relevant subgroups as identified in existing evidence. Description of plans for exploratory analyses, as relevant subgroups emerge, are also included.
8. Care Setting: When feasible and appropriate for answering the CED question, data for the study should come from beneficiaries in their expected sites of care.
9. Health Outcomes: The primary health outcome(s) for the study are those important to patients and their caregivers and that are clinically meaningful. A validated surrogate outcome that reliably predicts these outcomes may be appropriate for some questions. Generally, when study sponsors propose using surrogate endpoints to measure outcomes, they should cite validation studies published in peer-reviewed journals to provide a rationale for assuming these endpoints predict the health outcomes of interest. The cited validation studies should be longitudinal and demonstrate a statistical association between the surrogate endpoint and the health outcomes it is thought to predict.
10. Objective Success Criteria: In consultation with CMS and AHRQ, sponsors/investigators establish an evidentiary threshold for the primary health outcome(s) so as to demonstrate clinically meaningful differences with sufficient precision.
11. Data Quality: The data are generated or selected with attention to provenance, bias, completeness, accuracy, sufficiency of duration of observation to demonstrate durability of health outcomes, and sufficiency of sample size as required by the question.
12. Construct Validity: Sponsors/investigators provide information about the validity of drawing warranted conclusions about the study population, primary exposure(s) (intervention, control), health outcome measures, and core covariates when using either primary data collected for the study about individuals or proxies of the variables of interest, or existing (secondary) data about individuals or proxies of the variables of interest.
13. Sensitivity Analyses: Sponsors/investigators will demonstrate robustness of results by conducting pre-specified sensitivity testing using alternative variable or model specifications as appropriate.
14. Reporting: Final results are provided to CMS and submitted for publication or reported in a publicly accessible manner within 12 months of the study's primary completion date. Wherever possible, the study is submitted for peer review with the goal of publication using a reporting guideline appropriate for the study design and structured to enable replication. If peer-reviewed publication is not possible, results

may also be published in an online publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with incomplete results).

15. Sharing: The sponsors/investigators commit to making study data publicly available by sharing data, methods, analytic code, and analytical output with CMS or with a CMS-approved third party. The study should comply with all applicable laws regarding subject privacy, including 45 CFR § 164.514 within the regulations promulgated under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and 42 CFR, Part 2: Confidentiality of Substance Use Disorder Patient Records.
16. Governance: The protocol describes the information governance and data security provisions that have been established to satisfy Federal security regulations issued pursuant to HIPAA and codified at 45 CFR Parts 160 and 164 (Subparts A & C), United States Department of Health and Human Services (HHS) regulations at 42 CFR, Part 2: Confidentiality of Substance Use Disorder Patient and HHS regulations at 45 CFR Part 46, regarding informed consent for clinical study involving human subjects. In addition to the requirements under 42 CFR and 45 CFR, studies that are subject to FDA regulation must also comply with regulations at 21 CFR Parts 50 and 56 regarding the protection of human subjects and institutional review boards, respectively.
17. Legal: The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals, although it is acceptable for a study to test a reduction in toxicity of a product relative to standard of care or an appropriate comparator. For studies that involve researching the safety and effectiveness of new drugs and biological products aimed at treating life-threatening or severely-debilitating diseases, refer to additional requirements set forth in 21 CFR § 312.81(a).

Consistent with section 1142 of the Act, AHRQ supports clinical research studies that CMS determines meet all the criteria and standards identified above.

C. Other Uses of CCM

1) CCM for HF management is not covered for patients outside of a CMS-approved study.
2) Nothing in this NCD would preclude coverage of CCM for HF management through NCD 310.1 (Clinical Trial Policy) or through the Investigational Device Exemption (IDE) Policy.

See **Appendix A** for Medicare National Coverage Determinations Manual language.

II. Clinical Review

A. Background

1. Heart Failure Definitions & Classification

HF is a chronic syndrome in which the heart muscle is unable to pump enough blood to meet the body's needs. This condition results in protean symptoms, including fatigue and shortness of

breath, which limit an individual's ability to engage in everyday physical activities such as walking or climbing stairs. As the end-stage manifestation of most forms of heart disease, HF is affected by traditional cardiovascular risk factors, including age, diabetes, hypertension, hyperlipidemia, smoking, and obesity.

HF classification is commonly based on the left ventricular ejection fraction (LVEF), a measure of the fraction or percentage of blood volume pumped out of the heart with each contraction (Heidenreich et al., 2022). The most recent US and European diagnostic criteria for HF include three subtypes based on the LVEF (Ostrominski et al., 2024): HF with preserved ejection fraction (EF) (HFpEF), HR with mildly reduced EF (HFmrEF), and HR with reduced EF (HFrEF). In HFpEF, the LVEF is within the normal range of 50-70% and the muscles of the heart contract relatively normally but thickening of the heart muscle and diastolic dysfunction may result in high left ventricular (LV) filling pressures. In HFmrEF, the intermediary level between HFpEF and HFrEF, the LVEF is 41%-49%. In HFrEF, the LVEF is ≤ 40%, which indicates abnormalities in cardiac structure or functioning, including left ventricular dilatation. Of US adults with HF, approximately 41% have HFpEF, 14% have HFmrEF, and 45% have HFrEF (Bozkurt et al., 2023). The most recent US guidelines include a new subtype, HF with improved EF (HFimpEF), which indicates that the LVEF has improved from ≤ 40% to > 40% (Heidenreich et al., 2022). Based on a recent meta-analysis, the estimated prevalence of HFimpEF is 23% (He et al., 2021). HF classification is essential for treatment management, as it is predictive of adverse events (e.g., mortality and hospitalization) and the response to certain medical therapies (Dimond et al., 2024; He et al., 2021).

The severity of HF symptoms is commonly classified using the New York Heart Association (NYHA) Functional Classification system (Holland et al., 2010). The purpose of the classification is to describe the impact of HF on a person's physical activities using four categories: I=no limitation; II=slight limitation; III=marked limitation, but comfortable at rest; IV=unable to engage in any physical activity without discomfort and symptoms even at rest. Clinicians assign the classification based on how they interpret the symptoms reported by a patient, the patient's medical history, and results from clinical tests on cardiac functioning (Holland et al., 2010). HF treatment recommendations are commonly based on the NYHA classification (Rohde et al., 2023).

2. HF Prevalence, Incidence, and Mortality Rates

Approximately 6.7 million Americans are living with HF (Bozkurt et al., 2023), and the number is expected to grow through 2030. An estimated 650,000 new HF cases are diagnosed in the US each year (Malik et al., 2024), and the lifetime risk of HF in the US has increased from 1 in 5 to 1 in 4 (Bozkurt et al., 2023).

For individuals aged 65 to 70 years, the estimated prevalence of HF is expected to increase (Bozkurt et al., 2023). The reported HF incidence and prevalence rates vary based on the timeframe and HF ascertainment methodology (Bozkurt et al., 2023). An analysis of Medicare claims data for beneficiaries indicates that the estimated incidence rate declined by over 25%

from 2011 to 2016 (Khera et al., 2020). This decline occurred irrespective of sex or race/ethnicity (Khera et al., 2020). Over the nearly 20 years from 1999 to 2017, the estimated HF prevalence rate among adults aged 65 and older increased by over 15% (Bozkurt et al., 2023). In addition, the HF prevalence rate is expected to nearly double among 65- to 70-year-olds, from 4.3% in 2010 to 8.5% in 2030 (Bozkurt et al., 2023).

Disparities exist between ethnic groups for the key indicators of HF population burden (including incidence, prevalence, and outcomes). Blacks and Hispanics have a higher prevalence of HF than Whites, and Black women have the highest prevalence of all racial and ethnic groups (Tsao et al., 2022). HFpEF is the most prevalent HF phenotype for White women, while HFrEF predominates among Black women (Mwansa et al., 2021). Compared with Hispanics and non-Hispanic Whites, Black individuals have a higher incidence of HF (Bozkurt et al., 2023). Black patients not only have a higher incidence of heart failure than other racial groups, but they also have higher admissions for HFrEF and worse overall survival (Lewsey & Breathett, 2021; Miller et al., 2021). The MESA (Multi-Ethnic Study of Atherosclerosis) study reported incidence rates per 1,000 person-years of 4.6 for Blacks, 3.5 for Hispanics, and 2.4 for non-Hispanic Whites (Bahrami et al., 2008).

The HF prevalence rate among Black individuals increased from 2001 to 2016, compared to an unchanged prevalence rate for non-Hispanic White individuals. Black individuals with HF also experience a disproportionate prevalence of disability (Roger, 2021) and mortality (Glynn et al., 2019).

The HF mortality rate is difficult to estimate because HF-related deaths tend to be greatly undercounted (Bozkurt et al., 2023). In 2020, 85,855 US deaths were attributed to HF, although the total number is likely to be closer to the 415,922 reported deaths with HF as a contributing cause of death. From 2000 to 2012, the estimated HF mortality rate declined but has increased since 2012 (Bozkurt et al., 2023). The HF mortality rate also varies by ethnicity, similar to the prevalence rates. In the longitudinal ARIC (Atherosclerosis Risk in Communities) study, the 30-day, 1-year, and 5-year case fatality rates after hospitalization for HF were 10.4%, 22%, and 42.3%, respectively, with Black individuals having a greater 5-year case fatality rate than White individuals ($p<0.05$) (Loehr et al., 2008). Among Medicare beneficiaries, the age-adjusted HF mortality rate has increased, from 16.9% in 2011 to 20.4% in 2017 (Sidney et al., 2019).

3. Management of Heart Failure

The treatment approaches overlap considerably across the LVEF spectrum (von Haehling et al., 2024). For all patients, the treatment of choice is a lifestyle change that addresses the underlying cause of HF. Patients are counseled to limit salt consumption, quit smoking, improve diet and exercise, and lose weight (Heidenreich et al., 2022; von Haehling et al., 2024). Medication management of HF includes diuretics, vasodilators, and renin-angiotensin-aldosterone system blockers (Heidenreich et al., 2022). For HFrEF, the use of β-blockers is recommended, either alone or as part of a quadruple therapy with angiotensin receptor neprilysin inhibitors, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors

(Heidenreich et al., 2022). Quadruple therapy is estimated to reduce the hazard of cardiovascular death or HF hospitalization by up to 62% compared with limited conventional therapy (Vaduganathan et al., 2020). Recently, sodium-glucose cotransporter-2 inhibitors have reduced the combined risk of cardiovascular deaths and hospitalizations among individuals with HFmrEF (Solomon et al., 2022) and HFpEF (Anker et al., 2021; Solomon et al., 2022).

Several medical devices, including an implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT), may also improve outcomes for HFrEF patients who are refractory to medical therapy (Heidenreich et al., 2022). ICDs are approved for use in patients with HFrEF who have persistently low LVEF despite guideline-directed medical therapy (GDMT) and life expectancy of at least one year for the primary prevention of sudden cardiac death (Butler et al., 2022). The devices detect potentially fatal arrhythmias and deliver high-energy electric shocks intended to reestablish a normal heart rhythm. Although ICDs prevent fatal arrhythmias and improve survival, they do not treat the symptoms of HFrEF.

CRT devices may improve health outcomes for HF patients who have a QRS duration >150 ms and an LVEF ≤ 35% despite GDMT (Henin et al., 2020). In these patients, CRT may improve coordination of left ventricular contraction and may meaningfully improve patients' functional capacity, quality of life (QoL), and exercise tolerance while decreasing hospitalizations and mortality. However, for patients with a QRS duration <130ms, data indicate that CRT is not beneficial and may cause harm (Ruschitzka, 2013). Additional data suggests patients with right bundle branch block (RBBB) experience minimal to no benefit from CRT (Zareba et al., 2011).

4. Cardiac Contractility Modulation for Heart Failure

A CCM system consists of an implantable pulse generator, ventricular septal pacing leads, an external charger, and an external programming device. CCM devices deliver periodic, programmed electrical stimulation designed to alleviate symptoms associated with HF in order to improve QoL, restore functional capacity, and improve exercise tolerance. CCM delivers electrical stimuli to the ventricular septum during the absolute refractory period. As such, CCM is non-excitatory, meaning it does not trigger cardiac depolarization. The intent of CCM is not to cause the heart to contract, but rather to increase the strength of the heart's contraction (Abraham et al., 2018; Wiegn et al., 2020).

B. Food and Drug Administration Status

The FDA granted breakthrough device status for the three-lead OPTIMIZER Smart System on July 31, 2015, and granted premarket approval on March 21, 2019. Subsequent FDA approvals for CCM removed the requirement of a right atrial lead (October 2019), allowed commercial distribution of the Optimizer Smart Mini System (July 2021), and removed the requirement for normal sinus rhythm (October 2021).

As stated in the Summary of Safety and Effectiveness, the OPTIMIZER Smart System is currently FDA-indicated "to improve 6-minute hall walk distance, quality of life, and functional

status of NYHA Class III heart failure patients who remain symptomatic despite guideline directed medical therapy, who are in normal sinus rhythm, are not indicated for Cardiac Resynchronization Therapy, and have a left ventricular ejection fraction ranging from 25% to 45%".[1]

III. Evidence

This section provides a summary of the evidence considered during this review. The evidence presented here includes peer-reviewed publications of pertinent clinical research on CCM for HF management and evidence-based guidelines which we considered in our coverage analysis (See Section IV. B.).

A detailed account of the methodological principles of study design that CMS uses to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions may be found in the CMS National Coverage Analysis Evidence Review Guidance Document, published August 7, 2024.

A. Evidence Questions

The following questions guide this review and analysis of the evidence on the clinical utility of CCM (e.g., OPTIMIZER Smart System) for moderate to severe chronic systolic heart failure (EF 25-45%) that remains symptomatic despite guideline-directed medical therapy. We answer these questions in Section IV.B.2. following the CMS coverage analysis.

Question 1-Is the evidence sufficient to conclude that cardiac contractility modulation is reasonable and necessary for the treatment of Medicare beneficiaries with moderate to severe chronic systolic heart failure (EF 25-45%) that remains symptomatic despite guideline-directed medical therapy?

Question 2-Is there evidence that specific characteristics or comorbidities make patients more or less likely to benefit from cardiac contractility modulation?

Question 3-Are specific treatment conditions necessary to achieve cardiac contractility modulation outcomes similar to those demonstrated in the clinical studies reviewed in this analysis?

B. Technology Assessments

CMS did not request an external technology assessment (TA) on this issue. Our review did not identify any Cochrane or Evidence-based Practice Center (EPC) reviews of CCM for HF.

C. Medicare Evidence Development and Coverage Advisory Committee (MEDCAC)

A MEDCAC meeting was not convened on CCM for HF management.

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[1] Access@FDA.gov database Optimizer Smart System Approval History https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?pmanumber=P180036

D. Clinical Literature Search

A systematic literature review focused on CCM for HF management was undertaken to address the evidence questions in Section A above. Literature searches were conducted in PubMed, Scopus, Cochrane, and EMBASE was performed with the following search terms: (1) "cardiac contractility modulation;" (2) "optimizer smart;" or (3) "optimizer smart system." The review included peer-reviewed English-language medical literature from January 1, 2008, to April 9, 2024. Of the references identified in the searches, 22 were deemed eligible for inclusion. An additional 2 studies were included in response to public comments in the initial public comment period. See **Appendix B** for summary tables outlining the characteristics of included studies and study outcomes.

Of the 24 studies included in this review, three were randomized controlled trials (RCTs), one was a single-arm RCT extension study, one was an RCT post-hoc analysis, 18 were observational studies, and one was a meta-analysis. All reports included patient populations with moderate to severe chronic systolic heart failure (EF 25 – 45%). All patients were followed for 6 months – 5 years. The studies examined CCM therapy in patients with a wide range of NYHA, from class I-IV. Importantly, 960 patients were included in the six long-term registry-derived observational studies. See Table 1 for a list of devices used in the studies reviewed and the studies reviewed above for earlier iterations of CCM devices.

Table 1. Optimizer Systems Used by Study

Reference	Optimizer Version	Study	CCM	GDMT	Study type
Abraham et al. 2011	IV	FIX-HF-5	109	97	RCT
Kadish et al. 2011	IV	FIX-HF-5	215	213	RCT
Kuschyk et al. 2015	II or III	-	81	-	Retrospective cohort
Müller et al. 2017	III	CCM-HF	143	-	CCM HF Registry
Abraham et al. 2018	IV	FIX-HF-5C	74	86	RCT
Borggrefe et al. 2008	IV	FIX-CHF-4	80	84	RCT
Röger et al. 2017	III and IV	-	48	-	Prospective cohort
Röger et al. 2018	III and IV	-	20	-	Prospective one-arm
Anker et al. 2019	Smart	CCM-REG	140	-	Prospective registry

Wiegn et al. 2020	Smart	FIX-HF-5C2	60	-	Nonrandomized one-arm
Fastner et al. 2021	Smart	MAINTAINED	174	-	Retrospective registry
Kuschyk et al. 2021	Smart	CCM-REG	503	-	Prospective registry
Matta et al. 2021	Smart	-	10	-	Prospective cohort
Ansari et al. 2022	Smart (CE mark)	-	58	-	Prospective cohort
Fastner et al. 2022	Smart	MAINTAINED	172	-	Retrospective registry
Giallauria et al. 2022	-	-	861	-	Meta-analysis through Jan. 2020
Masarone et al. 2022	Smart	-	25	-	Prospective cohort
Yücel et al. 2022	II, III, IV, or Smart	MAINTAINED	172	-	Retrospective registry
Linde et al. 2022	Smart		47	-	Prospective pilot
Davtyan, et al. 2023	IV (n=3) and Smart (n=8)	NA	11	-	Prospective cohort
Masarone, et al. 2023	Smart	-	30	-	Prospective cohort
Pavlovskaya, et al. 2023	IV (n=51) and Smart (n=8)	-	59	-	Prospective cohort
Tint, et al. 2023	Smart	-	19	-	Prospective cohort
Deak, et al. 2024	Smart	-	31	-	Prospective cohort

Note: The 7 first rows (in gray) are previous versions of CCM devices

Table 2. Controlled trials reviewed to assess CCM (OPTIMIZER Smart System) for moderate to severe chronic systolic HF (EF 25 – 45%) that remains symptomatic despite GDMT

Study			**Patients (CCM; control)**				**24-week Outcomes (CCM; control)**			
Acronym	**Year**	**Type**	**Inclusion**	**(n)**	**Mean Age**	**Male %**	**Δ pVO_2**	**Δ NYHA**	**Δ 6MWT**	**Δ MLWHFQ**

FIX-CHF-4	2008	RCT (crossover)	LVEF ≤35%, NYHA II/III	80; 84	58.9; 59.9	88.8; 81.0	*Between-group difference* **0.52***	No significant between-group difference	No significant between-group difference	*Between-group difference* **2.93***
FIX-HF-5	2011	RCT	LVEF ≤35%, NYHA III/IV	215; 213	58.1; 58.6	73.5; 70.9	*% responder* 17.3; 13.7	*% responder* **49.2; 41.9****	*% responder* 34.2; 29.5	*% responder* **56.1; 41.8****
FIX-HF-5 subgroup analysis	2011	RCT	LVEF ≥25%, NYHA III/IV	109; 97	58.7; 60.3	70.6; 78.4	*% responder* **19.2; 3.95****	*% responder* **44.3; 23.2****	*% responder* 37.1; 25.3	*% responder* **59.4%; 41.7***
FIX-HF-5C	2018	RCT	LVEF 25-45%, NYHA III/IV	68; 86	63.0; 63.0	73.0; 70.1	*Between-group difference* **0.836***	*% responder* **81; 42*****	*Between-group difference* **33.7****	*Between-group difference* **11.7*****
FIX-HF-5C2 (2-lead CCM vs FIX-HF-5C controls)	2020	Single-arm extension	LVEF 25-45%, NYHA III/IV	60	66.3	88.3	*Between-group difference* **1.72*****	*% responder* **83.1; 42.7*****	NR	NR

Legend: 6MWT = 6-minute walk test; CCM = cardiac contractility modulation; LVEF = left ventricular ejection fraction; MLWHFQ = Minnesota Living With Heart Failure Questionnaire; NR = not reported; NYHA = New York Heart Association; pVO_2 = peak oxygen consumption; RCT = randomized control trial.
Only significant results are designated by an asterisk; *p<0.05; **p<0.01; ***p<0.001.
The 4 first rows (in gray) are previous versions of CCM devices reviewed.

E. Assessment of the Evidence

Currently, the Optimizer Smart System is the only device that delivers CCM therapy. Previous versions of the Optimizer device, Optimizer II-IV, were evaluated in these three RCTs and three observational studies, as described below. The RCTs, sub-group analysis of RCT, and single-arm study are discussed here while the observational studies and meta-analysis are reviewed in another section of this document.

The 3 randomized trials were:

- FIX-CHF-4 (Borggrefe et al., 2008)

- FIX-HF-5 (Kadish et al., 2011; *Abraham et al., 2011*)
- FIX-HF-5C (Abraham et al., 2018)

Additionally, there was a subgroup analysis *FIX-HF-5C2* (Single-arm extension of the *FIX-HF-5C;* Wiegn et al., 2020).

Data from *FIX-CHF-4* (Borggrefe et al., 2008) suggest that exercise tolerance and QoL improved when patients received 3-lead CCM therapy applied over a 3-month period in patients with LVEF ≤35%. *FIX-HF-5* (Kadish et al., 2011), a larger trial of CCM compared with optimal medical therapy (OMT) among patients with LVEF ≤35%, did not meet its primary efficacy endpoint (ventilatory anaerobic threshold). A retrospective subgroup analysis of *FIX-HF-5* suggested that patients with LVEF >25% who received the 3-lead CCM therapy had significant improvements in QoL and exercise capacity (Abraham et al., 2011). The authors note that this peak VO_2 (exercise capacity) increase is relevant to improvements typically observed in CRT therapy. Data from *FIX-HF-5C* (Abraham et al., 2018), designed to confirm these results prospectively, also suggested that 3-lead CCM therapy improves QoL and exercise tolerance amongst patients with LVEF 25-45%.

Wiegn et al. (2020) conducted *FIX-HF-5C2* (NCT03339310), a single-arm extension of the *FIX-HF-5C* RCT. Data from *FIX-HF-5C2* indicated statistically significant treatment effects in a similar patient population treated with 2-lead CCM therapy.

Additionally, data from the major trials support the safety of CCM devices. Serious adverse events (SAEs) were seen at similar rates in the CCM and control groups in *FIX-HF-5* and *FIX-HF-5C* (Abraham et al., 2011; Abraham et al., 2018; Kadish et al., 2011). Overall survival and hospitalization rates were similar for the CCM and control group in *FIX-HF-5C* (Abraham et al., 2018). The primary safety endpoint in *FIX-HF-5C2* was device- or procedure-related complications, which decreased the CCM-related complication rate compared to *FIX-HF-5C* (Wiegn et al., 2020).

1. Trial Design

FIX-CHF-4, the first RCT of CCM therapy, was a double-blind, double-crossover study. Subjects were randomly assigned to Group 1 (CCM ON for 3 months, CCM OFF for 3 months) or Group 2 (reversed treatment sequence). The co-primary endpoints were changes in peak VO_2 and Minnesota Living with Heart Failure Questionnaire (Borggrefe et al., 2008).

FIX-HF-5, the first US RCT of CCM therapy, was a prospective, randomized, unblinded, parallel-group, controlled trial comparing a group receiving optimal medical therapy (i.e., GDMT) versus a group receiving GDMT plus CCM (CCM group). *FIX-HF-5* study was initiated as *FIX-CHF-4* neared the end of its recruitment to confirm the safety and efficacy of CCM in a larger patient population. Along with its primary safety endpoint, *FIX-HF-5* had a unique primary efficacy endpoint that required an intention-to-treat (ITT) responder analysis of VO_2 at an anaerobic threshold (Kadish et al., 2011).

FIX-HF-5C (Abraham et al., 2018) was a confirmatory, prospective, multicenter, randomized, controlled, unblinded clinical trial comparing OMT versus OMT plus CCM. Subjects were randomly assigned to one of two treatment groups (CCM or Control) with an allocation ratio of 1:1. A prespecified Bayesian statistical approach was used to leverage data available from *FIX-HF-5* to decrease the number of patients required for the confirmatory study. The Bayesian model incorporated the 160 subjects enrolled in *FIX-HF-5C* and a prior distribution of the treatment effect from the *FIX-HF-5* subgroup. The *FIX-HF-5* subgroup could contribute ≤ 30% weight to the overall assessment, ensuring that the prospective *FIX-HF-5C* data would not be dominated by the prior subgroup data. The primary endpoint was the model-based estimated mean difference in peak VO_2 at 24 weeks between the CCM and Control groups. Secondary efficacy endpoints were tested using non-Bayesian methods.

FIX-HF-5C2 (Wiegn et al., 2020) was a single-arm, treatment-only, confirmatory extension study of subjects in a similar patient population as the FIX-HF-5C study to confirm the efficacy of a 2-lead CCM system. The same Bayesian statistical approach used for the primary analysis of the FIX-HF-5C study was incorporated for the FIX-HF-5C2 extension study, as were the data from the *FIX-HF-5C* study for comparison.

2. Study Population

Baseline patient characteristics were similar across the controlled trials, with a few notable exceptions. *FIX-CHF-4* (Borggrefe et al., 2008) included 164 HF subjects with LVEF ≤ 35% and NYHA class II or III symptoms who were ineligible for CRT. The authors did not specify why subjects were not eligible for CRT. The baseline QRS duration for all subjects was 118 ms. CRT therapy has a class I recommendation for patients with LVEF of ≤ 35% and QRS duration ≥ 150 ms (and left bundle branch block) and a class IIa indication for patients with LVEF < 35%, left bundle branch block, and QRS duration 120 to 149 ms (Heidenreich et al., 2022).

FIX-HF-5 (Kadish et al., 2011) included 428 HF subjects with LVEF ≤35% but who were ineligible for CRT (defined as QRS duration ≤ 130 ms) and NYHA class III or IV symptoms refractory to GDMT.

Similarly, *FIX-HF-5C* (Abraham et al., 2018) included 160 HF patients with QRS duration ≤ 130 ms and NYHA class III or IV symptoms refractory to GDMT but with LVEF between 25% and 45%.

FIX-HF-5C2 (Wiegn et al., 2020) included the same patient population as *FIX-HF-5C*, with the addition of subjects with atrial fibrillation (15% in *FIX-HF-5C2* vs. 0% in *FIX-HF-5C*). The *FIX-HF-5C2* study was conducted with a small sample of 60 patients.

The three RCTs, *FIX-CHF-4* (Borggrefe et al., 2008), *FIX-HF-5* (Abraham et al., 2011; Kadish et al., 2011), and *FIX-HF-5C* (Abraham et al., 2018), enrolled 752 patients, of whom 369 were implanted with the device. The mean age of the patients ranged from 58.1 to 63.0 years, and the percentage of male patients ranged from 70.1% to 88.8%.

It is important to note that the patient populations included in *FIX-CHF-4* and *FIX-HF-5* fall partially outside the patient population currently indicated for CCM therapy in the US (different LVEF range, QRS duration, and functional status).

Table 3. Comparison of baseline patient characteristics in the FIX-CHF-4, FIX-HF-5, FIX-HF-5C and FIX-HF-5C2 trials.

		FIX-CHF-4		**FIX-HF-5**		**FIX-HF-5C**		**FIX-HF-5C2**
		CCM-sham (n=80)	Sham-CCM (n=84)	CCM (n=215)	OMT (n=213)	CCM (n=68)	OMT (n=86)	CCM (n=60)
	Age (yr)	58.9±9.8	59.9±10.0	58.1±12.8	58.6±12.2	63.0±11.0	63.0±11.0	66.3±8.9
	Male (%)	88.8	81.0	73.5	70.9	73.0	70.1	88.3
	QRS (ms)	119.9±28.3	116.3±26.6	101.6±15.3	101.5±12.8	103.0±13.0	103.6±12.1	101.2±12.3
	LVEF (%)	29.3±6.6	29.8±7.8	25.7±6.6	26.1±6.5	33±6	33±5	34.1±6.1
NYHA Class (%)	II	27.5	20.0	0.0	0.47	0.0	0.0	0.0
	III	72.5	80.0	91.2	85.9	86.5	92.7	98.3
	IV	0.0	0.0	8.8	13.6	13.5	9.3	1.7

Legend: CCM = cardiac contractility modulation; LVEF = left ventricular ejection fraction; ms = millisecond; NYHA = New York Heart Association; OMT = optimal medical therapy; yr = year.

3. Background Medical Therapy

Table 4. Baseline rates of GDMT and device implantations in the FIX-CHF-4, FIX-HF-5, FIX-HF-5C, and FIX-HF-5C2 trials.

	FIX-CHF-4		**FIX-HF-5**		**FIX-HF-5C**		**FIX-HF-5C2**
	CCM-sham (n=80)	Sham-CCM (n=84)	CCM (n=215)	OMT (n=213)	CCM (n=68)	OMT (n=86)	CCM (n=60)
ACEi or ARB	NR	NR	91	91	82.4	83.7	75.0

ACEi	72.5	73	71	69	54.1	57.0	48.3
ARB	16	23	24	23	28.4	29.1	13.3
Beta Blocker	77.5	77	94	93	97.3	95.3	95.0
Diuretic	76	81	92	92	75.7	79.1	73.3
Second Diuretic	NR	NR	NR	NR	6.8	9.3	8.3
Ivabradine	NR	NR	NR	NR	2.7	4.7	5.0
Digoxin	39	42	39	46	13.5	9.3	6.7
Aldosterone Inhibitor	41	49	44	48	33.8	37.2	41.7
Hydralazine	NR	NR	NR	NR	5.4	11.6	5.0
Nitrates	NR	NR	NR	NR	24.3	30.2	18.3
Entresto	NR	NR	NR	NR	2.7	3.5	NR
Calcium Channel Blocker	NR	NR	NR	NR	12.2	9.3	NR
Anti-arrhythmic	NR	NR	17	14	17.6	14.0	31.7
Aspirin	NR	NR	NR	NR	73.0	68.6	NR
Coumadin	NR	NR	NR	NR	9.5	5.8	NR
Clopidogrel	NR	NR	NR	NR	20.3	29.1	NR
ICD	67	57	96	95	87.8	84.9	88.3

Legend: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCM = cardiac contractility modulation; ICD = implantable cardioverter defibrillator; NR = not reported; all values reported as %.

4. Intervention Setting

The four clinical trials were conducted in sites across the US and Europe. *FIX-CHF-4* was conducted entirely within Europe, and *FIX-HF-5* took place entirely within the US, while *FIX-HF-5C* and *FIX-HF-5C2* took place at sites across both the US and Europe. CCM systems were implanted and study follow-up visits took place in the hospital (inpatient and outpatient) and Ambulatory Surgery Center (ASC) settings.

5. Outcomes

A change in peak VO_2 was the primary efficacy endpoint for *FIX-CHF-4, FIX-HF-5C,* and *FIX-HF-5C2. FIX-HF-5* had a unique primary efficacy endpoint that required an ITT responder analysis of VAT and considered a change in peak VO_2 to be a secondary efficacy endpoint. Changes in MLWHFQ, 6MWT, and NYHA class were included as secondary efficacy endpoints in all trials except for *FIX-HF-5C2* (*FIX-CHF-4* included MLWHFQ as a co-primary efficacy endpoint). Primary safety outcomes included device-related complications, hospitalization, and mortality across all trials except for FIX-HF-5C2, which had a sole safety endpoint of device-related complications. All four trials had a 24-week follow-up duration for efficacy endpoints. *FIX-HF-5* extended the follow-up period to 50 weeks for safety endpoints.

6. Study Quality

Although all four studies reviewed above were multicenter and there was no evidence of selective outcome reporting, the RCTs were rated as low-quality overall. The main limitations were related to the high risk of bias, which reduced confidence in the strength of the evidence. Device trials typically have inherent restrictions on study design. As a result, sources of bias may affect internal and external validity quality assessments, such as lack of blinding and a lack of sham procedure (in some studies). Further downgrades in study quality were related to statistical imprecision (e.g., lack of any statistical analysis or wide variation around the effect estimate), low event rates, short follow-up duration, and/or small sample size. Below we review each study.

7. Synthesizing the Clinical Trial Evidence

FIX-CHF-4 (Borggrefe et al., 2008), a double-blind, double-crossover trial, was performed in Europe in 164 subjects with LVEF ≤35% and NYHA Class II or III symptoms. Subjects were randomized to CCM ON or CCM OFF for 12 weeks in Phase 1, followed by the opposite treatment for 12 weeks in Phase 2. Peak VO_2 increased similarly for both groups during the first 12 weeks, 0.40 (*SD* =3.0) compared to 0.37 (*SD* = 3.3). During the next 12 weeks, peak VO_2 decreased when CCM was switched OFF (-0.86, *SD* = 3.06) and increased when CCM was switched ON (0.16, *SD* = 2.50). Similarly, MLWHFQ improved in both groups during the first 12 weeks (-12.06, *SD* = 15.33 vs. -9.70, *SD* =16.17), worsened when CCM was switched OFF (+4.70, *SD* =16.57) and improved when CCM was switched ON (-0.70, *SD* =15.13) in the second 12 weeks. The 3-lead CCM therapy for three months led to statistically significant improvements at 24 weeks in peak VO_2 (GDMT vs. CCM, O2/kg/min: M = -0.46, SD = 0.33 vs. M = 0.53, SD =0.45; t = 2.16, p = 0.032), and QoL (GDMT vs. CCM, MLWHFQ: M = -7.4, SD = 2.2 vs. M = -10.4, SD =2.1; t = 2.20, p = 0.030) among patients with LVEF ≤ 35%. Although the difference in peak VO_2 was statistically significant, it failed to meet the 6% criteria for a clinically significant change among patients with HF (3.1% = 0.46/13.9 ml O2/min/kg) at baseline (Corra et al., 2006). The authors noted a significant placebo effect (due to unblinding) may have accounted for similar efficacy results during the first phase. Overall, across both phases, statistically significant improvements were seen in mean VO_2 (p=0.03) and mean MLWHFQ (p=0.03) during CCM ON periods compared to CCM OFF periods. The authors found no significant carryover or period effects. SAEs were comparable between CCM ON and

CCM OFF, with 45 events in 41 patients during CCM ON periods and 48 events in 40 patients during CCM OFF periods. The number of hospitalizations was also similar between periods, with 31 patients hospitalized in each.

*FIX-HF-5 (*Kadish et al., 2011), an unblinded, controlled trial, was performed in the US in 428 subjects with LVEF ≤35% and NYHA Class III or IV symptoms. Subjects were randomized to CCM plus GDMT or GDMT alone. The study did not meet its primary efficacy endpoint, an improvement in ventilatory anaerobic threshold (VAT) at 24 weeks. Both CCM and GDMT treatment arms saw a mean 0.14 mL/kg/min decrease in VAT, and the ITT responder analysis found the difference (17.7% vs. 12.2%) was not significant (p=0.314). However, compared to GDMT, CCM was seen to significantly improve peak VO_2 (p=0.024) and MLWHFQ (p<0.0001) at 24 weeks. Subjects in the CCM arm experienced non-significantly higher rates of all-cause hospitalization and mortality rates (52% vs. 48%, Blackwelder test difference of 3.7% with upper 1-sided 95% CI of 11.7%, which was below the prespecified allowable 12.5%). SAEs were similar between treatment groups, with 341 events in 129 subjects in the CCM arm and 326 events in 115 subjects in the GDMT arm. The most frequent SAEs were general medical issues and worsening HF. Device-related SAEs occurred in 6% of patients, with lead dislodgement reported most frequently.

A multi-regression analysis of *FIX-HF-5* (Abraham et al., 2011) identified NYHA class III and LVEF ≥25% as significant predictors of CCM efficacy. This retrospective analysis examined CCM therapy for the subgroup of patients with ≥ 25% LVEF (CCM: 109; GDMT: 97). Analysis revealed statistically and clinically significant improvements compared to GDMT in peak VO_2 (1.31 mL/kg-1min-1, p = 0.001), VAT (p=0.03), and QoL (MLWHFQ: 10.8 points; p = 0.003). Subsequently, *FIX-HF-5C* was designed to confirm these results prospectively.

FIX-HF-5C (Abraham et al., 2018)*,* an unblinded, controlled trial, was performed in the US and Europe in 160 subjects with LVEF between 25 and 45% and NYHA Class III or IV symptoms. Subjects were randomized to CCM plus GDMT or GDMT alone. The authors employed both a Bayesian and non-Bayesian (frequentist) approach to estimate their primary efficacy endpoint, the between-group differences in mean peak VO_2 at 24 weeks. Bayesian repeated measures linear modeling incorporated prior peak VO_2 data from *FIX-HF-5*, favoring CCM therapy. The model-based estimated mean difference in pVO_2 at 24 weeks between CCM treatment and control groups was 0.84 mL/kg/min, with a 95% Bayesian credible interval (95% BCI) of 0.12-1.55 O2/kg/min. The primary endpoint posterior probability of CCM treatment superiority versus control was 0.989 and was noted to exceed the 0.975 criteria required for statistical significance. Sensitivity analyses showed that CCM maintained superiority after accounting for methods of imputing missing data and site-to-site heterogeneity. However, details were not provided to document the magnitude of this superiority. The frequentist linear mixed model estimate of the mean difference, which does not pull data from *FIX-HF-5,* was 0.79 mL/kg/min (95% confidence interval: -0.10 to 1.68). MLWHFQ (p<0.001), 6MWT (p=0.02), and NYHA class (p<0.001) responder rates were higher with CCM compared to GDMT, although variability around the point estimates for mean changes in 6MWT and MLWHFQ was relatively high. SAEs

occurred in 27% and 22% of the CCM and GDMT groups, respectively, with device malfunction and general medical events reported most frequently in the CCM group and worsening HF and general medical events reported most frequently in the GDMT group. The CCM group had a 90% device- or procedure-related complication-free rate, with lead dislodgement accounting for five out of the seven complications observed. Although overall survival (98%, CCM vs. 95%, GDMT) and hospitalization-free survival (78% vs. 78%) were similar in both treatment arms, survival free from cardiac death and HF-related hospitalization was significantly improved in the CCM treatment arm (97% vs. 89%, p=0.036).

A secondary analysis undertaken as part of the *FIX-HF-5C* study examined treatment effects in patients with LVEF <35% versus LVEF ≥35% by pooling peak VO_2, MLWHFQ, and NYHA functional class data from *FIX-HF-5* and *FIX-HF-5C*. A total of 371 patients were included, of whom 275 were classified as LVEF <35% and 96 as LVEF ≥35%. Subgroup analyses showed positive treatment effects in each efficacy parameter in CCM versus GDMT patients for both LVEF subgroups, with those classified as LVEF ≥35% experiencing greater improvements. While statistical significance was determined for the differences in mean change between CCM versus OMT within each LVEF subgroup, a statistical analysis of the differences between LVEF subgroups was unavailable. The absence of a statistical analysis between LVEF subgroups limits the interpretability of these findings (Abraham et al., 2018).

Additionally, data from the three trials support the safety of the Optimizer IV device. The reported rates of SAEs were similar across the control groups in FIX-HF-5 (GDMT vs. CCM, events/patient-year: 1.505 vs.1.338) and FIX-HF-5C (GDMT vs. CCM, % of patients: 22 vs. 27%) (Abraham et al., 2018; Abraham et al., 2011; Kadish et al., 2011). Survival free of any hospitalization was also similar for the control groups in FIX-HF-5C (GDMT vs. CCM: 78% vs. 78%) (Abraham et al., 2018).

FIX-HF-5C2 (Wiegn et al., 2020), a single-arm, confirmatory extension study, was conducted on 60 subjects with LVEF between 25 and 45% and NYHA Class III or IV symptoms. All subjects received a 2-lead CCM system implant and were compared to control subjects from *FIX-HF-5C*. The studies were all performed with a 3-lead CCM system: one in the right atrium and two in the right ventricle (RV). This imposed a technical limitation on the use of CCM in patients with atrial fibrillation or atrial flutter. A 2-lead CCM device operates with just the two RV leads without requiring an atrial lead. Consistent with the goal of implementing the 2-lead CCM system in subjects with atrial fibrillation, 15% of the *FIX-HF-5C2* subjects (9 patients) had permanent atrial fibrillation (compared to 0% in *FIX-HF-5C*). The Bayesian model-based mean change in peak VO_2 from baseline to 24 weeks, the primary efficacy endpoint, was 1.72 (95% BCI:1.02 to 2.42) greater in the 2-lead CCM group than the control group. In addition, 83.1% of 2-lead subjects compared to 42.7% of controls experienced ≥1 class NYHA improvement (p<0.001). The 2-lead subjects, compared to *FIX-HF-5C* 3-lead CCM subjects, experienced a significant reduction in device-related adverse events (0% vs. 8%, p=0.03).

It is important to note that *FIX-CHF-4* and *FIX-HF-5* address patient cohorts outside the current FDA-labeled CCM therapy indication. While each of the reviewed studies was a critical trial that helped to establish efficacy and safety for CCM therapy, FDA approval of the OPTIMIZER Smart System was primarily supported by the *FIX-HF-5C* confirmatory trial, with data from a subgroup of patients from *FIX-HF-5* borrowed from the Bayesian Analysis of the *FIX-HF-5C2* primary endpoint. It is important to consider the results of the earlier studies in light of the populations specifically studied, given that they differ from the current FDA label.

In summary, the reviewed studies indicate that CCM is safe and may improve exercise tolerance and QoL in patients with HFrEF. In patients with LVEF ranging from 25-45%, QRS duration <130 ms, and NYHA III or IV symptoms despite guideline-directed medical therapy, data indicate CCM may improve peak VO_2, 6MWT, MLWHFQ, and NYHA functional class.

8. Evidence from observational studies, meta-analyses

In addition to the published RCTs and single-arm studies, a series of publications reflect the real-world experience of patients who received CCM for moderate to severe chronic systolic HF that persists despite GDMT. The RCT outcomes are broadly consistent with the observational studies and meta-analyses reviewed here, both in terms of enrolled patients, serious adverse events, and survival outcomes. Because CCM only received FDA market authorization in 2019, much of the published experience with CCM comes from Europe.

a. Controlled Observational Studies

No controlled observational studies met criteria for inclusion in this analysis.

b. Uncontrolled Observational Studies

Nineteen uncontrolled observational studies met the criteria for inclusion in this analysis, six of which were registry-derived. The observational studies are summarized briefly below, with detailed study characteristics and outcomes available in **Appendix B**.

c. Registry Studies

Six observational publications were conducted on three real-world registry studies (*CCM-HF, CCM-REG, MAINTAINED*).

CCM-HF was a multi-site registry enrolling 143 patients across 24 European sites (Müller et al., 2017). This study includes older versions of the current CCM device. Efficacy measures, adverse events, and all-cause mortality were tracked for a 24-month follow-up period. Enrolled subjects in CCM-HF were 76% male with a mean age of 62 (*SD* =12) years. Of the 106 CCM-HF patients who completed a 24-month follow-up, NYHA, MLWHFQ, and LVEF improved significantly across the total cohort and in a subgroup of patients with baseline LVEF <35%. Of the patients who completed a 24-month follow-up, the NYHA (baseline vs. 24 months: M = 2.9, *SD* = 0.5 vs. M = 2.2, *SD* = 0.8; $p < 0.05$), QoL (baseline vs. 24 months, MLWHFQ: M = 45.0, SD = 19.2 vs. M = 31.2, *SD* = 22.5; $p < 0.05$), and LVEF (baseline vs. 24 months, %: M = 28.3, *SD* = 6.4 vs. M

= 34.9, *SD* =8.8; $p < 0.05$) improved significantly across the total cohort. A subgroup of patients with baseline LVEF ≥35% also saw a significant improvement in NYHA class (baseline vs. 24 months, %: M = 26.1, *SD* = 5.0 vs. M = 33.0, *SD* =9.1; $p < 0.05$) and non-significant improvements in LVEF and MLWHFQ. 193 SAEs were observed in 91 subjects, with 32 SAEs in 25 subjects adjudicated as device-related. The overall 2-year survival rate was 86.4% (95% CI; 79.3-91.2), with 18 deaths occurring (7 CV-related, 8 non-CV-related, 3 unknown).

CCM-REG was a prospective registry that enrolled 503 patients across 51 European sites (Kuschyk et al., 2021). Efficacy measures and adverse events were tracked for a 24-month follow-up period, and mortality was tracked for 3 years. Patients were 79.7% male, with a mean age of 66.2 years (*SD* = 10.6). The analysis included three subgroups based on LVEF: 1) < 25%, 2) 26 - 34%, and 3) > 45%, thereby examining the use of CCM therapy in patients who do not meet the criteria specified in the FDA labeling, which requires LVEF in the range of 25 to 45%. The results revealed significant improvements in MLWHFQ, LVEF, and NYHA at 24 months for the entire cohort and each subgroup ($p < 0.0001$). Similarly, compared to the 12 months pre-treatment, the cardiovascular-related hospitalization rate improved significantly (1-year pre vs. 2-years post: 1.04 events/patient-year vs. 0.39 events/patient-year, $p < 0.0001$), with similar reductions in the hospitalization rate across the three LVEF subgroups. The overall 3-year survival curve was also significantly better than that predicted by the MAGGIC risk score ($p = 0.0244$) and for the LVEF subgroups, except for the subgroup with the worst symptoms, LVEF < 25% (Kuschyk et al., 2021).

CCM-REG has resulted in another study examining a smaller cohort of patients (n=140) with indications matching FDA labeling (Anker et al., 2019). In this study, NYHA and MLWHFQ improved significantly ($p < 0.001$) and progressively over 24 months of follow-up, suggesting that the likelihood of a placebo effect decreased with time (Anker et al., 2022). At the three-year follow-up, 201 SAEs were observed in 82 subjects, with 10 SAEs in 10 subjects adjudicated as device related. Compared to the 12 months pre-treatment, cardiovascular-related hospitalization rate improved significantly (1-year pre vs. 2-years post: 1.2/patient-year vs. 0.35/patient-year, $p < 0.0001$). However, the overall 3-year survival rate was similar to the prediction of the Seattle Heart Failure Model (actual survival vs. prediction: 82.8% vs. 76.7%; $p = 0.16$).

The *MAINTAINED* registry, which resulted in 3 separate subgroup analysis publications, retrospectively enrolled 174 patients in Germany (Fastner et al., 2021; Fastner et al., 2022; Yücel et al., 2022). The registry included efficacy and safety data across a five-year period. Patients enrolled in the registry were 84% male with a mean age of 63 (*SD* =12) years (Fastner et al., 2021). Efficacy parameters included changes in NYHA, LVEF, tricuspid annular plane systolic excursion (TAPSE), NT-proBNP, Kidney Disease Improving Global Outcomes Chronic Kidney Disease (KDIGO CKD) stage, and MLWHFQ. Safety parameters included SAEs, hospitalizations, and mortality. Outcomes were compared for the following subgroups: (1) NYHA class II vs. class III/IV (Fastner et al., 2022), (2) ischemic (ICM) vs. non-ischemic cardiomyopathy (NICM) (Fastner et al., 2021), and (3) baseline LVEF ≤30% vs. LVEF >30% (Yucel et al., 2022).

In Fastner et al. (2022), with patients in NYHA class II (10%) vs. class III/IV, a statistically significant between-group difference was only found in class III/IV patients related to improvement in the NYHA class over 5 years of CCM. The difference suggested a greater improvement for patients with worse symptoms (II: $M = 0.1$, $SD = 0.6$; $p = 0.96$ vs. III/IV: $M = -0.6$, $SD = 0.6$; $p < 0.0001$).

Fastner et al. (2021) examined ICM versus NICM and reported a statistically significant between-group difference was found for improvement in both LVEF (ICM: $M = 29$, $SD = 8$ vs. NICM: $M = 38$, $SD = 15$; p=0.009) and TAPSE (ICM: $M = 18$, $SD = 5$ vs. NICM: $M = 21$, $SD = 5$; p=0.044), favoring the NICM group (Fastner et al., 2021).

Similarly, in a comparison of LVEF subgroups (Yucel et al., 2022), a statistically significant between-group difference was found for improvement in LVEF (LVEF≤30%: $M = 32.1$, $SD = 11.8$ vs. LVEF >30%: $M = 41.4$, $SD = 13.1$; p<0.01), favoring the LVEF ≤30%. Like the study of NYHA subgroups (Fastner et al., 2022), a greater improvement was found for patients with worse symptoms.

No further between-group efficacy or safety comparisons were found to be statistically significant in any of the *MAINTAINED* registry studies. Although between-group statistical comparisons were not conducted, the observed 3-year survival rates were significantly better in the LVEF ≤30%, ICM, and NYHA III/IV subgroups compared to the MAGGIC risk score predictions (Fastner et al., 2022; Fastner et al., 2021; Yucel et al., 2022).

d. Single-Arm Studies

In addition to the registry studies, 10 single-arm studies were published in Europe (five in Germany, one in Russia and three in Italy) evaluating CCM for moderate to severe systolic heart failure (Ansari et al., 2022; Kuschyk et al., 2015; Linde et al., 2022; Masarone, Kittleson, De Vivo, D'Onofrio, Ammendola, et al., 2022; Masarone, Kittleson, De Vivo, D'Onofrio, Rao, et al., 2022; Matta et al., 2021; Pavlovskaya et al., 2023; Röger et al., 2017; Röger et al., 2018; Deak et al., 2024). These studies each enrolled 10-81 patients, with mean follow-up periods ranging from 6 months to 3 years.

Kuschyk et al. (2015) reported a single-site, retrospective cohort analysis (n=81) of subjects with HFrEF treated with CCM in Germany, with a mean follow-up period of 34.2, $SD = 28$ (6-123) months. This study includes older versions of the current CCM device. Enrolled subjects were 85.2% male with a mean age of 61 (SD =12) years. Long-term follow-up data indicated that CCM resulted in significant improvement in NYHA (baseline to follow-up: M = 3.0, $SD = 0.5$ to M = 2.3, $SD = 0.9$), LVEF (M = 23.1, $SD = 7.9$ to M = 29.4, $SD = 8.6$), MLWHFQ (baseline to follow-up: M = 49.9, $SD = 17.7$ to M = 32.2, SD 18.2), and N-terminal pro-brain natriuretic peptide (baseline to follow-up, ng/l: M = 4395, $SD = 3818$ to M = 2762, $SD = 3490$) (all $p < 0.05$), while increases in mean peak VO_2 were not statistically significant. The overall observed mortality rate, compared with that predicted by MAGGIC score, was significantly improved at 1

year (18.2% vs. 5.2%, p<0.001) but similar to predicted at 3 years. The authors further reported that 4 patients required lead replacement, 1 required device removal for infection, and 2 required device replacement because of malfunction. The overall device-related SAE rate was reported as "no higher" than that reported in *FIX-HF-5*.

Masarone and colleagues also reported a small, prospective, single-arm, single-site study (n=25) of CCM therapy for HFrEF in Italy that evaluated whether CCM therapy can improve myocardial mechano-energetic efficiency (MEE) and global longitudinal strain (GLS) (Masarone, Kittleson, De Vivo, D'Onofrio, Ammendola, et al., 2022). Enrolled subjects were 88% male with a mean age of 63 years (*SD* = 10). This study evaluated if CCM therapy can improve myocardial mechano-energetic efficiency (MEE) and global longitudinal strain (GLS). At six-months, significant echocardiographic improvements in mean LVEF (*M* = 30.8, *SD* = 7.1% vs. M = 36.1, *SD* =6.9%; *p* = 0.032), MEE (mL: *M* = 32.2, *SD* = 10.1 vs. M = 38.6, *SD* =7.6; p=0.013) and GLS (*M* = 10.3, *SD* = 2.7 vs. M = -12.9, *SD* =4.2; p=0.018) were reported. Significant improvements in NYHA (*M* = 3.1, *SD* = 0.62 vs. M = 2.3, *SD* =0.56; p=0.0001), MLWHFQ (*M* = 40.08, *SD* = 12.31 vs. M = 26.9, *SD* =10.8; p=0.0001), and NT-proBNP (*M* = 2975, *SD* = 1988 vs. M = 1911, *SD* = 1268; p=0.029) were also observed. This study did not report any data regarding safety or mortality outcomes.

In a separate study, Masarone et al. reported a second small, prospective study (n=30) of CCM therapy among patients with HFrEF in Italy (Masarone, Kittleson, De Vivo, D'Onofrio, Rao, et al., 2022). The study evaluated the effect of trans-tricuspid lead implantation on the severity of tricuspid regurgitation (TR) in patients who had previously undergone ICD implantation. The mean age of the patients was 59.5 years (*SD* = 12.9), and 83.4% were male. At the six-month follow-up, the outcomes assessed were right ventricular outflow tract proximal diameter (RVOT proximal), right ventricular outflow tract distal (RVOT distal), right ventricular basal dimension (RVD1), right ventricular mid-cavity dimension (RVD2), right ventricular longitudinal dimension (RVD3), TAPSE, peak systolic of the free wall of the RV (S wave), pulmonary artery systolic pressure (PASP), pulmonary artery mean pressure (PAMP), and pulmonary capillary wedge pressure (PCWP). There were significant differences between the baseline and six-month follow-up in all outcomes (all *p*s < 0.0001). As a result, the authors concluded that the implantation of right ventricular electrodes for the delivery of CCM therapy did not worsen TR.

Matta et al. (2021) reported the results of a small, prospective, single-arm, single-site study (n=10) of CCM therapy in subjects with LVEF ≤45% in Italy. Enrolled subjects were 100% male with a mean age of 70 (*SD* = 8) years. After a mean follow-up period of 15 months, significant improvements were seen in the NYHA class (*M* = 3.0, *SD* = 0.4 to *M* = 1.6, *SD* 0.5; *p* = 0.003), six-minute walk test (6MWT) (*M* = 179, *SD* = 73 to *M* = 304, *SD* = 99; p<0.001), and MLWHFQ (*M* = 59.6, *SD* = 49 to *M* = 34.2, *SD* = 32; p=0.037). The LVEF improved non-significantly (*M* = 29.4, *SD* = 8% to *M* = 32.2, *SD* = 10%; 0.092). No device-related complications were reported during the follow-up period, but 1 death occurred due to worsening HF in a subject with a baseline LVEF of 14%.

Röger et al. (2017) and associates conducted a study to demonstrate that CCM delivery through one ventricular lead would not be inferior (efficacy and adverse effects) to delivery through two ventricular leads. The study did not include a comparator control group with no device implanted. In this prospective blinded randomized trial, 48 patients were enrolled. Eligible subjects had symptoms despite optimal HF medications, left ventricular ejection fraction < 40%, peak $VO_2 \geq 9$ ml O_2/kg/min. All patients received a CCM system with two ventricular leads and were randomized to CCM active through both or just one ventricular lead; 25 patients were randomized to receive signal delivery through two leads (Group A) and 23 patients to signal delivery through one lead (Group B). The study compared the mean changes from baseline to 6 months follow-up in peak VO_2, New York Heart Association (NYHA) functional classification, and quality of life (by MLWHFQ). The study found similar and statistically significant improvements from baseline in NYHA functional classification (-0.7 $\pm$ 0.5 vs. - 0.9 $\pm$ 0.7), as well as MLWHFQ (-14 $\pm$ 20 vs. -16 $\pm$22) were observed in Group A and Group B. Peak VO_2 showed improvement trends in both groups (0.34 $\pm$ 1.52 vs. 0.10 $\pm$ 2.21 ml/kg/min), though not statistically significant. No deaths occurred in either group, nor serious adverse events between the two groups. Between the groups there were no statistically significant difference in any of the study endpoints. The study was able to show that CCM delivery through one ventricular lead was not inferior to delivery through two ventricular leads.

Röger et al. (2018) reported a small, prospective, single-arm, single-site study (n=20) of combined CCM and subcutaneous ICD (S-ICD) therapy in subjects with HFrEF in Germany. This study includes older versions of the current CCM device. Enrolled subjects were 90% male with a mean age of 54.3 (*SD* = 11.5) years. Patients received intraoperative crosstalk testing, S-ICD testing, and bicycle exercise testing while CCM was activated to exclude device interference. S-ICD performance was evaluated with both the CCM and S-ICD were active. The mean follow-up period was 34.3 months, and the mean follow-up time with both active devices was 22 months. Significant improvements were reported in NYHA (baseline to follow-up: M = 2.9, *SD* = 0.4 to M = 2.1, *SD* = 0.7; p<0.0001), MLWHFQ (baseline to follow-up: M = 50.2, *SD* = 23.7 to M = 29.6, *SD* = 22.8; p<0.0001), and LVEF (baseline to follow-up: M = 24.4%, *SD* = 8.1% to M = 30.9%, *SD* = 9.6%; p=0.002). Three patients received a total of 6 appropriate S-ICD shocks for sustained ventricular tachycardia, and 1 patient received 1 inappropriate S-ICD shock for non-sustained ventricular tachycardia. One patient had the CCM and S-ICD device switched off after receiving a left ventricular assist device due to progressive HF. That patient subsequently died of postoperative complications.

Although outside of the scope of this literature review, 1 additional single-arm pilot study in Germany was identified that evaluated CCM therapy in 47 subjects with LVEF ≥50% (Linde et al., 2022). Enrolled patients were 29.8% male, with a mean age of 74.3 (*SD* = 4.4 years). While efficacy data from this study is not directly applicable to patient cohorts that match current FDA labeling indications, the safety data contributes to a growing body of evidence regarding the overall safety of CCM therapy. There were 3 patients with reported procedure-related complications (2 lead dislodgments and 1 worsening tricuspid regurgitation, which resolved after

lead removal). Over 24 weeks of follow-up, there were no deaths or device-related SAEs reported.

Pavlovskaya et al. (2023) conducted a prospective study and examined CCM therapy in 59 patients with HFrEF and NYHA II/III for a mean follow-up period of 1916 days (*SD* =102). The average age of the patients was 52.3 years (*SD* =10.4), and 83% were male. A total of 51 patients were implanted with Optimizer IV, and 8 were implanted with the Optimizer Smart System. All-cause mortality and heart transplantation were considered as the primary composite endpoint. The secondary composite endpoint included all-cause mortality, heart transplantation, ICD shocks due to ventricular tachyarrhythmia, and hospitalizations due to decompensated HF. The three- and five-year survival rates were 79.7% and 66.1%, respectively, significantly higher than those predicted by MAGGIC ($p = 0.02$) and SHFM ($p = 0.01$). The annual mortality was 7%. The number of hospitalized patients due to HF decompensated significantly declined compared with the six months pre-implantation ($p < 0.001$).

Ansari et al. (2022) evaluated CCM therapy in a small cohort study of 58 patients in Germany to determine if septal myocardial scar burden predicts the response to CCM. The median age of the patients was 57 years (range: 28-81), and 50 (16.2%) of the patients were male. All patients had LVEF < 40% and NYHA class of I-IV. Outcomes assessed included QoL, NYHVA class, LVEF, NT-pro BNP, TAPSE, and mortality. At the one-year follow-up, patients were classified as responders if they had an improvement in NYHA of one or more classes (67%) or LVEF of 5% or more (55%). Overall, 74% of patients met at least one of the two criteria. Septal late gadolinium enhancement (LGE) was < 25% at the septal position of the leads in over 90% of the responder group, while 44% of the non-responder group had septal LGE > 25% ($p < 0.01$). The change was similar between the two groups for QoL (responders vs. non-responders, MLWHFQ: $M = -11.3$, $SD = 16.5$ vs. $M = -19.5$, $SD = 18.6$; $p = 0.20$) and NT-pro BNP (responders vs. non-responders, pg/mL: $M = -1995$, $SD = 2921$ vs. $M = 68.4$, $SD = 4170$; $p = 0.06$). However, there was a significant difference in TAPSE between responders and non-responders (mm: $M = 2.1$, $SD = 2.4$ vs. $M = 0.2$, $SD = 1.4$; $p < 0.01$, respectively).

Deak et al. (2024) conducted a mid-term clinical and functional assessment of CCM recipients in an urban population with heart failure. This single-arm, pre-test post-test study was conducted at a university setting. Participants included 31 HF patients with NYHA class III symptoms and EF 25‑45%. NYHA class, hospitalizations, EF, and weight were the outcomes of interest. The mean age and follow-up time was 63 $\pm$ 10 years and 1.4 $\pm$ 0.8 years, respectively. Most patients were Black, nearly half were women, half had NICM ($n = 15$), one with hypertrophic cardiomyopathy, the rest with idiopathic cardiomyopathy), and 68% had carried the diagnosis of cardiomyopathy for > 3 years. The study revealed that for this urban population, there was a statistically significant reduction in mean annualized hospitalizations compared to pre-CCM implantation (0.8 $\pm$ 0.8 versus 0.4 ≒ 1.0; p = 0.048). All patients had an improvement in NYHA functional classification (0.97; $p < 0.001$), and 29% experienced greater than one functional class improvement. Mean EF improved by 8% ($p = 0.002$), and mean weight change was 8.5 pounds lost, amounting to 4% of body weight ($p = 0.002$).

e. Post-CRT Studies

The two final studies investigated the use of CCM therapy in patients with HFrEF who had previously undergone CRT. Tint et al. (2023) conducted a prospective trial of patients with symptomatic HFrEF, NYHA Class III-IV, and LVEF≤ 35% who were implanted with a CCM device. The study included twenty patients (19 men) with a mean age of 66.5 years (*SD* = 6.9 years). The mean follow-up period was 321.7 days (*SD* = 113.5). Patients with atrial fibrillation and diabetes mellitus were included, and 60% of the patients had LVEF ≤25%. The cause of HF was ischemic in 80% of patients, while 45% had atrial fibrillation and 30% had diabetes mellitus. All patients had an ICD, and six (30%) had CRT. The pharmacological treatment had been optimized in all patients. The outcomes assessed were LVEF, NYHA, and exercise tolerance. All three outcome measures were significantly improved at the one-year follow-up: LVEF (baseline vs. 1-year follow-up: $M = 24.68\%$, $SD = 4.5\%$ vs. $M = 34.6\%$, $SD = 5\%$; $p < 0.0001$), NYHA (baseline vs. 1-year follow-up, class: $M = 3.2$, $SD = 0.5$ vs. $M = 1.4$, $SD = 0.5$; $p < 0.0001$), and the 6MWT (baseline vs. 1-year follow-up, m: $M = 307.9$, $SD = 74.1$ vs. $M = 567$, $SD = 99.5$; $p < 0.0001$). Most of the improvements occurred in the first six months. The authors also claimed fewer device-related problems in this study than in *FIX-HF-5C2*.

Davtyan et al. (2023) reported no clinical or functional improvements in a retrospective analysis of 11 patients in Russia. Patients were HFrEF, LVEF II-IV, left bundle branch block (LBBB), and a wide QRS complex. The median age was 61.5 years, and 8 patients were male. Ten patients had an implanted CRT at the time of inclusion. The primary study goal was to evaluate the interaction between implanted CCM and CRT systems. Two patients were implanted with the previous version of the Optimizer, Optimizer IV, while the remaining patients were implanted with the Optimizer Smart System. In five patients, the signal detection was optimized by lead relocation, and in six patients, signal sensitivity limitations were resolved by programming. All devices were successfully implanted, and no episodes of CCM recording interpreted as ventricular rhythm disturbances were recorded during checks of implanted CRT. At the one-year follow-up, there was a non-significant improvement in 6MWT (baseline vs. 12 months, meters: 300 vs. 305, $p = 0.093$), NYHA class (baseline vs. 12 months: 2.75 vs. 2, $p = 0.085$), MLWHFQ score (baseline vs. 12 months: 53 vs. 42, $p = 0.109$) and LVEF (baseline vs. 12 months: 30% vs. 33.5%, $p = 0.212$). At the two-year follow-up, four patients had died of non-cardiac causes.

f. Meta-Analyses

One meta-analysis was reviewed, with considerable overlap between it and the studies already included in this review. This meta-analysis was well designed, had pre-specified criteria, followed a methodological approach, and offered the benefits of pooled data and a systematic assessment of CCM studies.

Giallauria et al. (2020) reported results from a comprehensive meta-analysis of individual patient data (n = 861) from all known randomized CCM vs. control trials that measured functional capacity and/or QoL in patients with HF. Individual patient data from *FIX-HF-5C2* was also included in the meta-analysis. The pooled analysis showed that CCM significantly improved

peak VO_2 ($p < 0.00001$), 6MWT ($p = 0.005$), and MLWHFQ ($p < 0.00001$) compared with GDMT. A sub-group analysis of patient who were implanted with CCM revealed differences by gender, as significant 6MWT improvements were noted in men ($p = 0.003$), but not women ($p = 0.57$). Similarly, those CCM patients across the four included studies that had a nonischemic etiology saw no improvement in walking distance (mean difference: 4.87), while those with an ischemic etiology did demonstrate a 21.32 mean difference ($p = 0.002$). In the sub-group analysis, nonischemic patients were also found to have no improvement in QoL ($p = 0.19$) as measured by the MLWHFQ, but ischemic etiology patients did experience a significant change in QoL ($p < 0.00001$). The pooled analysis findings were consistent with those reported in the analyzed trials. The authors reported that this meta-analysis found that CCM was safe, with no increase or reduction in hospitalizations or mortality in any analyzed trials.

Outcomes for all observational studies are outlined in **Appendix B, Table B2**.

9. Limitations of Evidence

The evidence base has several important limitations:

- With the exception of the Abraham 2018 study, all other RCT clinical trials were designed to last 24 weeks (the Abraham study lasted 50 weeks). Observational studies and registries varied in duration from 320 days to 5 years.

- The use of a cross-over design might introduce a placebo effect. Though the study by Borggrefe was double blinded, the fact that participants know that they will get the intervention of interest could bias the results of the study. Given the high risk of bias inherent in unblinded studies, CCM studies should pre-specify both subjective (e.g., QoL, functional outcomes) and objective (e.g., heart failure hospitalization, heart failure hospitalization or heart failure hospitalization equivalent events, total hospitalizations, survival) outcome criteria.

- One study (Röger 2017) was designed to determine if a one-lead CCM device was inferior to a two-lead CCM device in terms of benefits to patients with HF. The study showed that the one-lead CCM device was not inferior to the two-lead CCM device. There was only one study testing the benefits of one-lead CCM devices. More evidence is needed to determine the effectiveness of one-lead CCM devices.

- Previous versions of the Optimizer device, Optimizer II-IV, were evaluated in only three RCTs and three observational studies.

- It was unclear from the evidence if specific treatment conditions are necessary to achieve the functional, QoL, and mortality outcomes demonstrated in the reviewed clinical studies.

- The observational studies provide real-world evidence and offer a more complete understanding of CCM therapy in a less stringent setting than clinical trials. Patients were also followed for substantially longer than 6 months, as was done in the RCTs that examined previous versions of the Optimizer Smart System. The following limitations of the observational data made it difficult to have a high degree of confidence in the findings:
    - Lack of a comparator group in all but one study
    - Apart from the registry studies, the studies were small, and many were single-site
    - Lack of data on procedural experience across sites and variable SAEs

In addition to the above limitations of the reviewed studies, other evidentiary gaps raised in the literature include:

- Study cohorts are relatively young compared to the Medicare population and predominantly male. Additional data is needed on CCM therapy for older individuals and women.
- Patients with permanent atrial fibrillation (AF) were initially excluded because the original 3-lead CCM device required detecting 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 some studies included patients with AF, but the number of such patients was small.
- As noted earlier, Black patients not only have a higher incidence of HF than other racial groups, but they also have higher admissions for HFrEF and worse overall survival (Lewsey & Breathett, 2021; Miller et al., 2021). Despite these statistics, these minorities were underrepresented in the reviewed RCTs of CCM for the treatment of HFrEF. *FIX-HF-5, FIX-HF-5C,* and *FIX-HF-5C2* each enrolled ≥ 66% White subjects. *FIX-CHF-4*, which was conducted outside of the US, did not report the racial/ethnic characteristics of enrolled subjects.

F. Evidence-Based Guidelines

The 2021 guideline issued by the European Society of Cardiology (ESC) indicated that CCM therapy was associated with a small improvement in exercise tolerance and QoL (McDonagh et al., 2022) in patients with NYHA class III-IV HF, an LVEF ≥ 25% to ≤ 45%, and QRS duration <130 ms for whom the device is indicated. However, the current evidence was insufficient to support a guideline recommendation of CCM therapy for reduced mortality or hospitalization. The ESC also specifically indicated that one of the evidence gaps in the treatment of individuals with HF, with regard to devices and interventions, is the need for larger RCTs of CCM.

The 2022 guideline of the American Heart Association (AHA)/ American College of Cardiology Foundation (ACC)/ Heart Failure Society of America (HFSA) for the management of HF indicated that CCM is FDA-approved for patients with NYHA class III and LVEF of 25% to 45% who are not candidates for CRT (Heidenreich et al., 2022). Although CCM is associated

with the augmentation of LV contractile performance and multiple RCTs have shown benefits in exercise capacity and QoL, there is no evidence of benefits in death or hospitalizations

G. Professional Society Recommendations / Consensus Statements / Other Expert Opinion

Rao et al. provided an expert opinion on CCM (Rao & Burkhoff, 2021). The authors indicated that in the next 5 years of advances in HF, CCM eligibility is expected to expand to include patients with EF 25–60% and CCM devices that incorporate therapies such as defibrillation and CRT in a single device. The Society for Cardiovascular Angiography and Intervention (SCAI) stated that CCM represents a unique device-based therapy for patients with HF and that robust evidence suggests improved QoL and functional status with CCM. They acknowledge that future trials are needed to confirm benefits on mortality, hospitalization, and the use of CCM in patients with HFpEF. As they note, CCM should be considered in patients with HFrEF and HFmrEF who have a narrow QRS complex and are symptomatic despite OMT.

H. Appropriate Use Criteria

An Appropriate Use Criteria for Implantable Cardioverter-Defibrillators, Cardiac Resynchronization Therapy, and Pacing was developed and published in 2025 by ACC/AHA/ASE/HFSA/HRS/SCAI/ SCCT/SCMR. The authors acknowledge that CCM has emerged as a promising treatment for patients with chronic HFrEF who are not indicated for CRT (Russo et al., 2025). Although the "2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure" acknowledges that CCM has been associated with augmentation of LV contractile performance, specific recommendations have not yet been included in their guideline. Similarly, the "2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure" acknowledged a small improvement in exercise tolerance and QoL with CCM in patients with NYHA functional class III to IV HF, with an LVEF >25% to < 45%, and a QRS interval of < 130 ms, but no specific guideline recommendations were listed.

I. Public Comments

First Comment Period: January 10, 2025 – February 9, 2025

During the first 30-day public comment period CMS received 15 timely comments. Fourteen commenters supported coverage of CCM, either in general terms or specifically supporting CED. One comment was unclear as it did not address the topic of CCM. All comments that were submitted during the comment period without personal health information may be viewed by using the following link: https://www.cms.gov/medicare-coverage-database/view/ncacal-public-comments.aspx?NCAId=317&ExpandComments=n.

Several commenters included references for evidence in response to the tracking sheet. Several physician/professional commenters who have utilized CCM among their patients and/or studied its effects provided anecdotes about treatment using CCM. Three consumers submitted comments; two supported coverage of CCM, the third commenter did not address CCM. One comment was received from the CCM medical technology manufacturer, Impulse Dynamics. Two comments were received from professional associations, including one from the American

Association of Heart Failure Nurses, and a joint comment from American College of Cardiology, Heart Failure Society of America, and Heart Rhythm Society. One comment was received from the trade association, AdvaMed.

Second Comment Period: July 10, 2025- August 9, 2025

During the second 30-day public comment period CMS received 8 pertinent comments posted to the CMS website. Similar to the initial public comment period, the majority of commenters wrote positively of the use of CCM and the proposed coverage through CED. One commenter did not support coverage of CCM because of limited evidence. All comments submitted during the comment period without personal health information may be viewed by using the following link: https://www.cms.gov/medicare-coverage-database/view/ncacal-public-comments.aspx?ncaid=317&doctype=all&timeframe=60&sortBy=updated&bc=2.

We received one comment from a patient advocate. We received one comment from Cleveland Clinic. We received one comment from medical technology manufacturer, Impulse Dynamics. Two comments were from industry organizations, the Advanced Medical Technology Association (AdvaMed) and Medical Device Manufacturers Association (MDMA). We received one joint comment from professional associations, American College of Cardiology (ACC), Heart Failure Society of America (HFSA) and Heart Rhythm Society (HRS). One comment was from the University of California San Francisco (UCSF) Team for High-Value Care. One comment was from an insurer, Blue Cross Blue Shield of Michigan.

1. Support for Medicare Coverage for CCM

Comment: The majority of commenters expressed support for coverage of CCM through CED, support for the proposed coverage criteria, and inclusion of CCM as a TCET pilot.

Response: We thank commenters for their support.

2. Non-Coverage for CCM

Comment: One commenter recommended noncoverage of CCM, due to a lack of evidentiary support to reach CED.

Response: We recognize the concerns the commenter raised. While we agree that there are evidence gaps that need to be addressed regarding CCM, the evidence overall is promising enough to allow coverage with evidence development (CED). As discussed in the analysis, several RCTs and registries showed HF patients with CCM had positive outcomes compared to HF patients without CCM. We agree there are evidence gaps regarding the overall effect on mortality, HF hospitalizations, and outcomes over longer durations. The final NCD includes CED study criteria that balance evidence generation and patient access.

3. Patient Criteria

Comment: A few commenters noted they had no additional recommendations for patient criteria. One commenter acknowledged that the patient criteria added by CMS beyond what was included in the FDA labeling align with best practices in clinical care. This commenter further stated that the proposed minimum interval of optimized GDMT and exclusion of prior heart transplant patients are appropriate and highly relevant as they ensure that only patients who have been adequately managed and are truly in need of the intervention are selected.

Response: We thank commenters for their support, and we are finalizing the patient criteria as proposed.

Comment: One commenter recommended adding several inclusion criteria, such as a diagnosis of HFrEF with NYHA class III, persistent symptoms despite stable GDMT for 90 days or more, in normal sinus rhythm, and not eligible for CRT.

Response: We note that these criteria were already included in the proposed Section I.B.1 Patient Criteria, through the requirement that patients must meet the FDA market-authorized indications. We do not believe that the NCD criteria need to duplicate listing all of the FDA labeling criteria and exclusions. We note that the current FDA labeling uses the term "are not receiving" Cardiac Resynchronization Therapy (CRT), instead of the term "lack of eligibility for" CRT.

Comment: One commentor recommended adding several exclusion criteria, such as myocardial infarction or coronary revascularization within 3 months, candidacy for CRT, permanent atrial fibrilization, life expectancy of less than one year due to noncardiac causes, and pregnancy or lactation.

Response: These exclusions are not included in the currently available FDA labeling. The patient's heart team should consider these factors for each patient. Up to 30-40% of conventional CRT patients do not respond to treatment (Leclerca et al. 2023). Some of these patients, if they meet the FDA label indications, may benefit from CCM (Kuschyk et al. 2019; Nagele et al. 2021; Fastner et al. 2008)

Comment: One commenter recommended CMS emphasize that patients should be receiving maximally tolerated GDMT before implantation, because CCM should only be considered after optimized GDMT, and should not be considered a substitute for GDMT. The commenter noted that clinical trials demonstrating the efficacy of CCM were conducted in the context of maximal GDMT, underscoring its role as a subsequent option.

Response: We agree with the commenter that CCM is a treatment that should only be considered for patients who remain symptomatic despite GDMT. We are finalizing the Section I.B.1 Patient Criteria as proposed, which includes the requirement for patients to remain symptomatic despite at least 3 months of optimized GDMT as determined by the heart team prior to CCM implantation.

As noted at the end of the acronym list in this document, the term Guideline-Directed Medical Therapy (GDMT) is used interchangeably with the term Optimal Medical Therapy (OMT). In this assessment, many articles used the term GDMT, just as many other articles used the term OMT. We used the term "optimized GDMT" in describing patient eligibility criteria for CCM CED. We note the literature frequently refers to "optimizing" care or "optimal" therapy or optimal management, and we believe the terms "maximally tolerated GDMT", "Optimal Medical Therapy" and "optimized GDMT" or "optimal GDMT" are interchangeable.

4. Physician/Facility Criteria

Comment: One commenter asked CMS to clarify that any qualified member of the cardiology care team may assess and manage GDMT prior to CCM implantation, and that any provider should be permitted to refer a patient to the cardiology care team for evaluation.

Response: We are finalizing the NCD without adding specific requirements and definitions for physician/ facility criteria. We believe it is important to provide flexibility for the heart teams to consult other specialists as clinically appropriate for each patient. Rather than specifying which practitioners should be involved in the procedures, we have amended the CED requirement regarding the care management plan to incorporate language that was initially included in the analysis section of the proposed NCA. The final NCD has been updated to reflect that a care management plan must identify "members, roles, and responsibilities of the clinical team that performs the follow-up CCM patient management." As we stated in the analysis for this CED requirement, patients should be under the care of a team who, together, can ensure that HF patients are appropriately managed before CCM, are appropriately selected for CCM and are appropriately managed post-procedure.

We believe that qualified members of the heart team who have been involved in the patient's management may assess and manage GDMT to reach optimization prior to CCM implantation. We note that specific decisions regarding optimized GDMT are often guided by cardiologists with training and expertise in HF management. CMS has not placed a restriction on who can refer a patient to the heart team for evaluation.

Comment: One commenter recommended that electrophysiology (EP) specialists be explicitly recognized in physician criteria for CCM delivery.

Response: We believe that consultation with an electrophysiologist may be appropriate in specific cases but should not be required for every procedure.

Comment: One commenter recommended that CMS establish minimum training and proctoring requirements for implanting physicians.

Response: We are finalizing the NCD without establishing specific training or proctoring requirements. We expect that physicians involved in the procedure would have device specific training as required by the manufacturers.

Comment: One commenter recommended that CMS limit coverage to CCM procedures performed at centers with heart failure specialty services.

Response: We disagree. The evidence base does not provide conclusive evidence in support of establishing specific institutional criteria. Additionally, as other commenters noted, there are a limited number of board-certified advanced HF specialists nationwide. Therefore, we believe adding facility criteria could hamper patient access, particularly in rural areas or areas with fewer board-certified HF specialists.

5. CED Criteria for CCM

Registry

Comment: One commenter recommended CMS require enrollment in a national registry for CCM data collection, and another commenter encouraged CMS to support the use of national, audited registries maintained by professional societies.

Response: We appreciate these comments. The purpose of CED is to address the evidence gaps detailed in the analysis section of this document. We note that data from the MAINTAINED Registries (Fastner et al. 2021; Fastner et al. 2022; Yucel et al. 2022); the CCM-HF Registry (Muller et al. 2017) and the CCM-REG Registries (Kuschyk et al. 2021; Anker et al. 2019), were assessed and used as part of this NCA. The final NCD criteria do not preclude coverage of a registry-based study of CCM if that study satisfies the requirements of the NCD and the study protocol has been reviewed and approved by CMS.

Outcomes

Comment: One commenter recommended that the CED study requirements include all-cause mortality as a singular primary outcome and all hospitalizations (not solely heart failure hospitalizations) as an additional outcome.

Response: We are finalizing the CED study criteria outcomes measures as proposed. The CED study criteria strike the appropriate balance between evidence generation and patient access. Composite endpoints offer a comprehensive view of treatment effects because hospitalization reflects the disease burden and its influence on quality of life and mortality, which are important patient-centered outcomes. To ensure that treatment effects are consistent across all elements of the composite endpoint, we required sponsors to report individual outcome measures separately, demonstrating consistency across each component of the composite endpoint. We are concerned that all-cause hospitalizations might not accurately reflect meaningful clinical improvements for heart failure patients. The advantages of cardiac devices can be hidden by unrelated hospital stays, which may obscure the true impact of the treatment. Therefore, we are using a more targeted approach when evaluating clinical outcomes in this group.

Sham control

Comment: One commenter recommended that the CED study mandate a sham procedure control arm to mitigate any placebo effect.

Response: We recognize the methodological concerns raised regarding placebo effects and study design. Real World Evidence (RWE) does not replace the need for rigorous evidence, such as sham-controlled RCTs, but offers different yet equally valuable insights that address gaps inherent in clinical trials, especially for the Medicare population and long-term outcomes. Furthermore, when sham-controlled trials are not ethically feasible for implanted devices, RWE provides a strong alternative focused on objective endpoints. RWE comparative effectiveness studies use advanced statistical methods, including propensity score matching, which can create comparable control groups, reduce potential bias, account for known confounders, and potentially identify residual and unmeasured confounders. Additionally, the multi-year follow-up often included in RWE studies provides long-term outcome data and larger sample sizes than clinical trials typically can. RWE studies can deliver evidence quality approaching that of RCTs for objective outcomes like mortality and hospitalization. By emphasizing objective endpoints rather than quality of life measures or functional tests, RWE sidesteps concerns about the placebo effect that drive the need for sham controls. Outcomes such as death and hospitalization are objective and cannot be influenced by patient or provider awareness of treatment status. RWE eliminates placebo effect concerns because these outcomes are not affected by treatment knowledge.

Subgroup analyses

Comment: One commenter agreed with Section I.B.2.d.4 subgroup analysis of "No CRT, Prior CRT, Current CRT," particularly including "prior CRT," stating that CRT non-responders often have few remaining therapeutic options, and CCM may offer symptom relief and improved quality of life. One commenter recommended removing "prior CRT" from this subgroup analysis stating that it will not be possible to collect this data through a real-world evidence dataset-based study. The commenter recognized the value of this information, but stated that electronic health record and claims data can identify patients who have undergone CRT implantation but due to the current limitations in CPT and ICD-10-PCS codes and code descriptors, electronic health record and claims data can identify patients who have undergone CRT implantation but cannot delineate whether CRT is currently active, nor whether it has been active in the past. Additionally, the commenter noted that wording used in free text notes in a patient's electronic medical record is highly inconsistent, making Natural Language Processing (NLP) models infeasible. The commenter recommended revising the subgroup analysis to "CRT, No CRT" for the purposes of a RWE study.

Response: We recognize the challenges raised by the commenter in using electronic health records (EHR) and claims data to distinguish prior and current CRT. Therefore, we have changed the subgroup analysis to "No CRT, CRT." However, we believe this subgroup should be the subject of future research. CMS encourages evidence generation of health outcomes in subgroups beyond those required by the CED requirements in the NCD. All available evidence will be assessed in the future reconsideration of this NCD and high-quality evidence on relevant subgroups will be helpful to inform a coverage determination.

6. Miscellaneous Comments

Comment: One commenter suggested that CMS incentivize documentation of GDMT optimization.

Response: Generally, the patient's medical record must contain sufficient documentation of the patient's condition to substantiate the necessity for any services provided and the type and quantity of any items ordered. As such, we would expect the provider or care team to appropriately document in the medical record ongoing GDMT and track optimization through the care plan. However, any specific requirements for certain types of documentation are more appropriately addressed in other Medicare manuals and guidance, not a NCD.

Comment: One commenter provided suggestions for the general CED paradigm.

Response: We appreciate these comments. The general processes of the CED paradigm are outside the scope of this NCD, which is specific to CCM. For information on the CED paradigm, please refer to the CED guidance document, which can be found here: https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?mcdid=38.

IV. CMS Coverage Analysis

A. CMS Coverage Authority

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§ 1869(f)(1)(B) of the Social Security Act (the Act)). In general, in order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B and must not be otherwise excluded from coverage. Moreover, with limited exceptions, items or services must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§ 1862(a)(1)(A) of the Act).

When the available evidence is insufficient to demonstrate that the items and services are reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member under section 1862(a)(1)(A) of the Act, coverage with evidence development (CED) has been used to support evidence development for certain items and services that are likely to show benefit for the Medicare population. [2] CED has been a pathway whereby, after a CMS and AHRQ review, Medicare covers items and services on the condition that they are furnished in the context of clinical studies or with the collection of additional clinical data.[3] CED relies primarily on the statutory exception in section 1862(a)(1)(E) of the Act, which effectively permits Medicare payment for items and services that are reasonable and necessary to carry out research conducted pursuant to section 1142 of the Act. Section 1142 of the Act describes the authority of AHRQ to conduct and support research that appropriately reflects the needs and priorities of the Medicare program.[4]

[2] CMS' CED Guidance Document (2024), 2, 3.
[3] CMS' CED Guidance Document (2024), 4
[4] CMS' CED Guidance Document (2024), 6. This document also contains information on the purpose, principles, and process of CED.

B. CMS Analysis for Coverage of CCM for HF Management

This section includes CMS' analysis of the evidence related to CCM for HF Management. Relevant details from studies listed in Table 1: Key Studies for CCM for Heart Failure Management above are provided in context when key study findings or limitations are discussed with respect to coverage.

The evidence in Sections III.D-E indicates that there is some benefit for some HF patients with CCM in defined clinical study conditions. However, as identified in Section III.E.9 Limitations of Evidence, there are crucial limitations to the evidence base for CCM for HF management and questions relating to appropriateness for Medicare patients and the clinical utility of CCM HF management that need to be answered before CMS would be able to determine if coverage is reasonable and necessary under § 1862(a)(1)(A) of the Act.

As further discussed below in the analysis, we are covering CED for CCM for HF Management. In Section IV.B.1-2 below, we analyze key findings and shortcomings of the evidence, and we describe how those elements translate into the evidence-based rationale for each of the CED study parameters (e.g., patient, physician, study criteria) that aim to fill the evidence gaps.

The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that the specific assessment questions raised in a National Coverage Analysis (NCA) can be answered conclusively. When conducting NCAs for an item or service under the reasonable and necessary statute, CMS generally makes three kinds of assessments: (1) The quality of relevant individual studies; (2) What conclusions can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential harms and benefits; and (3) The generalizability of findings from relevant studies to the Medicare beneficiary population. (See CMS' Evidence Review Guidance Document.)

The peer-reviewed medical literature has demonstrated that the use of CCM, in conjunction with optimal medical therapy (OMT), can produce meaningful health benefits for some HF patients (Abraham et al. 2011; Abraham et al. 2018; Borggrefe et al. 2008; Anker et al. 2019).

1. Rationale for Coverage Requirements for CCM for HF Management (Patient and CED Study criteria)

The Centers for Medicare & Medicaid Services (CMS) covers cardiac contractility modulation under Coverage with Evidence Development (CED) for heart failure management according to the provisions in sections I.B (Coverage Criteria) and I.C (Other Uses of CCM) under the Decision section of this document, which are explained below.

Patient Criteria

Patients must meet the FDA market-authorized indications for use and remain symptomatic despite at least 3 months of optimized guideline-directed medical therapy (GDMT) as determined by the heart team prior to CCM implantation.

Patients are excluded from coverage if they meet any of the following criteria:

- Meet any of the contraindications in the FDA labeling; or,
- Have had a heart transplant; or,
- Are younger than 18 years old.

Rationale for patient criteria:
These criteria are consistent with the CCM pivotal trial inclusion criteria and FDA-approved labeling indications[5]. The FDA labeling indications are inclusive of patients with moderate to severe heart failure. Specifically, the labeling uses the following language, "…NYHA Class III heart failure patients who remain symptomatic despite guideline directed medical therapy, who are in normal sinus rhythm, are not receiving Cardiac Resynchronization Therapy (CRT), and have a left ventricular ejection fraction ranging from 25% to 45%." Medical literature has demonstrated that these populations of HF patients who remain symptomatic despite optimized GDMT have some benefit from CCM. However, those findings cannot be extrapolated to a broader HF population. The contraindications are also consistent with the FDA labeling and the published literature, and we have concerns that this contraindicated population would not see the benefits identified in previous studies. Also, several evidence-based guidelines have recommended the use of CCM in patients with moderate to severe HF. Both the 2021 European Society of Cardiology, and the 2022 guideline of the American Heart Association (AHA)/ American College of Cardiology Foundation (ACC)/ Heart Failure Society of America (HFSA) for the management of HF identify patients with having EF of between 25% and 45% benefit from CCM. We note that in this final decision we have made minor editorial changes to the references to FDA labeling for accuracy.

CED Study Criteria
All CMS-approved CED studies must meet the patient criteria above and include:

> (a) Primary outcomes of all-cause mortality, HF hospitalizations, or a composite of these, through a minimum of 24 months. Each component of a composite outcome must be individually reported.

Rationale for (a): Our focus on, and metrics for, HF hospitalizations derive from recent trials, independent expert opinion, and public comments. While the primary metric for HF hospitalizations is the cumulative number at a minimum of 24 months, time-to-event analysis and total days in hospital (or the converse, days alive out of hospital) should be reported. All-cause mortality is a core patient-centered outcome, accounts for competing causes of death without further adjudication, and appears in composite primary outcomes of reviewed trials along with HF hospitalizations. The 24-month minimum period for CED studies expands evidence for durability of outcomes beyond past trials.

[5] Access@FDA.gov Optimizer Smart System FDA approval history https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?pmanumber=P180036

Each component of a composite outcome must be individually reported to assess which component(s) is(are) driving the outcome. For example, if a substantial reduction in a composite of all-cause mortality and HF hospitalizations were driven by the latter, and mortality actually increased slightly, that benefit (substantially decreased hospitalizations) and harm (slightly increased mortality) would be important for physicians and patients to know when making decisions.

Finally, we are not requiring specific secondary outcomes, with the expectation that a number of these will inherently be included in CED study protocols. For example, these might include, at a minimum, any hospitalization, any emergency room visit, cardiac mortality, and QoL (e.g., Kansas City Cardiomyopathy Questionnaire; Milwaukee Living With Heart Failure Questionnaire).

(b) An active comparator.

Rationale for (b): Benefits and harms cannot be assessed without a comparator. An "active comparator" is inherent in RCTs that prospectively compare randomized intervention and control groups, but may be seen in other study designs, such as those employing propensity-score matching or regression discontinuity designs. The latter studies can be many times larger than RCTs, and we believe can help fill in evidence gaps, especially for subgroups, left in the wake of the foundational but limited RCTs for CCM.

(c) A care management plan that identifies members, roles, and responsibilities of the clinical team that performs the follow-up CCM patient management.

Rationale for (c): In the trials that generated the promising evidence for CCM, patients were full participants in their own care and understood (through physician-patient shared decision-making (SDM)) that consistent, long-term adherence to a care plan is needed to achieve beneficial outcomes. This physician-patient SDM, and full patient participation, is needed in CED studies to replicate those trial results. The entire care plan developed by study investigators and embedded in CED study protocols would provide an evidence-based roadmap for real-world clinical care after CED studies are completed. As noted above, patient management with GDMT and patient selection for CCM are critical to achieving the beneficial outcomes shown in the literature and should be under the care of a team who, together, can ensure that HF patients are appropriately managed before CCM, are appropriately selected for CCM and are appropriately managed post-procedure. We note that in the summary of the proposed decision, we listed "care management plan" but inadvertently left out the rest of the statement of what the plan identifies. We have corrected this in this final decision.

(d) Design sufficient for subgroup analyses by:
1. Age (Stratify <65, 65-74, and 75+);
2. Other clinically important patient demographic factors;
3. Ischemic cardiomyopathy versus non-ischemic cardiomyopathy;

4. No CRT, CRT;
5. LVEF ≥35% versus <35%;
6. Systolic blood pressure ≥ median versus < median;
7. Diabetic vs non-diabetic.

Rationale for (d): More evidence is needed about the above subgroups to determine which patients will clinically benefit from CCM. We are finalizing the subgroup analyses with modification to #4, changing "No CRT, Prior CRT, current CRT" to "No CRT, CRT" due to challenges raised by a commenter in using electronic health records (EHR) and claims data to try to distinguish prior and current CRT. However, CMS encourages evidence generation of health outcomes in subgroups beyond those required by the CED requirements in the NCD. All available evidence will be assessed in the future reconsideration of this NCD and high-quality evidence on relevant subgroups will be helpful to inform a coverage determination.

A CED study would be considered successful if it demonstrated:

- A substantial reduction in HF hospitalizations alone for the treatment arm, with a decrease or no change in all-cause mortality, compared to the control, would be sufficient.
- A substantial comparative decrease in HF hospitalizations without a corresponding increase in non-HF hospitalizations would be further reassuring.

2. Evidence Questions – Answered

Our initial literature search and review of the evidence on the clinical utility of CCM for Medicare beneficiaries with HF were guided by three general questions. Answers to these questions inform the overarching question of whether CCM meets the reasonable and necessary standard under § 1862(a)(1)(A) of the Act.

Question 1-Is the evidence sufficient to conclude that cardiac contractility modulation is reasonable and necessary for the treatment of Medicare beneficiaries with moderate to severe chronic systolic heart failure (EF 25-45%) that remains symptomatic despite guideline-directed medical therapy?

No - The quality and strength of the evidence are insufficient to make this determination, and CCM in this population is not reasonable and necessary under § 1862(a)(1)(A) of the Act because critical evidentiary gaps remain.

While the studies did demonstrate that the use of CCM in certain HF patients resulted in improved outcomes (e.g., VO_2, 6MWR, MLWHFQ, NYHA functional classification), there are significant evidence gaps, the most glaring of which is the short duration of follow-up. When looking at the totality of studies, the clinical trials (*FIX-HF-5*, *FIX-HF-5C*, *FIX-HF-5C2*, *FIX-CHF4)*, and the meta-analysis of those clinical trials comprised the vast majority of CCM patients studied. With the exception of the Abraham 2018 *FIX-HF-5* study, which lasted 50 weeks, all the other RCTs lasted only 24 weeks. This short duration of study is inadequate to determine that CCM is reasonable and necessary for the treatment of Medicare beneficiaries with

moderate to severe chronic systolic HF (EF 25-45%) that remains symptomatic despite GDMT. The study design with the second largest group of patients receiving CCM was registries (MAINTAINED, CCM-REG, CCM-HF), and the duration varied between two and five years. Though this is the time period we would expect, these studies lacked randomized controls and were retrospective in nature. Other study designs, which were prospective cohort studies, had durations of study between 322 days and five years. Like registry studies, their duration of study might be sufficient, and they were prospective in nature, but they suffered from a small number of participants.

Another issue that was not adequately addressed is study quality. The high risk of bias was not considered in these studies, especially in the study that involved crossover because of the potential of the placebo effect, and many studies included participants which were not Medicare-aged. Again, short follow-up duration, and/or small sample size limit both internal and external validity.

And finally, question one addresses patients with moderate to severe chronic systolic HF (EF 25-45%) that remain symptomatic despite GDMT. Of the 24 studies included in this assessment, only five specifically state that patients included in the study had EFs between 25% and 45% (Abraham et al. 2018; Wiegan et al. 2020; Fastner et al. 2021; Fastner et al. 2022; Asher et al. 2019). The other studies either stated that they had included patients with EFs higher than 45% (the Linde study's inclusion criteria stated that EF was equal of greater than 50%), studies included patients with EFs less than 25% (the Davtyan study included patients with EFs ranging between 20% and 33% but did not separately assess patients with EF of 25% or higher), or used ill-defined values that make it difficult to say that they are in the 25% to 45% range (e.g., Röger uses EF of < 35%, which might indicate that it included EF values as low as 24% or less). The variation in reporting EFs represents another evidence gap, and we are not able to conclude that the evidence is sufficient to conclude that CCM is reasonable and necessary for the treatment of Medicare beneficiaries with moderate to severe chronic systolic HF (EF 25-45%) that remains symptomatic despite GDMT.

Question 2 -Is there evidence that specific characteristics or comorbidities make patients more or less likely to benefit from cardiac contractility modulation?

Uncertain- Given the short-term nature of the studies, few RCTs, along with breadth of concomitant medical conditions that can accompany HF and affect health status, we have some information, but it is not sufficient to establish which specific characteristics or comorbidities predict benefit.

When looking specifically at studies that included a comparison group, many medical conditions were found equally in both the intervention and the control groups. While the analyses failed to demonstrate that those conditions affected the benefit of CCM in either group, we look to future studies to show that there are no long-term differences in outcomes and that additional comorbidities are included in real-world study designs.

A medical condition noted in this assessment was the presence of cardiomyopathy and its etiology (e.g., ischemia, dilated or idiopathic). Some wondered if patients with ischemic cardiomyopathy who receive CCM fared worse than patients with other forms of cardiomyopathy. A number of studies evaluated this question (e.g., Anker, Masarone, Tint, Wiegn, Borggrefe, Kadish). The findings from those studies failed to show that patients with ischemic cardiomyopathy who had received CCM had worse outcomes than patients with other forms of cardiomyopathy.

Question 3-Are specific treatment conditions necessary to achieve cardiac contractility modulation outcomes similar to those demonstrated in the clinical studies reviewed in this analysis?

Uncertain– Some of the studies in this analysis listed the medical treatments that patients had received for their HF (e.g., Angiotensin-converting enzyme inhibitors (ACEi), Angiotensin receptor blocker (ARB), Beta-blocker, Loop diuretics, Aldosterone inhibitor, Nitrates, Calcium channel blockers, Antiarrhythmics). When evaluating research designs that used comparators, these medical treatments were found equally distributed amongst both groups (intervention and control group). However, there is little evidence to date that outcomes achieved in rigorous trials, even those with comparable populations and medications, have been replicated in the real world. The goal of CED is to ensure that the outcomes achieved in the previous rigorous protocols can be achieved in community-based settings. When considering the totality of the findings of the studies in this assessment, we found that there are no specific treatment conditions necessary to achieve CCM outcomes besides those incorporated into the clinical studies reviewed in this analysis.

Gaps in the current evidence should be filled before answering any of these questions in the affirmative. When assessing the evidence base at the conclusion of CED, CMS will review the totality of the evidence. CED studies must be fit-for-purpose, as detailed in our CMS National Coverage Analysis Evidence Review and Coverage with Evidence Development guidance documents. That is, the study design, analysis plan, and data used must be appropriate to the question the study seeks to answer. In most RCT studies, detailed protocols and intensive follow-up may diverge extensively from real-world use conditions. Observational studies may be developed to include an active comparator, and statistical methods may be applied to mitigate confounding risk and allow for causal inference.

Based on the totality of the evidence, CMS finds further justification that coverage under CED is appropriate. We believe that CMS-approved clinal studies could fill these gaps in the evidence base regarding clinical utility of CCM for HF management for Medicare beneficiaries.

C. Benefit Category

For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories outlined in §1812 (Scope of Part A); §1832 (Scope of Part B); or §1861(s) (Definition of Medical and Other Health Services) of the Act.

CCM qualifies as:

- Inpatient Hospital Services
- Outpatient Hospital Services Incident to a Physician's Service
- Physicians' Services
- Prosthetic Devices

Note: This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

D. Shared Decision-Making

CMS recognizes the importance of SDM in many clinical scenarios and has required SDM in other NCDs (for example, implantable cardiac defibrillators: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=110). CMS supports clinician-patient SDM for CCM for HF but recognizes that there is no fully developed tool available at this time. CMS strongly encourages standardized decision aids or tools.

V. History of Medicare Coverage

A. Current National Coverage Request

Prior to this final NCD, coverage of CCM for HF was at the discretion of Medicare Administrative Contractors (MACs).

This is CMS' first NCA on CCM. This request was externally initiated. CMS received a complete, formal request to open an NCA on the topic of CCM from Impulse Dynamics. The request letter is available at https://www.cms.gov/files/document/id317.pdf. Impulse Dynamics is participating in the Transitional Coverage for Emerging Technologies (TCET) pilot program and tested the processes and concepts of TCET.

B. Timeline of NCA Milestones

Date	Milestone
January 10, 2025	CMS posts a tracking sheet announcing the opening of the NCA. The first 30-day public comment period begins.
February 9, 2025	First public comment period ends. CMS receives 15 comments.
July 10, 2025	CMS posts proposed Decision Memorandum. Second 30-day public comment period begins.
August 9, 2025	Second public comment period ends. CMS receives eight comments.
XXX	CMS posts final Decision Memorandum.

VI. Appendices

A. Appendix A: Medicare National Coverage Determinations Manual Language

Medicare National Coverage Determinations Manual
Draft

This draft NCD is subject to formal revisions and formatting changes prior to the release of the final NCD, contractor instructions, and publication in the Medicare National Coverage Determinations Manual.

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(Rev.)

NCD XXX – Cardiac Contractility Modulation (CCM) for Heart Failure

A. General

Cardiac Contractility Modulation (CCM) is used in the treatment of heart failure.

B. Nationally Covered Indications
The Centers for Medicare & Medicaid Services (CMS) covers Cardiac Contractility Modulation (CCM) for heart failure (HF) management under Coverage with Evidence Development (CED) when furnished according to a Food and Drug Administration (FDA) market-authorized indication and all of the following conditions are met:

1. *Patient Criteria*
   Patients must meet the FDA market-authorized indications for use and remain symptomatic despite at least 3 months of optimized guideline-directed medical therapy (GDMT) as determined by the heart team prior to CCM implantation.

   Patients are excluded from coverage if they meet any of the following criteria:
   - *Meet any of the contraindications in the FDA labeling; or,*
   - *Have had a heart transplant; or,*
   - *Are younger than 18 years old.*

2. *CED Study Criteria*
   The CCM and related items and services are furnished in the context of a CMS-approved CED study. CMS-approved CED study protocols must: include only those patients who meet the criteria above; and include all of the following:
   a) *Primary outcomes of all-cause mortality, HF hospitalizations, or a composite of these, through a minimum of 24 months. Each component of a composite outcome must be individually reported.*
   b) *An active comparator.*
   c) *A care management plan that identifies members, roles, and responsibilities of the clinical team that performs the follow-up CCM patient management.*

d) Design sufficient for subgroup analyses by:

1. *Age (Stratify <65, 65-74, 75+);*
2. *Other clinically important patient demographic factors;*
3. *Ischemic cardiomyopathy versus non-ischemic cardiomyopathy;*
4. *No CRT, CRT;*
5. *Left ventricular ejection fraction (LVEF) ≥35% versus <35%;*
6. *Systolic blood pressure ≥ median versus < median;*
7. *Diabetic vs non-diabetic.*

e) In addition, CMS-approved CED studies must adhere to the scientific standards (criteria 1-17 below) that have been identified by the Agency for Healthcare Research and Quality (AHRQ):

1. *Sponsor/Investigator: The study is conducted by sponsors/investigators with the resources and skills to complete it successfully.*
2. *Milestones: A written plan is in place that describes a detailed schedule for completion of key study milestones, including study initiation, enrollment progress, interim results reporting, and results reporting, to ensure timely completion of the CED process.*
3. *Study Protocol: The CED study is registered with ClinicalTrials.gov and a complete final protocol, including the statistical analysis plan, is delivered to CMS prior to study initiation. The published protocol includes sufficient detail to allow a judgment of whether the study is fit-for-purpose and whether reasonable efforts will be taken to minimize the risk of bias. Any changes to approved study protocols should be explained and publicly reported.*
4. *Study Context: The rationale for the study is supported by scientific evidence and study results are expected to fill the specified CMS-identified evidence deficiency and provide evidence sufficient to assess health outcomes.*
5. *Study Design: The study design is selected to safely and efficiently generate valid evidence of health outcomes. The sponsors/investigators minimize the impact of confounding and biases on inferences through rigorous design and appropriate statistical techniques. If a contemporaneous comparison group is not included, this choice should be justified, and the sponsors/investigators discuss in detail how the design contributes useful information on issues such as durability or adverse event frequency that are not clearly answered in comparative studies.*
6. *Study Population: The study population reflects the demographic and clinical diversity among the Medicare beneficiaries who are the intended population of the intervention, particularly when there is good clinical or scientific reason to expect that the results observed in premarket studies might not be observed in older adults or subpopulations identified by other clinical or demographic factors.*
7. *Subgroup Analyses: The study protocol explicitly discusses beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion requirements effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. In the protocol, the sponsors/investigators describe plans for analyzing demographic subpopulations as well as clinically-relevant subgroups as identified in existing evidence. Description of plans for exploratory analyses, as relevant subgroups emerge, are also included.*

8. *Care Setting: When feasible and appropriate for answering the CED question, data for the study should come from beneficiaries in their expected sites of care.*
9. *Health Outcomes: The primary health outcome(s) for the study are those important to patients and their caregivers and that are clinically meaningful. A validated surrogate outcome that reliably predicts these outcomes may be appropriate for some questions. Generally, when study sponsors propose using surrogate endpoints to measure outcomes, they should cite validation studies published in peer-reviewed journals to provide a rationale for assuming these endpoints predict the health outcomes of interest. The cited validation studies should be longitudinal and demonstrate a statistical association between the surrogate endpoint and the health outcomes it is thought to predict.*
10. *Objective Success Criteria: In consultation with CMS and AHRQ, sponsors/investigators establish an evidentiary threshold for the primary health outcome(s) so as to demonstrate clinically meaningful differences with sufficient precision.*
11. *Data Quality: The data are generated or selected with attention to provenance, bias, completeness, accuracy, sufficiency of duration of observation to demonstrate durability of health outcomes, and sufficiency of sample size as required by the question.*
12. *Construct Validity: Sponsors/investigators provide information about the validity of drawing warranted conclusions about the study population, primary exposure(s) (intervention, control), health outcome measures, and core covariates when using either primary data collected for the study about individuals or proxies of the variables of interest, or existing (secondary) data about individuals or proxies of the variables of interest.*
13. *Sensitivity Analyses: Sponsors/investigators will demonstrate robustness of results by conducting pre-specified sensitivity testing using alternative variable or model specifications as appropriate.*
14. *Reporting: Final results are provided to CMS and submitted for publication or reported in a publicly accessible manner within 12 months of the study's primary completion date. Wherever possible, the study is submitted for peer review with the goal of publication using a reporting guideline appropriate for the study design and structured to enable replication. If peer-reviewed publication is not possible, results may also be published in an online publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with incomplete results).*
15. *Sharing: The sponsors/investigators commit to making study data publicly available by sharing data, methods, analytic code, and analytical output with CMS or with a CMS-approved third party. The study should comply with all applicable laws regarding subject privacy, including 45 CFR § 164.514 within the regulations promulgated under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and 42 CFR, Part 2: Confidentiality of Substance Use Disorder Patient Records.*
16. *Governance: The protocol describes the information governance and data security provisions that have been established to satisfy Federal security regulations issued pursuant to HIPAA and codified at 45 CFR Parts 160 and 164 (Subparts A &*

C), United States Department of Health and Human Services (HHS) regulations at 42 CFR, Part 2: Confidentiality of Substance Use Disorder Patient and HHS regulations at 45 CFR Part 46, regarding informed consent for clinical study involving human subjects. In addition to the requirements under 42 CFR and 45 CFR, studies that are subject to FDA regulation must also comply with regulations at 21 CFR Parts 50 and 56 regarding the protection of human subjects and institutional review boards, respectively.

17. *Legal: The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals, although it is acceptable for a study to test a reduction in toxicity of a product relative to standard of care or an appropriate comparator. For studies that involve researching the safety and effectiveness of new drugs and biological products aimed at treating life-threatening or severely-debilitating diseases, refer to additional requirements set forth in 21 CFR § 312.81(a).*

C. Nationally Non-Covered Indications

CCM for HF management is not covered for patients outside of a CMS-approved study.

D. Other

Nothing in this NCD would preclude coverage of CCM for HF management through NCD 310.1 (Clinical Trial Policy) or through the Investigational Device Exemption (IDE) Policy.

B. Appendix B: Referenced Materials

Table B1. Characteristics of Included Studies

Study Details	Patients	Intervention(s)	Outcomes Assessed
Randomized Controlled Trials			
Reference: Borggrefe et al. 2008 **Study Acronym**: FIX-CHF-4 **Country:** Czech Republic, France, Germany, Italy, Netherlands **Study Design:** Prospective, multicenter, randomized, double-blind, double-crossover **Funding Source:** IMPULSE Dynamics	**Number of Patients:** 164 **Total:** 164 CCM-sham (CCM for 12 weeks followed by sham for 12 weeks): 80 Sham-CCM (sham for 12 weeks followed by CCM for 12 weeks): 84 **Diagnosis:** HFrEF with LVEF ≤35%, NYHA class II or III, normal QRS duration **Mean Age, Years (SD):** CCM-sham: 58.9 (9.8) Sham-CCM: 59.9 (10) **Female N (%):** CCM-sham: 9 (11.2) Sham-CCM: 16 (19) **Inclusion/Exclusion Criteria:** **Inclusion:** LVEF ≤35%, NYHA class ≥II, pVO_2 10-20 mL O_2/min/kg, on appropriate stable medical treatments for HF including diuretic, ACE inhibitor, and/or ARB and β-blocker, implanted PM or ICD if indicated **Exclusion:** Eligible for CRT, atrial fibrillation, MI within 3 months, clinically significant angina, hospitalized for HF requiring IV treatments within 30 days, ≥8900 PVCs per 24 hours	**Intervention:** CCM **Comparator:** Sham **Follow-up Period:** 24 weeks	• pVO_2 • MLWHFQ • 6MWT • NYHA Functional Class
Reference: Kadish et al. 2011 **Study acronym:** FIX-HF-5 **Country:** USA (50 sites)	**Number of Patients:** **Total:** 428 CCM: 215 OMT: 213	**Intervention:** CCM **Comparator:** OMT **Follow-up Period:** 24 weeks for efficacy endpoint; 50 weeks for safety endpoint	• VAT measured on CPX • pVO_2 • MLWHFQ • NYHA functional class • 6MWT

Study Details	Patients	Intervention(s)	Outcomes Assessed
Study Design: Prospective, multicenter, randomized, unblinded, parallel-group, controlled trial **Funding Source:** IMPULSE Dynamics (manufacturer of the CCM device)	**Diagnosis:** HFrEF with LVEF ≤35%, NYHA class III or IV, narrow QRS **Mean Age, Years (SD):** CCM: 58.09 (12.79) OMT: 58.55 (12.23) **Female N (%):** CCM: 57 (26.5) OMT: 62 (29.1) **Inclusion/Exclusion Criteria:** **Inclusion:** LVEF ≤35%, NYHA class III or IV symptoms despite treatment with ACE inhibitor and/or ARB and β-blockers for at least 3 months, baseline pVO_2 on CPX ≥9 mL/kg/min, normal sinus rhythm, narrow QRS duration, not indicated for CRT device (QRS <130ms), implanted ICD **Exclusion:** Hospitalization within 30 days of enrollment, inotrope dependent, >8,900 PVCs per 24 hours, permanent atrial fibrillation, MI within 90 days, PCI within 30 days or CABS within 90 days of enrollment		• All-cause mortality and all-cause hospitalization (composite endpoint) • Adverse events
Reference: Abraham et al. 2011 **Study Acronym:** FIX-HF-5 subgroup analysis **Country:** USA **Study Design:** Subgroup analysis of FIX-HF-5 study involving 48% of the primary study's patients with LVEF ≥25% and NYHA class III symptoms **Quality rating:** see Kadish et al. 2011 **Funding Source:** IMPULSE Dynamics	**Number of Patients:** **Total:** 206 CCM: 109 OMT: 9 **Diagnosis:** HFrEF with LVEF ≥25%, NYHA class III **Mean Age, Years (SD):** CCM: 58.7 (12.0) OMT: 60.3 (12.1) **Female N (%):** CCM: 32 (29.4) OMT: 21 (21.6) **Inclusion/Exclusion Criteria:** **Inclusion:** LVEF ≥25%, NYHA class III	**Intervention:** CCM **Comparator:** OMT **Follow-up Period:** 24 weeks for efficacy endpoint; 50 weeks for safety endpoint	• VAT measured on CPX • pVO_2 • NYHA functional class • MLWHFQ • 6MWT • Mortality • Serious adverse events
Reference: Abraham et al. 2018	**Number of Patients:** **Total:** 160	**Intervention:** CCM **Comparator:** OMT	• pVO_2 • MLWHFQ

Study Details	Patients	Intervention(s)	Outcomes Assessed
Study Acronym: FIX-HF-5C **Country:** USA (32 sites), Czech Republic (1 site), Germany (9 sites) **Study Design:** Prospective, multicenter, randomized, unblinded, controlled, confirmatory study of FIX-HF-5 among patients with LVEF 25-45% **Funding Source:** IMPULSE Dynamics	CCM: 74 (68 implanted) OMT: 86 **Diagnosis:** HFrEF with LVEF 25-45%, NYHA class III and IV, narrow QRS **Mean Age, Years (SD):** CCM: 63 (11) OMT: 63 (11) **Female N (%):** CCM: 20 (27) OMT: 18 (20.9) **Inclusion/Exclusion Criteria:** **Inclusion:** LVEF 25-45%, NYHA class III or ambulatory class IV HF despite OMT, normal sinus rhythm, narrow QRS duration (≤130 ms), implanted ICD if LVEF ≤35% **Exclusion:** Hospitalization for HF requiring inotropic support within 30 days of enrollment, >8,900 PVCs per 24 hours, permanent atrial fibrillation, CABS within 90 days or PCI within 30 days of enrollment, MI within 90 days of enrollment, cardioverted within 30 days of enrollment	**Follow-up Period:** 24 weeks	• NYHA functional class • 6MWT • All-cause, cardiac-related, and HF-related hospitalization • All-cause, cardiac, and HF mortality • Device- or procedure-related complications • Other adverse events
Secondary analysis: The authors assessed treatment effects in patients with LVEF <35% vs. ≥35% by pooling data from FIX-HF-5 and FIX-HF-5C. Findings were reported within the Abraham et al. 2018 manuscript's Results section.	**Number of Patients:** **Total:** 371 EF <35%: CCM: 130, OMT: 145 EF≥35%: CCM: 47, OMT: 49 **Mean Age, Years (SD):** EF <35%: CCM: 60.6 (11.4), OMT: 61.4 (12.2) EF≥35%: CCM: 60.6 (12.3), OMT: 60.4 (10.4) **Female N (%):** EF <35%: CCM: 33 (25.4), OMT: 33 (22.8) EF≥35%: CCM: 18 (38.3), OMT: 12 (24.5)	**Intervention:** CCM **Comparator:** OMT	• pVO_2 • MLWHFQ • NYHA functional class
Reference: Wiegn et al., 2020	**Number of Patients:** 60	**Intervention:** 2-lead CCM	• pVO_2

Study Details	Patients	Intervention(s)	Outcomes Assessed
Study Acronym: FIX-HF-5C2 **Country:** USA, Germany **Study Design:** Prospective, multi-center, single-arm, FIX-HF-5C parallel confirmatory extension study **Funding Source:** IMPULSE Dynamics	**Diagnosis:** HFrEF with LVEF ≥25% and ≤45%, NYHA class III and IV, narrow QRS **Mean Age, Years (SD):** 66.3 (8.9) **Female N (%):** 7 (11.7) **Inclusion/Exclusion Criteria:** **Inclusion:** Age ≥18 years, HFrEF with LVEF ≥25% and ≤45%, NYHA class III and IV, narrow QRS, not indicated for CRT **Exclusion:** IV loop diuretics/inotropes/hemofiltration within 30 days, potentially correctible cause of HF, exercise tolerance limited by a condition other than HF, scheduled for or had recent CABS/PCI/MI.	**Comparator:** FIX-HF-5C control group **Follow-up Period:** 24 weeks	• NYHA functional class • Adverse events
Non-Comparative / Observational Studies			
Reference: Davtyan et al., 2023 **Study Acronym:** NA **Country:** Russia **Study Design:** Prospective cohort, single site **Funding Source:** None **Note:** Nine of the patients were implanted with the Optimizer Smart and two were implanted with the Optimizer IV.	**Number of Patients:** 11 **Diagnosis:** HFrEF with LVEF<40% and NYHA class II-IV **Median Age, Years:** 61.5 **Female N (%):** 3 (27.3) **Inclusion/Exclusion Criteria:** **Inclusion:** Age >18 years, HFrEF with NYHA ≥ II FC, presence of implanted CRT-D and no increase in LVEF (less than 5%), decrease in end-systolic volume (less than 15%), NYHA reduction of I or more, after CRT-D implantation, QRS complex width after CRT-D implantation ≥130 ms. **Exclusion:** Waiting for heart transplantation, myocardial infarction, coronary artery bypass surgery or angioplasty with coronary artery stenting less than 3 months before inclusion, acute myocarditis, hypertrophic cardiomyopathy, reversible causes of heart failure, mechanical tricuspid valve, severe comorbid pathology	**Intervention:** CCM **Comparator:** NA **Follow-up Period:** 1 year, 2 years	• Death • NYHA • LVEF • 6MWD • Mitral regurgitation • Tricuspid regurgitation • NTproBNP • MLWHFQ
Reference: Masarone, Kittleson, De Vivo, D'Onofrio, Rao, et al., 2022	**Number of Patients:** 30	**Intervention:** CCM **Comparator:** NA	• Degree of tricuspid regurgitation • TAPSE

Study Details	Patients	Intervention(s)	Outcomes Assessed
Study Acronym: NA **Country:** Italy **Study Design:** Prospective cohort, single site **Funding Source:** None	**Diagnosis:** HFrEF with LVEF<40% and NYHA class II-III **Mean Age, Years (SD):** 59.5 (12.9) **Female N (%):** 5 (16.6) **Inclusion/Exclusion Criteria:** **Inclusion:** LVEF<40%; NYHA class II–III; referral for CCM implant due to the >2 unplanned visits or hospitalization in the last 12 months and/or the persistence of HF-related symptoms despite the use of optimal medical therapy; QRS duration of <120 msec. **Exclusion:** Acute coronary syndrome in the previous 3 months; ICD implantation in the previous 12 months; severe tricuspid regurgitation (i.e., vena contracta >7 mm, proximal isosurface radius >9 mm)	**Follow-up Period:** 6 months	• Laboratory values
Reference: Pavlovskaya et al., 2023 **Study Acronym:** NA **Country:** Russia **Study Design:** Prospective cohort, pilot **Funding Source:** Ministry of Science and Higher Education of the Russian Federation	**Number of Patients:** 59 **Diagnosis:** HFrEF with LVEF≤35% and NYHA class II or III **Mean Age, Years (SD):** 52.3 (10.4) **Female N (%):** 10 (16.9) **Inclusion/Exclusion Criteria:** **Inclusion:** HFrEF of NYHA functional class II and III, sinus rhythm, QRS <130 ms or QRS <150 ms in the presence of non-specific intraventricular block, optimal and stable CHF drug therapy for at least 3 months. **Exclusion:** A permanent atrial fibrillation, high-grade premature ventricular contractions; acute myocardial infarction or major heart surgery, percutaneous coronary intervention, valvuloplasty within 12 months and hospitalization due to decompensated HF within 3 months prior to inclusion in the study.	**Intervention:** CCM **Comparator:** NA **Follow-up:** 3 years, 5 years **Mean Follow-up Period, Months (SD):** 63.9 (3.4)	• Peak VO_2 • Cardiovascular death • Heart transplantation • Ventricular tachyarrhythmia, requiring ICD shocks • Hospitalizations due to decompensated HF • Hospitalizations, all-cause • Mortality, observed vs. predicted
Reference: Tint & Micu, 2023 **Study Acronym:** NA	**Number of Patients:** 19 **Diagnosis:** HFrEF with LVEF≤35% and NYHA class III or IV	**Intervention:** CCM **Comparator:** NA	• NYHA class • LVEF level • 6MWT

Study Details	Patients	Intervention(s)	Outcomes Assessed
Country: Romania **Study Design:** Prospective cohort, pilot **Funding Source:** NR	**Mean Age, Years (SD):** 66.5 (6.9) **Female N (%):** 1 (5.0) **Inclusion/Exclusion Criteria:** **Inclusion:** Clinically significant symptomatic HFrEF (e.g., NYHA Class III or IV and LVEF≤35%) despite an appropriate therapy for chronic HF (diuretic, beta-blocker, and ACE inhibitor/ARB/sacubitril–valsartan, SGLT2 inhibitors, and devices ICD or CRT-D) **Exclusion:** NR	**Mean Follow-up Period, Days (SD):** 321.7 (113.5)	
Reference: Ansari et al., 2022 **Study Acronym:** NA **Country:** Germany **Study Design:** Prospective cohort, single-center **Funding Source:** Impulse Dynamics Note: This study specified use of the Optimizer system instead of the Optimizer "Smart" system. It was assumed that it was the same system. Group A included patients with single active lead as well as patients with both leads from the dual lead system, which were all positioned at scar (LGE > 25%). Group B included patients with a single active lead, where tips were not positioned at scar, or when they had a dual lead system, at least one lead was not positioned at scar since it used two right ventricular pacing leads and an atrial sensing lead.	**Number of Patients:** 58 **Diagnosis:** HFrEF with LVEF<40% and NYHA class 1-IV **Median Age, Years (IQR):** 57 (28-81) **Female N (%):** 8 (13.8) **Inclusion/Exclusion Criteria:** **Inclusion:** Above 18 years of age, resistant to optimal medical therapy (OMT) for HF, a reduced LVEF (< 40%) as estimated by echocardiography, and a QRS-duration of < 120 ms **Exclusion:** Decompensated states of HF and reversible causes of HF such as valvular heart disease, scheduled for a coronary intervention or underwent such a procedure during the last 3 months, evidence of active ischemia, and a recent history of myocardial infarction (< 3 months)	**Intervention:** CCM **Comparator:** NA **Follow-up Period:** 1 year	• MLWHFQ • NYHA class • LVEF level • NT-pro BNP • TAPSE
Reference: Linde et al., 2022 **Study Acronym:** CCM-HFpEF **Country:** EU and Australia	**Number of Patients:** 47 **Diagnosis:** HFpEF with LVEF ≥50% and NYHA class II or III	**Intervention:** CCM **Comparator:** NA **Follow-up Period:** 24 weeks	• KCCQ overall summary score • Adverse events

Study Details	Patients	Intervention(s)	Outcomes Assessed
Study Design: Prospective cohort, multicenter, pilot **Funding Source:** IMPULSE Dynamics	**Mean Age, Years (SD):** 74.3 (4.4) **Female N (%):** 33 (70.2) **Inclusion/Exclusion Criteria:** **Inclusion:** Age 40-80 years, LVEF ≥50%, NYHA class II or III, stable optimal medical therapy for HF for 3 months **Exclusion:** Dilated left ventricle, primary cardiac valvular disease, congenital or untreated ischemic heart disease, infiltrative/inflammatory/genetic cardiomyopathy, unstable angina pectoris, inotropic support within 30 days, MI within 90 days, cardioversion within 30 days, mechanical tricuspid valve, dialysis or documented GFR <30 ml/min, uncorrected severe anemia, other major medical disorder		
Reference: Masarone, Kittleson, De Vivo, D'Onofrio, Ammendola, et al., 2022 **Study Acronym:** NA **Country:** Italy **Study Design:** Prospective cohort, single site **Funding Source:** None	**Number of Patients:** 25 **Diagnosis:** HFrEF with LVEF ≤40% and NYHA class II-IV **Mean Age, Years (SD):** 63 (10) **Female N (%):** 3 (12) **Inclusion/Exclusion Criteria:** **Inclusion:** HFrEF with LVEF ≤40%, NYHA class II-IV, persistence of symptoms or >2 hospitalizations in previous 12 months despite OMT, QRS <120 ms **Exclusion:** ACS in previous 3 months, CRT implantation in previous 12 months, non-target dose of OMT, end-stage kidney disease	**Intervention:** CCM **Comparator:** NA **Follow-up Period:** 6 months	• LVEF • LV MEE • LV GLS
Reference: Matta et al., 2021 **Study Acronym:** NA **Country:** Italy **Study Design:** Prospective cohort, single site **Funding Source:** NR	**Number of Patients:** 10 **Diagnosis:** HFrEF with LVEF ≤45% and NYHA class II-IV **Mean Age, Years (SD):** 70 (8) **Female N (%):** 0 (0) **Inclusion/Exclusion Criteria:**	**Intervention:** CCM **Comparator:** NA **Follow-up Period:** 1 year	• MLWHFQ • 6MWT • NYHA functional class • LVEF • Overall survival • Incidence of hospitalizations • Adverse events

Study Details	Patients	Intervention(s)	Outcomes Assessed
	Inclusion: Age ≥18 years, symptomatic CHF, LVEF ≤45%, NYHA class II-IV, narrow QRS or wide QRS with documented CRT non-response, OMT **Exclusion:** Contraindication to interventional procedures, absence of vascular access, life expectancy <1 year secondary to non-cardiac comorbidities		
Reference: Deak et al. 2024 **Study Acronym:** NA **Country:** USA **Study Design:** Retrospective review, single-site university setting **Funding Source:** None	**Number of Patients:** 31 **Diagnosis:** HF patients with EF < 45% **Mean Age, Years (SD):** Mean age was 63 ± 10 years **Female N (%):** 26 **Inclusion/Exclusion Criteria:** NYHA functional status, LVEF > 45%, patient symptoms, hospitalization data, weight, and echocardiogram reports Inclusion: Consecutive patients admitted to the hospital were included in the study **Exclusion:** 2 patients who died during study were excluded from analysis, and 2 patients excluded from echocardiogram related endpoints due to failure to obtain repeat echocardiograms by the time of the analyses.	**Intervention:** CCM (type not specified) **Comparator:** NA **Follow-up Period**: 1.4 ± 0.8 years	• NYHA functional class • LVEF • Mean annualized hospitalizations • Mean weight change • Adverse event
Reference: Röger et al. 2017 **Study Acronym:** NA **Country:** Germany **Study Design:** Prospective, blinded trial. **Funding Source**: None	**Number of Patients:** 48 **Diagnosis:** HF patients with NYHA Classes II–III) and reduced left ventricular ejection fraction (LVEF < 40%) **Mean Age, Years (SD):** 60 ± 11.4 **Female N (%):** 6% **Inclusion/Exclusion Criteria:** Subjects must be over 18 years of age and have received optimal medical therapy. Includes patients with symptomatic heart failure (NYHA Classes II–III) and reduced left ventricular ejection fraction (LVEF < 40%) who were implanted with a CCM Optimizer™ device. left ventricular ejection fraction <40% and peakVO_2 ≥ 9 ml ml O2/kg/min. **Exclusion:** NR	**Intervention: 25 patients were randomized to receive signal delivery through two leads (Group A)** **Comparator:** 23 patients to signal delivery through one lead (Group B). **Follow-up Period:** 6 months	• NYHA functional class • MLWHFQ • LVEF • Peak VO_2
Reference: Röger et al. 2018	**Number of Patients:** 20	**Intervention:** CCM and S-ICD	• NYHA functional class

Study Details	Patients	Intervention(s)	Outcomes Assessed
Study Acronym: NA **Country:** Germany **Study Design:** Prospective, single-arm, single site **Funding Source:** NR	**Diagnosis:** HFrEF with LVEF ≤35% **Mean Age, Years (SD):** 54.3 (11.5) **Female N (%):** 2 (10) **Inclusion/Exclusion Criteria:** **Inclusion:** HFrEF with LVEF ≤35%, OMT **Exclusion:** NR	**Comparator:** NA **Follow-up Period:** 3 years	• MLWHFQ • LVEF • S-ICD performance • Mortality • Adverse event
Reference: Kuschyk et al. 2015 **Study Acronym:** NA **Country:** Germany **Study Design:** Retrospective cohort analysis, single site **Funding Source:** NR	**Number of Patients:** 81 **Diagnosis:** HFrEF with CCM implantation **Mean Age, Years (SD):** 61 (12) **Female N (%):** 12 (14.8) **Inclusion/Exclusion Criteria:** **Inclusion:** CCM implantation at study site between 2004 and 2012 **Exclusion:** None	**Intervention:** CCM **Comparator:** NA **Follow-up Period:** mean 34.2 ± 28 months (6-123 months)	• NYHA functional class • MLWHFQ • LVEF • Laboratory values • pVO_2 • Mortality • Adverse events
MAINTAINED Registry			
Reference: Fastner et al., 2022 **Study Acronym:** MAINTAINED **Country:** Germany **Study Design:** Retrospectively enrolled registry subgroup analysis; CCM-therapy in NYHA class II vs class III/IV **Funding Source:** NR	**Number of Patients:** **Total:** 172 NYHA class II: 18 NYHA class III: 132 NYHA class ambulatory IV: 22 **Diagnosis:** HFrEF with CCM implantation **Mean Age, Years (SD):** NYHA class II: 59 (10) NYHA class III/IV: 66 (12) **Female N (%):** NYHA class II: 2 (11) NYHA class III/IV: 25 (16) **Inclusion/Exclusion Criteria:** **Inclusion:** All patients with CCM implantation at the University Centre Mannheim since 2002 **Exclusion:** None	**Intervention:** CCM **Comparator:** NA **Follow-up Period:** 5 years	• NYHA functional class • KDIGO CKD stage • LVEF • TAPSE • Laboratory values • Mortality • Adverse events
Reference: Yucel et al., 2022 **Study Acronym:** MAINTAINED	**Number of Patients:** **Total:** 172 LVEF ≤30%: 152 LVEF >30%: 20	**Intervention:** CCM **Comparator:** NA	• NYHA functional class • LVEF • MLWHFQ

Study Details	Patients	Intervention(s)	Outcomes Assessed
Country: Germany **Study Design:** Retrospectively enrolled registry subgroup analysis; CCM-therapy in LVEF ≤30% vs LVEF >30% **Funding Source:** NR	**Diagnosis:** HFrEF with CCM implantation **Mean Age, Years (SD):** LVEF ≤30%: 69 (12) LVEF >30%: 71 (9) **Female N (%):** LVEF ≤30%: 25 (17) LVEF >30%: 2 (10) **Inclusion/Exclusion Criteria:** **Inclusion:** All patients with CCM implantation at the University Centre Mannheim since 2002 **Exclusion:** None	**Follow-up Period:** 5 years	• TAPSE • Laboratory values • Mortality • Adverse events
Reference: Fastner et al., 2021 **Study Acronym:** MAINTAINED **Country:** Germany **Study Design:** Retrospectively enrolled registry subgroup analysis; CCM-therapy in ischemic vs non-ischemic cardiomyopathy **Funding Source:** NR	**Number of Patients:** **Total:** 174 ICM: 107 NICM: 67 **Diagnosis:** HFrEF with CCM implantation **Mean Age, Years (SD):** ICM: 66 (12) NICM: 58 (13) **Female N (%):** ICM: 15 (14) NICM: 13 (19) **Inclusion/Exclusion Criteria:** **Inclusion:** All patients with CCM implantation at the University Centre Mannheim since 2002 **Exclusion:** None	**Intervention:** CCM **Comparator:** NA **Follow-up Period:** 5 years	• NYHA functional class • KDIGO CKD stage • LVEF • TAPSE • Laboratory values • Mortality • Adverse events
CCM-HF Registry			
Reference: Müller et al. 2017 **Study Acronym:** CCM-HF **Country:** EU	**Number of Patients:** **Total:** 143 LVEF ≥35%: 28 LVEF <35%: 114 **Diagnosis:** HFrEF with CCM implant for LVEF <45%	**Intervention:** CCM **Comparator:** NA **Follow-up Period:** 24 months	• NYHA functional class • MLWHFQ • 6MWT • LVEF • pVO_2 • Adverse events

Study Details	Patients	Intervention(s)	Outcomes Assessed
Study Design: Multi-site prospective registry subgroup analysis **Funding Source:** IMPULSE Dynamics	**Mean Age, Years (SD):** LVEF ≥35%: 65 (12) LVEF <35%: 63 (12) **Female N (%):** LVEF ≥35%: 6 (21) LVEF <35%: 27 (24) **Inclusion/Exclusion Criteria:** **Inclusion:** CCM implant at a participating center between 2010 and 2015. **Exclusion:** None\		• Mortality
CCM-REG Registry			
Reference: Kuschyk et al., 2021 **Study Acronym:** CCM-REG **Country:** EU **Study Design:** Prospective registry; retrospective analysis of all registry patients with subgroup analysis **Funding Source:** IMPULSE Dynamics	**Number of Patients:** **Total:** 503 LVEF ≤25%: 178 LVEF 26–34%: 164 LVEF ≥35%: 161 **Diagnosis:** HF and CCM implantation **Mean Age, Years (SD):** LVEF ≤25%: 64.3 (11.3) LVEF 26–34%: 67.55 (10.16) LVEF ≥35%: 66.92 (10.13) **Female N (%):** LVEF ≤25%: 31 (17.4) LVEF 26–34%: 35 (21.3) LVEF ≥35%: 36 (22.4) **Inclusion/Exclusion Criteria:** **Inclusion:** CCM implantation at a participating center between 2013 and 2019. **Exclusion:** None	**Intervention:** CCM **Comparator:** NA **Follow-up Period:** 3 years	• NYHA functional class • MLWHFQ • LVEF • Hospitalizations • Survival
Reference: Anker et al., 2019 **Study Acronym:** CCM-REG **Country:** EU	**Number of Patients:** **Total:** 140 LVEF 25-34%: 83 LVEF 35-45%: 57 **Diagnosis:** HFrEF with LVEF 25-45% and CCM implantation	**Intervention:** CCM **Comparator:** NA **Follow-up Period:** 3 years	• NYHA functional class • MLWHFQ • LVEF • Hospitalizations • Mortality

Study Details	Patients	Intervention(s)	Outcomes Assessed
Study Design: Prospective registry; retrospective subgroup analysis of patients matching FDA indications **Funding Source:** IMPULSE Dynamics	**Mean Age, Years (SD):** LVEF 25-34%: 66 (11) LVEF 35-45%: 67 (11) **Female N (%):** LVEF 25-34%: 18 (22) LVEF 35-45%: 14 (25) **Inclusion/Exclusion Criteria:** **Inclusion:** HFrEF with LVEF 25-45% and CCM implantation at participating centers between 2013 and 2017, NYHA class III/IV, QRS <130 ms **Exclusion:** Patients not matching FDA indications (LVEF outside 25-45% range)		
Meta - Analysis			
Reference: Giallauria et al. 2020 **Study Acronym**: NA **Country**; Italy **Study Design**: Meta-Analysis of FIX-HF5 Pilot (Neelagaru et al. 2006), FIX-CHF-4 (Borggrefe et al.2008), FIX-HF-5 (Kadish et al. 2011), FIX-HF-5C (Abraham et al. 2018), and FIX-HF-5C2 (Wiegn et al. 2020) **Funding Source:** Impulse Dynamics	**Number of patients:** **Total**: 861 (49 from FIX-HF-5 Pilot; 164 from FIX-CHF-4; 428 from FIX-HF-5; 160 from FIX-HF-5C; 60 from FIX-HF-C2) **Diagnosis:** HF and CCM implantation **Mean Age, Years:** As specified by individual FIX trial **Female N (%):** As specified by individual FIX trial **Inclusion/Exclusion Criteria:** As specified by individual FIX trial	FIX-HF-5 Pilot Intervention: CCM Comparator: Sham Follow-up Period: 24 weeks FIX-CHF-4 Intervention: CCM Comparator: Sham Follow-up Period: 24 weeks **FIX-HF-5** Intervention: CCM Comparator: OMT Follow-up Period: 24 weeks for efficacy endpoint; 50 weeks for safety endpoint **FIX-HF-5C** Intervention: CCM Comparator: OMT Follow-up Period: 24 weeks **FIX-HF-5C2** Intervention: CCM Comparator: 2-lead system versus 3-lead system Follow-up Period: 24 weeks	• NYHA functional class • MLWHFQ • LVEF • pVO_2

Study Details	Patients	Intervention(s)	Outcomes Assessed

Abbreviations: 6MWT=6-minute walk test; ACS=acute coronary syndrome; CCM=cardiac contractility modulation; CHF=congestive heart failure; CKD=chronic kidney disease; CRT=cardiac resynchronization therapy; EU=European Union; FDA=Food and Drug Administration; GFR=glomerular filtration rate; GLS=global longitudinal strain; HF=heart failure; HFpEF=HF with preserved ejection fraction; HFrEF=HF with reduced ejection fraction; IV=intravenous; KCCQ=Kansas City Cardiomyopathy Questionnaire; KDIGO=Kidney Disease Improving Global Outcomes; LV=left ventricular; LVEF=left ventricular ejection fraction; MEE=mechano-energetic efficiency; MI=myocardial infarction; MLWHFQ=Minnesota Living with Heart Failure Questionnaire; NA=not applicable; NR=not reported; NYHA=New York Heart Association; O_2=oxygen; OMT=optimal medical therapy; pVO_2=peak oxygen consumption; S-ICD=subcutaneous implantable cardioverter defibrillator; SD=standard deviation; TAPSE=tricuspid annular plane systolic excursion

Table B2. Study Outcomes

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ**	**Functional Outcomes**	**Adverse Events**
Comparative Studies					
FIX-CHF-4					
Borggrefe et al. 2008, FIX-CHF-4	**Intervention:** CCM **Comparator:** Sham	**pVO_2, mean change, mL/kg/min (SD):** <u>Phase I, 0-12 weeks:</u> ***CCM***-sham: 0.40 (3.0) ***Sham***-CCM: 0.37 (3.3) <u>Phase II, 12-24 weeks:</u> CCM-***sham***: -0.86 (3.06) Sham-***CCM***: 0.16 (2.50) Overall, mean (SD) pVO_2 improved while on CCM vs. sham by 0.52 (1.39)*	**MLWHFQ, mean change from baseline (SD):** <u>Phase I, 0-12 weeks:</u> **CCM**-sham: -12.06 (15.33) **Sham**-CCM: -9.70 (16.71) <u>Phase II, 12-24 weeks:</u> CCM-**sham**: 4.70 (16.57) Sham-**CCM**: -0.70 (15.13)	**NYHA Class (at 24 weeks), % patients in each class, CCM-sham vs. sham-CCM:** Class I: 8 vs. 9 Class II: 46 vs. 50 Class III: 24 vs. 23 Class IV: 2 vs. 2 **6MWT, mean change from baseline (SEE):** <u>Phase I, 0-12 weeks:</u> ***CCM***-sham: 16.9 (8.9)	**Mortality, n patients:** <u>Phase I, 0-12 weeks:</u> ***CCM***-sham: 0 ***Sham***-CCM: 1 <u>Phase II, 12-24 weeks:</u> CCM-***sham***: 1 Sham-***CCM***: 2 **Hospitalization:** <u>CCM vs. sham (0-12 weeks), total # of events:</u> 14 vs. 20

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ**	**Functional Outcomes**	**Adverse Events**
		mL/kg/min, 95% CI: 0.04 to 0.99.	Overall, mean (SD) MLWHFQ score improved while on CCM vs. sham by 2.93 (8.01)*, 95% CI: 0.29 to 5.56.	***Sham***-CCM: 10.8 (8.8) Phase II, 12-24 weeks: CCM-***sham***: -6.3 (10.4) Sham-***CCM***: 19.6 (9.1)	CCM vs. sham (0-24 weeks), total # of events (n patients): 41 (31) vs. 46 (31) **Arrhythmia, CCM vs. sham, median PVCs/hour (range):** CCM-sham: 20 (0-777) vs. 16 (0-1,007) Sham-CCM: 17 (0-459) vs. 15 (0-764) Cardiovascular related SAEs (at 24 weeks), CCM vs. sham, # of events (n patients): **HF decompensation:** 7 (6) vs. 8 (8) **Bleeding at CCM site:** 0 vs. 0 **CCM pocket infection:** 1 (1) vs. 3 (2) **ICD sensing defect:** 1 (1) vs. 0 **CCM lead dislodgement:** 1 (1) vs. 0
FIX-HF-5C and FIX-HF-5C2					
Kadish et al. 2011, FIX-HF-5	**Intervention:** CCM **Comparator:** OMT	**VAT (at 24 weeks):** Mean change from baseline: Decreased by 0.14 $mL/kg^{-1}/min^{-1}$ in both groups Responders (ITT), n (%, LCL to UCL): CCM vs OMT: 38 (17.7, 12.8 to 23.4) vs. 28 (12.2, 8.9 to 18.4)	**MLWHFQ (at 24 weeks), responders, n (%, LCL to UCL):** CCM: 110 (56.1, 48.9 to 63.1), OMT: 77 (41.8, 34.6 to 49.3) Difference in % responders (LCL to UCL): 14.3 (4.2 to 24.1)**	**NYHA Class (at 24 weeks), responders, n (%, LCL to UCL):** CCM: 94 (49.2, 41.9 to 56.5), OMT: 63 (34.4, 27.6 to 41.8) Difference in % responders (LCL to UCL): 14.8 (4.8 to 24.5)** Note: Patient considered responder if at least one-class	**All-cause hospitalization and all-cause mortality composite endpoint (ITT), # of events (%):** CCM: 112 (52.1), OMT: 103 (48.4) Difference: 3.7% (upper 1-sided 95% CL: 11.7%[α])*

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ**	**Functional Outcomes**	**Adverse Events**
		Difference in % responders (LCL to UCL): 4.5 (-2.4 to 11.5), p=0.314 Note: Patient considered responder if VAT increased by ≥20% **pVO_2 (at 24 weeks):** Difference in mean change from baseline between CCM and OMT: 0.65 mL/kg/min*, favoring CCM Responders, n (%, LCL to UCL): CCM: 31 (17.3, 12.1 to 23.7), OMT: 23 (13.7, 8.9 to 19.8) Difference in % responders (LCL to UCL): 3.6 (-4.1 to 11.3), p=0.233 Note: Patient considered responder if pVO_2 increased by 20%	Note: Patient considered responder if 10-point reduction seen in score	change seen in NYHA classification **6MWT (at 24 weeks), responders, n (%, LCL to UCL):** CCM: 65 (34.2, 27.5 to 41.4), OMT: 51 (29.5, 22.8 to 36.9) Difference in % responders (LCL to UCL): 4.7 (-4.9 to 14.2), p=0.197 Note: Patient considered responder if 6MWT increased by ≥40m	**Mortality at 50 weeks (ITT), n (%):** CCM: 13 (6.0), OMT: 7 (3.3), p=0.25 vs. OMT AEs from SSD to 1 year, CCM vs. OMT, # of events (n patients): **Arrhythmia:** 40 (29) vs. 30 (25) **Worsening HF:** 72 (50) vs. 85 (50) **ICD/PM system related:** 13 (11) vs. 7 (6) **Bleeding:** 8 (6) vs. 8 (8) **Localized infection:** 33 (27) vs. 36 (29) CCM lead-related SAEs from SSD to 1 year, total # of events (n patients): **Total incidence of lead complications, n (%):** 14 (7) **Lead fracture:** 3 (3) **RV lead dislodgement:** 6 (6) **RA lead dislodgement:** 6 (5) **Lead perforation:** 2 (2)
Abraham et al. 2011, FIX-HF-5 subgroup analysis	**Intervention:** CCM **Comparator:** OMT (Subgroup analysis of FIX-HF-5C study involving 48% of the primary study's	**VAT (at 24 weeks):** Mean change from baseline, $mL/kg^{-1}/min^{-1}$ (SD): CCM: 0.10 (2.36), OMT: -0.54 (1.83) Difference in mean change (ITT): 0.64 mL kg^{-1} min^{-1} *	**MLWHFQ (at 24 weeks):** Difference in mean change from baseline between CCM and OMT: 10.8 points**, favoring CCM	**NYHA Class (at 24 weeks):** Difference in mean change from baseline between CCM and OMT: -0.29**, favoring CCM Responders, n (%): CCM: 43 (44.3), OMT: 19 (23.2)	**Mortality (from SSD to 1 year), n (%):** CCM: 4 (2.0), OMT: 2 (0.9) SAEs from SSD to 1 year, CCM vs. OMT, # of events (n patients): **Arrhythmia:** 11 (8) vs. 10 (8)

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ**	**Functional Outcomes**	**Adverse Events**
	patients with LVEF ≥25% and NYHA class III symptoms)	Responders (ITT), n (%): CCM: 23 (21.5), OMT: 9 (9.4) Difference in % responders: 12.1* **pVO_2 (at 24 weeks):** Mean change from baseline, $mL/kg^{-1}/min^{-1}$ (SD): CCM: 0.34 (3.11), OMT: -0.97 (2.21) Difference in mean change: 1.31 $mL/kg^{-1}/min^{-1}$ **, favoring CCM Responders, n (%): CCM: 18 (19.2), OMT: 3 (3.95) Difference in % responders: 15.2** Note: "Responder" criteria were the same as FIX-HF-5 study for all outcomes	Responders, n (%): CCM: 60 (59.4), OMT: 35 (41.7) Difference in % responders: 17.7*	Difference in % responders: 21.1%** **6MWT (at 24 weeks), responders, n (%):** CCM: 36 (37.1), OMT: 20 (25.3) Difference in % responders: 11.8%, p=0.065	**Worsening HF:** 18 (14) vs. 27 (16) **ICD/PM system related:** 5 (4) vs. 3 (3) **Bleeding:** 2 (2) vs. 6 (6) **Localized infection[β]:** 15 (14) vs. 20 (15) Lead-related SAEs from SSD to 1 year, total # of events (n patients): **Lead fracture:** 1 (1) **RV lead dislodgement:** 4 (4) **RA lead dislodgement:** 1 (1) **Lead perforation:** 1 (1)
Abraham et al. 2018, FIX-HF-5C	**Intervention:** CCM **Comparator:** OMT (Confirmatory study of FIX-HF-5 subgroup analysis among patients with LVEF 25% to 45%)	**pVO_2 (at 24 weeks):** Bayesian analysis, mean difference between CCM and OMT (95% BCI): 0.836* mL/kg/min (0.12 to 1.55); probability of CCM superiority: 0.989 Non-Bayesian analysis, mean difference between CCM and OMT (95% CI): 0.79 mL/kg/min (-0.10 to 1.68)	**MLWHFQ (at 24 weeks):** Mean change (SD) from Baseline, CCM vs. OMT: -21.3 (23.8) vs. -10.2 (18.5) Mean difference between CCM and OMT (95% CI): -11.7 points (-17.6 to	**NYHA Class (at 24 weeks):** Responders, n (%): CCM: 57 (81) OMT: 32 (42) OR (CCM vs. OMT): 5.97***, favoring CCM Note: Patient considered responder if at least one-class change seen in NYHA classification	Device- or procedure-related complications, # of events: **Lead dislodgement:** 5 **Deep vein thrombosis:** 1 **Generator erosion:** 1 **Complication-free rate**: 89.7% (95% CI: 79.9 to 95.8) Mortality outcomes (at 24 weeks): **Mortality, n:** CCM: 2, OMT: 4

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ**	**Functional Outcomes**	**Adverse Events**
		Sensitivity analyses: Accounted for various methods of missing data imputation and site-to-site heterogeneity; showed consistency of CCM superiority across all analyses and statistical significance in Bayesian analysis with any borrowing weight of ≥0.11 * Data pulled from the online data supplement Note: Authors conducted two analyses of pVO_2: (1) Bayesian repeated measures linear model with 30% borrowing weight of corresponding FIX-HF-5 subgroup treatment group difference; posterior probability of positive treatment difference in favor of CCM set at >0.975 (2) Non-Bayesian repeated measures model without borrowing to summarize treatment difference independent of FIX-HF-5 data	-5.9)***, favoring CCM	**6MWT (at 24 weeks), mean change (SD):** CCM: 43.0 m (80.7) OMT: 9.3 m (87.4), p=0.0093 between groups	**Overall survival, %:** CCM: 98, OMT: 95 **Survival free of cardiac death and HF hospitalization, %:** CCM: 97.1, OMT: 89.2 Adjudicated SAEs, n (%), CCM vs. OMT: **Arrhythmia:** 3 (4.1) vs. 2 (2.3) **Worsening HF:** 3 (4.1) vs. 7 (12.8) **Bleeding:** 0 (0.0) vs. 1 (1.2) **Local infection:** 1 (1.4) vs. 4 (4.7) **ICD/PM malfunction:** 2 (2.7) vs. 0 (0.0)
Secondar-y analysis	**Intervention:** CCM **Comparator:** OMT (Secondary analysis assessing LVEF <35% vs. ≥35% by	**pVO_2, mean difference (95% CI) in ≥35% subgroup:** 1.76 mL/kg/min (0.45 to 3.07)**, favoring CCM	**MLWHFQ, mean difference (95% CI) in ≥35% subgroup:** -15 units (-23 to -8)**, favoring CCM	**NYHA Class, % responders (95% CI) in ≥35% subgroup:** CCM: 71 (55 to 83), OMT: 57 (NR), p=0.012 between groups Note: Patient considered responder if at least one-class	NA

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ**	**Functional Outcomes**	**Adverse Events**
	pooling data from FIX-HF-5 and FIX-HF-5C)			change seen in NYHA classification	
Wiegn et al., 2020, FIX-HF-5C2	**Intervention:** 2-lead CCM **Comparator:** 3-lead CCM (data for this historical control group pulled from FIX-HF-5C)	**pVO_2, Bayesian model-based mean change from baseline at 24 weeks:** 2-lead CCM: 0.80 (95% BCI: 0.18,1.40) mL/kg/min FIX-HF-5C control: -0.93 (95% BCI: -1.46, -0.39) mL/kg/min Difference between groups: 1.72 (95% BCI: 1.02,2.42) mL/kg/min***	NA	**NYHA class, change from baseline at 24 weeks, 2-lead CCM vs. FIX-HF-5C control:** Improved by ≥1 class change: 83.1% vs. 42.7%*** No change: 17% vs. 56% Worsened: 0% vs. 1%	**All-cause mortality through 24 weeks, 2-lead CCM vs. FIX-HF-5C control, n:** 0 vs. 4 **2-lead CCM vs. FIX-HF-5C 3-lead CCM complication rate:** 1.7% vs. 10.3%; p=0.07 **Adjudicated device- or procedure-related complication through 24 weeks, 2-lead CCM:** 1 observed (hematoma, procedure-related)

[α] Below prespecified allowable 12.5%

[B] Localized infection was defined as all nonseptic infections with a documented location (e.g., upper respiratory bronchitis, pneumonia, otitis media, urinary tract, gastrointestinal, cellulitis, etc.)

*p<0.05, **p<0.01, ***p<0.001

Abbreviations: 6MWT=6-minute walk test; AEs = adverse events; BCI=Bayesian credible interval; CCM=cardiac contractility modulation; CI=confidence interval; CL=confidence limit; HF=heart failure; ICD=implanted cardioverter defibrillator; ITT=intent-to-treat; LCL=lower confidence limit; LVEF=left ventricular ejection fraction; MLWHFQ=Minnesota Living with Heart Failure Questionnaire; NA=not applicable; NR= not reported; NYHA=New York Heart Association; OMT=optimized medical therapy; OR=odds ratio; PM=pacemaker; PVCs=premature ventricular contractions; pVO_2=peak oxygen consumption; RA=right atrium; RV=right ventricle; SAEs=serious AEs; SD = standard deviation; SSD=study start date (scheduled implant date); UCL=upper confidence limit; VAT=ventilatory anaerobic threshold

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ and KCCQ**	**Functional Outcomes**	**Adverse Events**
Non-Comparative / Observational Studies					

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ and KCCQ**	**Functional Outcomes**	**Adverse Events**
Reference: Davtyan et al., 2023	**Intervention:** CCM **Comparator:** NA		**MLWHFQ, change from baseline to 1-year follow-up, median (IQR):** 53 (36.0-58.5) vs 42 (30.0-53.5), p=0.109	**NHYA functional class, change from baseline to 1-year follow-up, median (IQR):** 3 (2-3) vs. 2 (2-3), p=0.085 **LVEF, change from baseline to 1-year follow-up, median (IQR):** 30 (24.0-32.75) vs. 30.4 (25.25-35.75), p=0.212 **6MWD, change from baseline to 1-year follow-up, median (IQR):** 300 (180-310) vs. 300 (270-320), p=0.095 **Mitral regurgitations, change from baseline to 1-year follow-up, median (IQR):** 2 (2-3) vs. 2 (2-3) **Tricuspid regurgitations, change from baseline to 1-year follow-up, median (IQR):** 2 (2-3) vs. 2 (2-3) **NTproBNP, change from baseline to 1-year follow-up, median (IQR):** 1319 (185-3760) vs. 916 (173-1165), p=0.225	**Death, at 2-year follow-up:** 4, due to non-cardiac causes
Masarone, Kittleson, De Vivo, D'Onofrio, Rao, et al., 2022	**Intervention:** CCM **Comparator:** NA			**TAPSE, pre-implant to 6-month follow-up, mm, M (SD):** 13.6 (5.6) vs. 16.7 (4.6), p= 0.012	**Tricuspid regurgitation, pre-implant to 6-month follow-up, vena contracta, cm, M (SD):** 0.40 (0.19) vs. 0.45 (0.23), p = 0.33 **Tricuspid regurgitation, pre-implant to 6-month follow-up, proximal isosurface area radius, cm, M (SD):** 0.54 (0.22) vs. 0.62 (0.20), p = 0.18

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ and KCCQ**	**Functional Outcomes**	**Adverse Events**
Pavlovskaya et al., 2023	**Intervention:** CCM **Comparator:** NA	**Peak VO_2, ml/kg/min, Survived vs. Died or had a heart transplant, M (SD)**: 3 years: 16.7 (5.61) vs. 15.1 (4.6), NS 5 years: 23.7 (5.56) vs. 14.1 (4.5), p= 0.043			**Cardiovascular death, % patients:** 3 years (n=59): 83.3 5 years (n=56): 73.6 **Heart transplantation, n patients, %:** 3 years: 2 (3) 5 years: 2 (3.5) **Ventricular tachyarrhythmia, requiring ICD shocks, n patients, %:** 3 years: 0 5 years: 9 (16) **Patients hospitalized due to decompensated HF, n patients, %:** 3 years: 19 (32) 5 years: 28 (50) **Hospitalizations, all-cause, n events:** 3 years : 48 5 years: 70 **Mortality, observed vs. predicted from MAGGIC risk score, %:** 3 years: 20.3 vs. 22.6, p=0.024

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ and KCCQ**	**Functional Outcomes**	**Adverse Events**
					Mortality, observed vs. predicted from Seattle Heart Failure Model, %: 5 years: 33.9 vs. 44.3, p=0.012
Reference: Tint & Micu, 2023	**Intervention:** CCM **Comparator:** NA	NA		**NYHA class, baseline vs. last follow-up, mean (SD):** 3.2 (0.5) vs. 1.4 (0.5)*** **LVEF, baseline vs. last follow-up, mean (SD), %:** 24.68 (4.5) vs. 34.6 (5)*** **6MWT, baseline vs. last follow-up, mean (SD), m:** 307.9 (74.1) vs 567 (99.5)***	
Reference: Ansari et al., 2022	**Intervention:** CCM **Comparator:** NA		**MLWHFQ change score at 1-year follow-up, Responders to CCM (based on LVEF) (n=26) vs. Non-responders (n=32), M (SD):** −11.3 (16.5) vs. −19.5 (18.6), p=0.20 **MLWHFQ change score at 1-year follow-up, Responders to CCM (based on NYHA) (n=39) vs. Non-responders (n=19), M (SD):** −19.3 (17.4) vs. -5.6 (16.4), p=0.06	**NYHA class, improvement of 1 or more levels from baseline to 1 year, %:** 67.2 **LVEF change ≥ 5% from baseline to 1 year, %:** 44.8 **NT-pro BNP (pg/mL) change from baseline to 1 year, Responders to CCM (based on LVEF) (n=26) vs. Non-responders (n=32), M (SD):** −1995 (2921) vs. 68.4 (4170), p=0.06 **NT-pro BNP (pg/mL) change from baseline to 1 year, Responders to CCM (based on NYHA) (n=39) vs. Non-responders (n=19), M (SD):** −1912 (2490) vs. 1431 (5178), p<0.01	
Reference: Linde et al.,	**Intervention:** CCM	NA	**KCCQ overall summary score, mean (SD) change at 24 weeks:**	**NYHA class, mean (SD) improvement at 24 weeks:**	**SAEs, n patients (total events):**

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ and KCCQ**	**Functional Outcomes**	**Adverse Events**
2022, CCM-HFpEF	**Comparator:** NA		18.0 (16.6)*** **KCCQ clinical summary score, mean (SD) change at 24 weeks:** 15.3 (19.4)***	0.5 (0.6)*** **NT-proBNP, median (range) change at 24 weeks, pg/mL:** 23.0 (-2399 to 1710)	Total: 12 (20) Device related: 0 (0) Procedure related: 3 (3) Deaths, all cause: 0 **Hospitalization, n (total events):** Unplanned hospitalization: 12 HF related hospitalization: 2 (4)
Reference: Masarone, Kittleson, De Vivo, D'Onofrio, Ammendola, et al., 2022	**Intervention:** CCM **Comparator:** NA	NA	**MLWHFQ score, baseline vs. 6-month follow-up, mean (SD):** 40.08 (12.31) vs. 26.9 (10.8)***	**LVEF, baseline vs. 6-month follow-up, mean (SD), %:** 30.8 (7.1) vs. 36.1 (6.9)* **GLS, baseline vs. 6-month follow-up, mean (SD), %:** 10.3 (2.7) vs. -12.9 (4.2)* **MEE, baseline vs. 6-month follow-up, mean (SD), mL/s:** 32.2 (10.1) vs. 38.6 (7.6)* **MEE index, baseline vs. 6-month follow-up, mean (SD), mL/s/g:** 18.4 (6.3) vs. 24.3 (6.7)* **NT-proBNP, baseline vs. 6-month follow-up, mean (SD), pg/mL:** 2975 (1988) vs. 1911 (1268)*	NA
Reference: Matta et al., 2021	**Intervention:** CCM **Comparator:** NA	NA	**MLWHFQ score, baseline vs. last follow-up, mean (SD):** 59.6 (49) vs. 34.2 (32)*	**NYHA class, baseline vs. last follow-up, mean (SD):** 3.0 (0.4) vs. 1.6 (0.5)**	**Mortality, all cause, n (%):** 1 (10)

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ and KCCQ**	**Functional Outcomes**	**Adverse Events**
				LVEF, baseline vs. last follow-up, mean (SD), %: 29.4 (8) vs. 32.2 (10) **6MWT, baseline vs. last follow-up, mean (SD), m:** 179 (73) vs 304 (99)***	**Hospitalization, n (%):** Total: 3 (30) Pneumonia: 1 Worsening HF: 1 Sustained ventricular tachycardia: 1
Reference: Deak et al., 2024	**Intervention:** CCM **Comparator:** NA	NA	NA	**NYHA class vs. last follow-up, improved by** 0.97 functional classes ($p < 0.001$), and improvement occurred in 68% of patients. **Mean Annual Hospitalization,** improved (0.8 ± 0.8 vs. 0.4 ± 1.0 hospitalizations/year, $p = 0.048$), **LVEF,** Mean EF improved by 8% ($p = 0.002$), **Mean Weight Change.** Mean weight change was 8.5 pounds lost, amounting to 4% of body weight ($p = 0.002$	**NA**
Röger et al. 2017	**Intervention:** one-lead CCM device (Group A) **Comparator:** two leads CCM device (Group B)	Peak $O_{2,}$ ml/kg/min, PeakVO_2 showed improvement trends in both groups (0.34 ± 1.52 vs. 0.10 ± 2.21 ml/kg/min; p = ns).	**MLWHFQ score, baseline vs. last follow-up, mean (SD):** MLWHFQ (-14 ± 20 vs. – 16 ± 22) were observed in Group A and in Group B. (p = ns).	**NYHA class, baseline vs. last follow-up, mean (SD):** Improvements from baseline in NYHA (- 0.7 ±_0.5 vs. - 0.9 ±0.7) (p = ns).	**Adverse events, n:** No statistically significant difference was observed between the groups with regard to the percentage of patients experiencing at least one SAE in any of the cardiac-related
Röger et al. 2018	**Intervention:** CCM	NA	**MLWHFQ score, baseline vs. last follow-up, mean (SD):**	**NYHA class, baseline vs. last follow-up, mean (SD):**	**Adverse events, n:**

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ and KCCQ**	**Functional Outcomes**	**Adverse Events**
	Comparator: NA		50.2 (23.7) vs. 29.6 (22.8)***	2.9 (0.4) vs. 2.1 (0.7)*** **LVEF, baseline vs. last follow-up, mean (SD) %:** 24.4 (8.1) vs. 30.9 (9.6)**	CCM lead-revision required: 3 Postoperative wound-healing delay: 1 Subclavian vein thrombosis: 1 Skin abscess on thoracic wall, requiring S-ICD removal: 1 **Arrythmias, n patients (total events):** Sustained VT, appropriate ICD shock: 3 (6) Non-sustained VT, inappropriate ICD shock: 1 (1) **Mortality, n (%):** 1 (5) All-cause: 1 (5) While treated with CCM: 0 (0) While CCM switched off: 1 (5)
Kuschyk et al. 2015	**Intervention:** CCM **Comparator:** NA	**pVO_2, baseline vs. last follow-up, mean (SD) mL/kg/min:** 13.9 (3.3) vs 14.6 (3.5)	**MLWHFQ score, baseline vs. last follow-up, mean (SD):** 49.9 (17.7) vs. 32.2 (18.2)***	**NYHA class, baseline vs. last follow-up, mean (SD):** 3.0 (0.5) vs. 2.3 (0.9)*** **LVEF, baseline vs. last follow-up, mean (SD) %:** 23.1 (7.9) vs. 29.4 (8.6)*** **NT-proBNP, baseline vs. last follow-up, mean (SD) mg/dl:** 4395 (3818) vs. 2762 (3490)***	**Adverse events, n:** CCM lead dislodgment or fracture: 4 Infection requiring CCM removal: 1 CCM replacement due to malfunction: 2 Persistent atrial fibrillation: 12 Permanent atrial fibrillation: 3 **Mortality, n (%):** 21 (25.9) Cardiac causes: 11 (52.4)

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ and KCCQ**	**Functional Outcomes**	**Adverse Events**
					Non-cardiac causes: 10 (47.6) **Mortality, observed vs. predicted from MAGGIC risk score:** 1 year: 5.2% vs. 18.4%*** 3 year: 29.5% vs. 40%
MAINTAINED Registry					
Reference: Fastner et al., 2022	**Intervention:** CCM **Comparator:** NA	NA	NA	**NYHA class change over follow up, p-value:** NYHA II: 0.96 NYHA III/IV: <0.0001*** NYHA II vs. III/IV: <0.0001*** **LVEF change over follow up, p-value:** NYHA II: 0.0072** NYHA III/IV: <0.0001*** NYHA II vs. III/IV: 0.83 **TAPSE change at 5-year follow up, p-value:** NYHA II: 0.20 NYHA III/IV: 0.0397* NYHA II vs. III/IV: 0.34 **KDIGO CKD stage change at 5-year follow up, p-value:** NYHA II: 0.12 NYHA III/IV: 0.60	**Device- or procedure-related SAEs, that led to explant or revision of CCM, NYHA II vs. III/IV, n (%):** Total: 3 (17) vs. 25 (16), p=1.00 Endocarditis: 0 vs. 5 Battery depletion: 0 vs. 9 Other: 3 vs. 11 **SAEs that led to lead replacement, NYHA II vs. III/IV, n (%):** 4 (22) vs 16 (10), p=0.23 **All-cause mortality, NYHA II vs. III/IV, n:** 1-year: 0 vs. 12 3-year: 3 vs. 27 5-year: 2 vs. 14 **Cardiovascular related mortality, NYHA II vs. III/IV:**

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ and KCCQ**	**Functional Outcomes**	**Adverse Events**
				NYHA II vs. III/IV: 0.99 **NT-proBNP change at 5-year follow up, p-value:** NYHA II: 0.48 NYHA III/IV: 0.68 NYHA II vs. III/IV: 0.12	6% vs. 8%, p=1.00 **3-year mortality, observed vs. predicted by MAGGIC risk score:** NYHA II: 17% vs. 31%, p=0.44 NYHA III/IV: 26% vs. 42%, p=0.0038
Reference: Yucel et al., 2022	**Intervention:** CCM **Comparator:** NA		**MLWHFQ score change at 3-year follow up:** LVEF ≤30% vs. LVEF >30%: p=0.61	**NYHA class change at 5-year follow up, p-value:** LVEF ≤30%: <0.01** LVEF >30%: <0.01** LVEF ≤30% vs. LVEF >30%: 0.56 **LVEF change at 5-year follow up, p-value:** LVEF ≤30%: <0.01** LVEF >30%: 0.27 LVEF ≤30% vs. LVEF >30%: <0.01** **TAPSE change at 5-year follow up, p-value:** LVEF ≤30%: 0.01* LVEF >30%: 0.79 LVEF ≤30% vs. LVEF >30%: 0.4 **NT-proBNP change at 5-year follow up, p-value:** LVEF ≤30%: 0.14 LVEF >30%: 0.18	**Device- or procedure-related SAEs, that led to explant or revision of CCM, n:** Total: 28 Endocarditis: 5 Battery depletion: 9 Other: 14 LVEF ≤30% vs. LVEF >30%: p=0.07 **SAEs that led to lead replacement:** Total: 20 LVEF ≤30% vs. LVEF >30%: p=0.31 **Total study population survival:** 1-year: 90.96% 3-year: 69.27% 5-year: 56.23% **Mean survival time:** 4.2 years

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ and KCCQ**	**Functional Outcomes**	**Adverse Events**
				LVEF ≤30% vs. LVEF >30%: 0.28	**Cardiovascular related mortality, LVEF ≤30% vs. LVEF >30%:** 6% vs. 8%, p=1.00 **3-year mortality, observed vs. predicted by MAGGIC risk score:** LVEF ≤30%: 27% vs. 41%, p<.01 LVEF >30%: NR
Reference: Fastner et al., 2021	**Intervention:** CCM **Comparator:** NA	NA	NA	**NYHA class change at 5-year follow up, p-value:** ICM: <0.0001*** NICM: <0.0001*** ICM vs. NICM: 0.25 **LVEF change at 5-year follow up, p-value:** ICM: 0.0121* NICM: <0.0001*** ICM vs. NICM: 0.009** **TAPSE change at 5-year follow up, p-value:** ICM: 0.41 NICM: 0.0351* ICM vs. NICM: 0.044* **KDIGO CKD stage change at 5-year follow up, p-value:** ICM: 0.64	**Device- or procedure-related SAEs, that led to explant or revision of CCM, n (%):** Total: 28 (16) Endocarditis: 5 (3) Battery depletion: 9 (5) Other: 14 (8) **SAEs that led to lead replacement, n (%):** 20 (11) **All-cause mortality, n (%):** 1-year: 15 (9) 3-year: 30 (23) 5-year: 16 (19) **Cardiovascular related mortality, n:** 16 (25% of all deaths)

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ and KCCQ**	**Functional Outcomes**	**Adverse Events**
				NICM: 0.98 ICM vs. NICM: 0.48 **NT-proBNP change at 5-year follow up, p-value:** ICM: 1.00 NICM: 0.89 ICM vs. NICM: 0.09	**3-year mortality, observed vs. predicted by MAGGIC risk score:** ICM: 35% vs. 43%, p<0.0395 NICM: 29% vs. 37%, p=0.19
CCM-REG Registry					
Reference: Kuschyk et al., 2021	**Intervention:** CCM **Comparator:** NA	NA	**MLWHFQ score, mean (SD) change at 24 months:** Total cohort: 10 (21)***	**NYHA class, mean (SD) improvement at 24 months:** 0.6 (0.7)*** **LVEF, mean (SD) change at 24 months, %:** Total cohort: 5.6 (8.4)*** LVEF ≤25%: 10 (10)*** LVEF 26–34%: 4.2 (8.1)** LVEF ≥35%: 3.3 (5.5)**	**Hospitalizations, CV related, pre-treatment vs. 2-year post CCM implant, per patient-year:** Total cohort: 1.04 vs. 0.39*** LVEF ≤25%: 1.28 vs. 0.53*** LVEF 26–34%: 0.96 vs. 0.39*** LVEF ≥35%: 0.86 vs. 0.27*** **Survival curve, 1 year observed vs. predicted from MAGGIC risk score:** Total cohort: p=0.0108* LVEF ≤25%: p=0.6875 LVEF 26–34%: p=0.0015** LVEF ≥35%: p=0.0116* **Survival curve, 3-year observed vs. predicted from MAGGIC risk score:**

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ and KCCQ**	**Functional Outcomes**	**Adverse Events**
					Total cohort: p=0.0244* LVEF ≤25%: p=0.6392 LVEF 26–34%: p=0.0041** LVEF ≥35%: p=0.0551
Anker et al., 2019	**Intervention:** CCM **Comparator:** NA	NA	**MLWHFQ score, mean change from baseline, total cohort:** 6 months: -11.7*** 12 months: -11.8*** 18 months: -11.4*** 24 months: -17.1***	**NYHA class, mean improvement from baseline, total cohort:** 6 months: 0.6*** 12 months: 0.7*** 18 months: 0.7*** 24 months: 0.8*** **LVEF, mean (SD) baseline vs. at 6 months, %:** Total cohort: 32.8 (4.9) vs. 35.8 (8.2)** LVEF 25–34%: 29.7 (2.7) vs. 32.8 (7.3)* LVEF 35-45%: 38.2 (2.4) vs. 41.0 (7.2)	**SAEs over 3-year follow-up, n patients (total events):** Total reported: 82 (201) CCM lead fracture or failure: 1 (1) CCM related, other: 9 (9) Worsening HF: 32 (61) Arrythmia: 9 (10) Cardiac, other: 9 (12) Infection: 2 (2) **Hospitalizations, CV related, pre-treatment vs. 2 years post CCM implant, per patient-year:** Total cohort: 1.2 vs. 0.35*** LVEF 25-34%: 1.18 vs. 0.42*** LVEF 35-45%: 1.23 vs. 0.24*** **Survival, 3-year observed vs. predicted by SHFM risk score:** Total cohort: 82.8% vs. 76.7%

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ and KCCQ**	**Functional Outcomes**	**Adverse Events**
					LVEF 25-34%: 79.4% vs. 78.0% LVEF 35-45%: 88.0% vs. 74.7%*
CCM-HF Registry					
Müller et al. 2017	**Intervention:** CCM **Comparator:** NA	Dataset underpowered for statistical analysis of pVO_2 or 6MWT	**MLWHFQ score, mean (SD) change from baseline at 24 months:** Total cohort: -13.6 (20.6)* LVEF <35%: -15.0 (21.6)* LVEF ≥35%: -9.4 (18)	**NYHA class, mean (SD) baseline vs. at 24 months:** Total cohort: 2.9 (0.5) vs. 2.2 (0.8)* LVEF <35%: 2.9 (0.5) vs. 2.2 (0.9)* LVEF ≥35%: 2.8 (0.4) vs. 2.3 (0.7)* **LVEF, mean (SD) change at 24 months, %:** Total cohort: 6.5 (8.7)* LVEF <35%: 7.5 (9.3)* LVEF ≥35%: 3.5 (6.0)	**SAEs over 2-year follow-up, n patients (total events):** Total reported: 91 (193) Device related: 25 (32) Procedure related: 20 (28) Worsening HF: 37 (55) Cardiopulmonary, general: 23 (30) Arrythmia: 14 (20) Infection: 14 (16) Bleeding: 4 (5) ICD related: 4 (5) General medical: 29 (41) **Hospitalizations, all cause, over 2-year follow-up, n:** 171 **Mortality, over 2-year follow-up, n:** All cause: 18 Cardiovascular: 7 Non-cardiovascular: 8 Unknown: 3

Author, Year, Study	Intervention and Comparators	Study Outcomes			
		pVO_2 and VAT	**MLWHFQ and KCCQ**	**Functional Outcomes**	**Adverse Events**
					Device related: 0 **Survival, proportion (95% CI):** 1 year: 94.2% (88.8, 97.1%) 2 years: 86.4% (79.3, 91.2%)

[α] Below prespecified allowable 12.5%

[B] Localized infection was defined as all nonseptic infections with a documented location (e.g., upper respiratory bronchitis, pneumonia, otitis media, urinary tract, gastrointestinal, cellulitis, etc.)

*p<0.05, **p<0.01, ***p<0.001

Abbreviations: 6MWT=6-minute walk test; AEs = adverse events; BCI=Bayesian credible interval; CCM=cardiac contractility modulation; CI=confidence interval; CL=confidence limit; CV=cardiovascular; HF=heart failure; ICD=implanted cardioverter defibrillator; ITT=intent-to-treat; LCL=lower confidence limit; LVEF=left ventricular ejection fraction; MLWHFQ=Minnesota Living with Heart Failure Questionnaire; NA=not applicable; NR= not reported; NYHA=New York Heart Association; OMT=optimized medical therapy; OR=odds ratio; PM=pacemaker; PVCs=premature ventricular contractions; pVO_2=peak oxygen consumption; RA=right atrium; RV=right ventricle; SAEs=serious AEs; SD = standard deviation; SHFM=Seattle heart failure model; SSD=study start date (scheduled implant date); UCL=upper confidence limit; VAT=ventilatory anaerobic threshold

C. Appendix C: Heart Failure Quality of Life and Functional Measures

Measure	Description	References
New York Heart Association (NYHA) classification	Class and Patient Symptoms • I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath. • II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath or chest pain. • III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath or chest pain. • IV: Symptoms of heart failure at rest. Any physical activity causes further discomfort.	https://doi.org/10.1161/CIR.0b013e31829e8807 (see Table 4) https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure The Criteria Committee of the New York Heart Association. (1994). *Nomenclature and criteria for diagnosis of diseases of the heart and great vessels* (9th ed.), Boston, Mass: Little & Brown.

Kansas City Cardiomyopathy Questionnaire (KCCQ)	The KCCQ captures how heart failure affects patients' lives. The KCCQ has a 2-week recall period and includes 23 items that map to 7 domains: symptom frequency; symptom burden; symptom stability; physical limitations; social limitations; quality of life; and self-efficacy.	https://doi.org/10.1016/S0735-1097(00)00531-3 https://doi.org/10.1016/j.jacc.2020.09.542
Short Form Health Survey (SF-36)	The SF-36 is a self-reported outcome measure assessing the impact of health on an individual's everyday life. Also, the survey can be administered by a trained interviewer in person or by telephone. The SF-36 evolved from the Medical Outcomes Study. Eight domains: 1. Limitations in physical activities because of health problems. 2. Limitations in social activities because of physical or emotional problems 3. Limitations in usual role activities because of physical health problems 4. Bodily pain 5. General mental health	https://doi.org/10.1097/00005650-199303000-00006 https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/survey-instrument.html Ware, J. E., Jr, & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care*, *30*(6), 473–483. https://doi.org/10.1136/bmj.305.6846.160

	(psychological distress and well-being) 6. Limitations in usual role activities because of emotional problems 7. Vitality (energy and fatigue) 8. General health perceptions	
6-minute walk distance (6MWD)	The six-minute walk test is a simple cardiopulmonary functional testing modality. Its results can help ascertain the degree of functional impairment.	https://doi.org/10.1177%2F1753944719870084 https://www.ncbi.nlm.nih.gov/books/NBK576420/
Katz Index of Independence in Activities of Daily Living	The Katz Index of Independence in Activities of Daily Living assesses functional status as a measurement of the patient's ability to perform activities of daily living (ADL) independently. It quantifies ADL across a wide range of patient populations.	https://doi.org/10.1002/acr.20638
Minnesota Living with Heart Failure Questionnaire (MLHFQ)	The Minnesota Living with Heart Failure Questionnaire (MLHFQ) assesses health - related quality of life for patients living with heart failure. Questions focus on the physical, emotional and socioeconomic ways heart failure adversely affects patients.	https://doi.org/10.1186/s12955-016-0425-7 https://license.umn.edu/product/minnesota-living-with-heart-failure-questionnaire-mlhfq

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