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Review Article

Impact of Cardiac Contractility Modulation on Left Ventricular Ejection Fraction and Clinical Outcomes in Heart Failure: A Systematic Review and Meta-Analysis

I Nyoman Wiryawan[1], David Yobel[1], Gusti Ngurah Prana Jagannatha[1], Ni Kadek Aristia Dewi[1], Cindy Amanda Shandy[1], Hendy Wirawan[1]

Abstract

Patients with heart failure and narrow QRS often remain symptomatic despite Optimal Medical Therapy (OMT), while CRT is usually not indicated. Cardiac Contractility Modulation (CCM) may improve symptoms and quality of life in this population. This systematic review and meta-analysis included studies comparing CCM to either OMT alone or OMT with CRT. Assessed outcomes included improvements in clinical, structural, and physiological domains. Random-effects models were applied for all analyses, and results were reported as Odds Ratios (OR) or Mean Differences (MD) with 95% Confidence Intervals (CI). All statistical analyses were conducted using Review Manager V.5.4. A total of eight studies involving 1,486 patients with heart failure were included in this analysis. In terms of structural outcomes, CCM demonstrated improvements in LVEF comparable to those of CRT, with no statistically significant difference between the two therapies ($p>0.05$). Compared to the OMT-only group, CCM showed significantly greater improvements in VO_2 max (MD 0.91; 95%CI 0.44-1.37; $p<0.001$; $I^2=33\%$), 6MWD (MD 17.95; 95% CI 5.45-30.45; $p=0.005$; $I^2=0\%$), and MLHFQ (MD -7.56; 95% CI -11.65 to -3.47; $p<0.001$; $I^2=39\%$). Although no significant differences were observed between CCM and control in terms of all-cause mortality, MACE, or rehospitalization ($p>0.05$), CCM group showed significant improvements in quality of life, as measured by NYHA functional class (MD 2.74; 95%CI 1.47-5.12; $p<0.001$; $I^2=76\%$). CCM is a promising therapy for heart failure, offering structural benefits comparable to CRT in narrow QRS patients and improving function and quality of life beyond OMT, despite no significant reduction in hard clinical outcomes.

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Keywords: Device based therapy, Cardiac resynchronization therapy, Cardiac contractility modulation, Heart failure, Optimal medical therapy

[1]Department of Cardiology and Vascular Medicine, Universitas Udayana/ Prof. dr. I.G.N.G Ngoerah General Hospital, Denpasar, Indonesia

Correspondence:
I Nyoman Wiryawan,

Department of Cardiology and Vascular Medicine, Udayana University/ Prof. dr. I.G.N.G Ngoerah General Hospital, Denpasar, Indonesia

Email: dr_wiryawan@yahoo.com

Introduction

Despite major advancements in pharmaceutical therapy, heart failure remains a significant worldwide public health burden, marked by high rates of morbidity, death, and hospitalization. According to current estimates, millions of people worldwide suffer from heart failure, and as the population ages and survival rates from acute cardiovascular problems improve, the prevalence of heart failure continues to climb. A substantial percentage of patients with Heart Failure with reduced Ejection Fraction (HFrEF) continue to experience symptoms, recurrent hospitalizations, and progressive myocardial deterioration despite optimal guideline-directed medical therapy, such as neurohormonal blockade and more recent disease-modifying medications. This ongoing clinical load emphasizes the necessity of treatment approaches that go beyond pharmaceutical optimization.[1-2]

Device-based therapies are indicated for patients who continue to have symptoms after receiving Optimal Medical Therapy (OMT). Cardiac Resynchronization Therapy (CRT) is one of these devices; in patients with heart failure and Left Ventricular (LV) systolic dysfunction accompanied by electrical dyssynchrony, it improves symptoms, hospitalization rates, and survival. However, approximately 30% of patients do not show adequate response, and its application is not recommended in individuals with a QRS duration of less than 120 milliseconds. Therefore, even with OMT, the majority of heart failure patients remain symptomatic and ineligible for CRT.[1–3]

This therapeutic gap can be filled by Cardiac Contractility Modulation (CCM), which does not require electrical resynchronization. By delivering high-voltage, biphasic, non-excitatory electrical impulses during the absolute refractory phase, CCM improves myocardial contractility by modulating gene expression and calcium handling, thereby enhancing contraction without increasing myocardial oxygen demand. Because of this QRS-independent mechanism, CCM is a good choice for patients who are not candidates for or respond poorly to CRT.[2-3]

In patients with heart failure and reduced ejection fraction who continue to experience symptoms while receiving OMT, CCM has consistently demonstrated improvements in functional capacity, quality of life, New York Heart Association functional class, and Left Ventricular Ejection Fraction (LVEF). Notably, the data suggest a specific advantage for individuals with a narrow QRS duration and an intermediate LVEF — a population for which there have traditionally been few treatment options. As an adjunctive device-based therapy, CCM is increasingly being incorporated into modern heart failure treatment algorithms as a result of these findings, which have led to regulatory approval in several regions.[2-3]

In light of these recent findings, this systematic review and meta-analysis aim to evaluate the effects of CCM in patients with heart failure, with a particular focus on structural and functional parameters and clinical endpoints, clarifying its role within the modern heart failure therapeutic landscape.

Methods

Study Design and Protocol Registration

The study design of this meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and the Cochrane Handbook for Systematic Reviews of Interventions, version 6.5.[4-5] The study protocol was registered in PROSPERO with the registration number CRD420251273539.

Search Strategies

A systematic literature search was carried out comprehensively through seven different databases, including PubMed, Embase, and Cochrane Library, up until March 2025. The search strategy employed boolean operator with the following keywords: [("Heart Failure" OR "HF") AND ("CCM" OR "Cardiac Contractility Modulation") AND ("Optimal Medical Therapy") AND ("CRT" OR "Cardiac Resynchronization Therapy") AND ("randomized control trial" OR random OR randomized OR randomized OR RCT)]. All terms were aligned with the MeSH (Medical Subject Headings).

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were predefined prior to the literature search to ensure the homogeneity and methodological rigor of the included studies. Studies were eligible for inclusion if they met the following criteria: (1) study focuses on adult patients aged more than or equal to 18 years old with documented heart failure with a New-York Heart Association (NYHA) functional class of 2 or above, (2) evaluated CCM as the intervention (3) used optimal medication therapy alone or combined with CRT as the control group, (4) reported primary outcomes surrounding clinical parameters such as, NYHA functional class, Major Adverse Cardiovascular Event (MACE), and all-

cause mortality, with or without secondary outcomes such as LVEF, rehospitalization, 6-Minute Walk Distance (6MWD), Minnesota Living with Heart Failure Questionnaire (MLHFQ), and VO_2max. Studies were excluded if the corresponding authors did not respond to full-text requests after two contact attempts. No restrictions were placed on the publication date. Study eligibility was independently assessed by the authors, and any discrepancies were resolved through discussion and consensus.

Screening and Data Extraction

Database screening was independently conducted by two reviewers (INW and DY), and any conflicts were resolved by a third reviewer (GNPJ). Duplicate studies were removed manually. Eligible studies were extracted and organized into a Microsoft Excel 2021 spreadsheet. Additional data, including country, number of participants, gender distribution, and specifics of the intervention, were also collected. Study characteristics and outcomes were assessed qualitatively by two reviewers (DY and PJ), while NKAD and CAS reviewed the extracted data for accuracy and performed statistical analyses.

Qualitative Appraisal

Risk of bias was assessed using the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2.0). This evaluation was applied to all studies included in the meta-analysis, following the standardized methodology developed by the Cochrane Collaboration. Two authors (INW and DY) independently conducted the assessments, and any discrepancies were resolved by the third reviewer (GNPJ). The results were recorded in a structured spreadsheet (.xlsx) and uploaded to the ROBVIS tool to generate visual summaries of the risk of bias. A traffic light plot was used to display the domain-specific and overall risk assessments.

Quantitative Analysis

The meta-analysis was performed using RevMan 5.4. Primary outcomes were analyzed as mean differences, while secondary outcomes were analyzed as Odds Ratios (OR) with their respective 95% Confidence Intervals (95% CI). All analyses were conducted using a random-effects model. An additional funnel plot will be generated to assess small-study bias, with an additional Egger's test only when at least 10 studies are available.

Results

Study Selection

Through database searches of PubMed, Embase, and the Cochrane Library, 196 entries were found. There were 158 unique items left for screening after 38 duplicate data points were eliminated. 131 items were eliminated during the title and abstract screening process because they dealt with unrelated subjects, animal research, or editorial-style publications. The eligibility of twenty-seven full-text publications was then evaluated. Nineteen of these studies were eliminated due to the lack of a comparator group, inadequate outcome data (n = 10), duplicate populations and overlapping datasets (n = 3), or non-original study designs, such as case reports or reviews (n = 6). Eight articles were ultimately included in the systematic review and meta-analysis after meeting the inclusion criteria. Figure 1 provides a more detailed explanation.

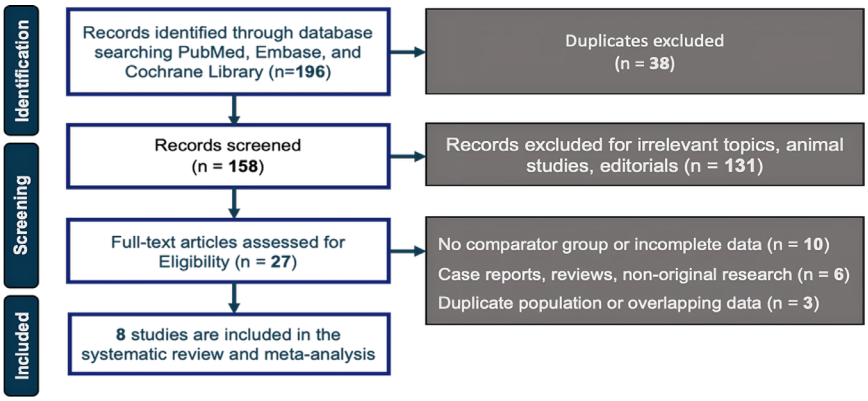

Figure 1. PRISMA chart.

Risk of Bias

The risk of bias of the included studies was assessed using the Cochrane Risk of Bias tool version 2.0 (RoB 2.0) for the 5 Randomized Controlled Trials (RCTs), and the 3 cohorts were assessed using the Newcastle Ottawa Scale (NOS) tool, with the detailed judgments summarized in Figure 2 and Figure 3, respectively. The randomized clinical trial included in this meta-analysis showed a low risk across all RoB2 domains, including the randomization process, blinding, deviations from the intended intervention, missing outcome data, appropriate measurements, and reporting results. The cohorts also showed a similar low risk of bias according to the NOS, based on their selection protocols, sample comparability, and assessment of study outcomes.

Characteristics of Included Studies

A total of eight studies were analyzed; these studies comprised of five RCTs, with three cohorts. Sample sizes varied across studies, with CCM groups ranging from 25 to 215 participants and control groups from 24 to 220 participants. Most studies enrolled patients with HFrEF, while several included mixed populations with Heart Failure with mildly reduced Ejection Fraction (HFmrEF). Across trials, most participants were male and classified as New York Heart Association functional class III–IV. Notably, two studies used CRT combined with OMT as the control group, whereas the remaining studies employed OMT alone as the comparator. Follow-up duration ranged from 12 to 72 weeks. Most studies consistently reported background medical

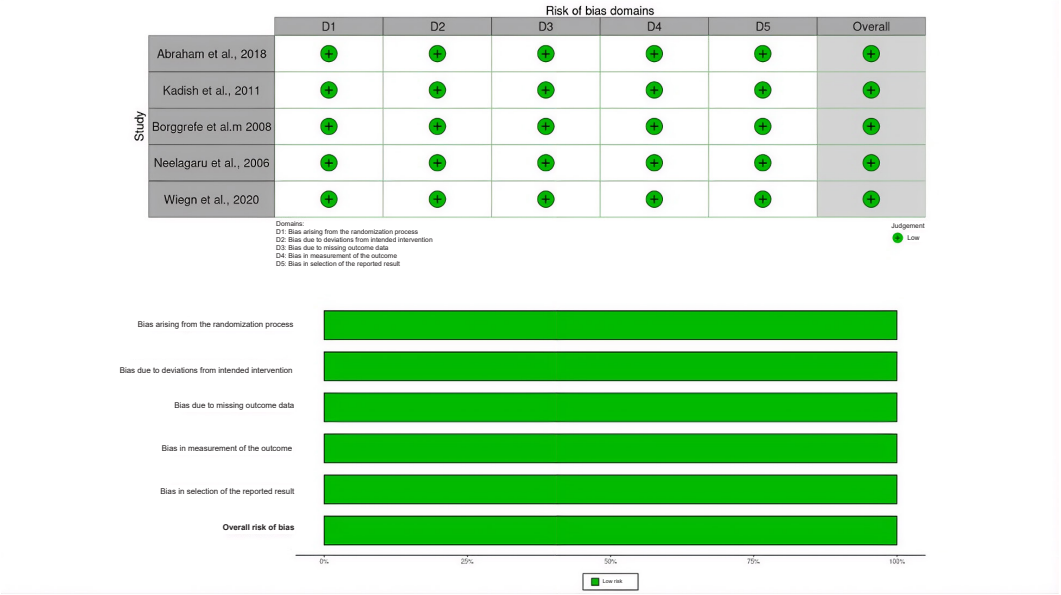

Figure 2. Traffic light plot depicting risk of bias assessment summarizing the risk of bias evaluation for the included studies using Revised Risk of Bias in Randomized Trials 2 tool.

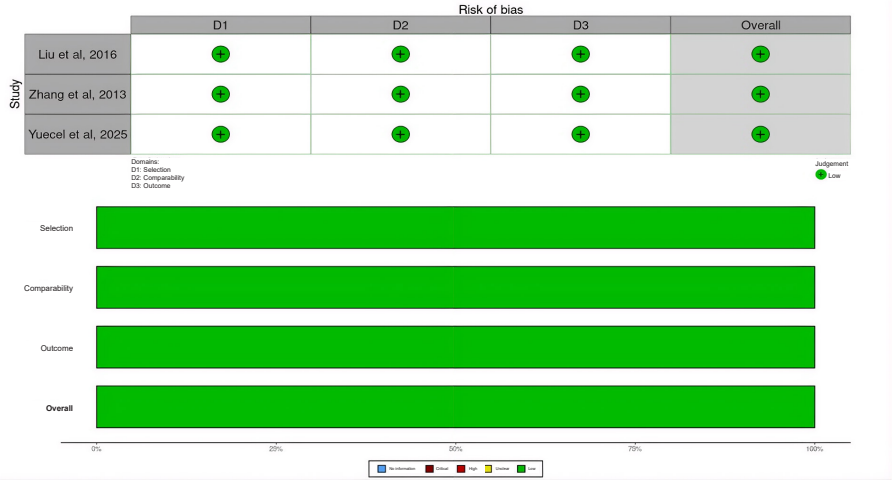

Figure 3. Traffic light plot depicting risk of bias assessment summarizing the risk of bias evaluation for the included studies using Newcastle Ottawa Scale tool.

therapy, which frequently included beta-blockers, mineralocorticoid receptor antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor–neprilysin inhibitors, diuretics, and sodium–glucose cotransporter-2 inhibitors. More detailed baseline characteristics can be viewed in Table 1.

NYHA functional class improvement

The analysis of NYHA functional class improvement includes three RCTs and two cohort studies. 574 patients were in the control group, and 404 patients were in the CCM group. The random-effects meta-analysis showed a higher likelihood of increasing NYHA functional class by up to 174% than the control group, with a pooled OR of 2.74 (95% confidence range of 1.47 to 5.12; p = 0.002). This result is similar across the subgroups comparing CCM with OMT and CCM with CRT; the corresponding pooled ORs were 4.17 (95% CI of 1.92 to 9.07) and 1.52 (95% CI of 0.88 to 2.63). With an I^2 value of 76% (τ^2 = 0.44; p = 0.001) for the overall pooled effect and 72% (τ^2 = 0.34; p = 0.03) for the CCM vs. OMT pooled effect, there was significant heterogeneity aside from the subgroup analysis between CCM and CRT. Conversely, CCM vs. CRT only displayed an I^2 value of 26% (τ^2 = 0.07; p = 0.26), which is not statistically significant. Except for the CCM vs. CRT subgroup (p = 0.26), both the overall pooled effect (p = 0.001) and the CCM vs. OMT subgroup pooled effect (p = 0.03) are statistically significant. The corresponding forest plot result is shown in Figure 4.

Table 1. Baseline characteristics.

Author	Design	CCM (n)	Control (n)	Type of Control	Mean QRS duration (SD)	Mean LVEF% (SD)	Male (%)	Mean Age (SD)	Follow-up (weeks)
Yuecel et al. 2025[6]	Cohort	105	220	OMT+CRT	141.2 (28.2)	25.4 (6.5)	78,4	67.2 (11.7)	52
Wiegn et al., 2020[7]	RCT	60	86	OMT	102.6 (12.2)	33.2 (5.6)	82,8	64.2 (11.2)	24
Abraham et al. 2018[8]	RCT	191	198	OMT	103.3 (12.49)	33.0 (5.4)	76,2	63.0 (11.0)	24
Zhang et al. 2012[9]	Cohort	33	99	OMT+CRT	139.4 (30.9)	26.6 (8.0)	71,2	63.8 (1.9)	72
Kadish et al. 2011[10]	RCT	215	213	OMT	101.6 (14.1)	25.9 (6.5)	71,9	58.3 (12.5)	12
Borggrefe et al. 2008[11]	RCT	80	84	OMT	118.1 (27.7)	29.5 (7.2)	84,7	59.4 (9.9)	50
Neelagaru et al. 2006[12]	RCT	25	24	OMT	105.9 (15.4)	28.1 (7.6)	69,3	57.0 (14.1)	24
Liu et al. 2016[13]	Cohort	41	41	OMT	<130	27.0 (6.5)	85,3	62.5 (10.6)	24

RCT: Randomized Controlled Trials; OMT: Optimal Medical Therapy; LVEF: Left Ventricular Ejection Fraction; SD: Standard Deviation.

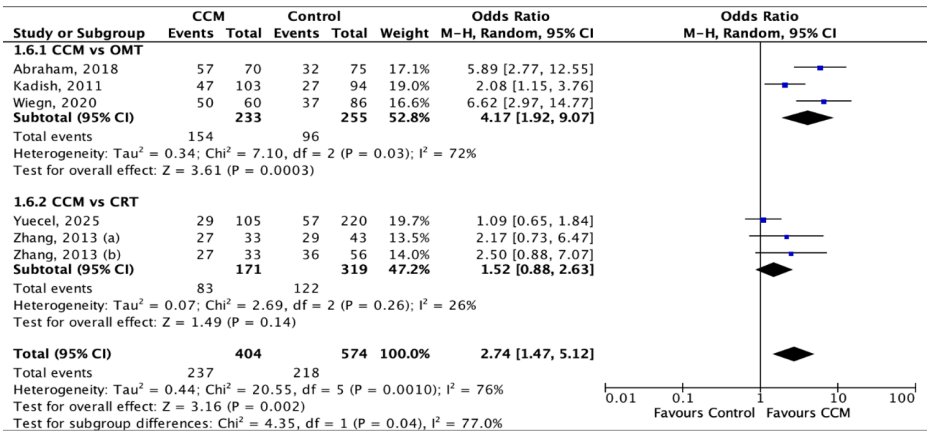

Figure 4. Forest plot depicting the subgroup analysis for NYHA functional class.

All-Cause Mortality

The analysis of all-cause mortality included five RCTs and two cohort studies, including 750 patients in the control group and 592 patients in the CCM group. CCM has a lower all-cause mortality rate than OMT, with or without RCTs, as evidenced by a 25% lower odds of all-cause mortality, according to the random-effects meta-analysis, which reported a pooled OR of 0.75 (95% CI, 0.35 to 1.61). With an I^2 score of 46% (τ^2 = 0.43; p = 0.08), between-

study heterogeneity was moderate. Nevertheless, the outcome (p = 0.47) was not statistically significant. The corresponding forest plot result is shown in Figure 5.

Further sensitivity analysis was performed, in which only five RCTs, including 446 patients in the CCM group and 489 in the control group, were considered to reduce heterogeneity. CCM here did not show a lower all-cause mortality rate compared to the control, as indicated by the pooled OR of 0.95 (95% CI of 0.35 to 1.61; p = 0.89). Heterogeneity is lower than in the previous pooled result, with an I^2 score of 0% (τ^2 = 0.00; p = 0.52). However, both the summary effect and the heterogeneity in this analysis have failed to reach statistical significance. The corresponding forest plot result is shown in Figure 6.

Major Adverse Cardiovascular Events

The MACE analysis included five RCTs and one cohort study with 563 patients in the CCM group and 709 patients in the control group. The CCM group had a higher overall incidence of MACE, with an odds ratio 58% higher than the control group, according to the pooled effect estimate, yielding an OR of 1.58 (95% CI of 0.85 to 2.93). With an I^2 score of 67% (τ^2 = 0.38; p = 0.01), between-study heterogeneity was moderate to high. The overall effect was not statistically significant (p = 0.15), even though the direction of effect indicated a higher incidence of MACE in the CCM group. The corresponding forest plot result is shown in Figure 7.

Further sensitivity analysis was conducted on five RCTs along with 458 patients in the CCM group and 489 patients in the control group. The CCM still showed a higher MACE incidence, with a pooled OR of 1.28 and a 95% CI of 0.83 to 1.96 (p = 0.27). Heterogeneity has dropped to an I^2 score of 0% (τ^2 = 0.00; p = 0.52). Both the summary effect and the heterogeneity in this analysis, however, have failed to reach statistical significance. The corresponding forest plot result is shown in Figure 8.

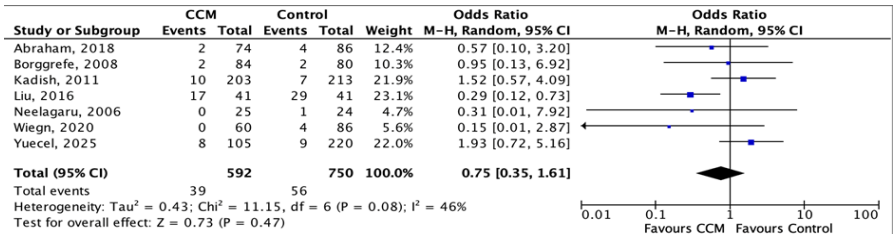

Figure 5. Forest plot depicting the analysis for all-cause mortality event.

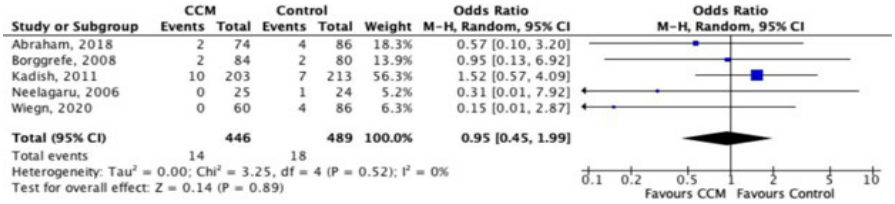

Figure 6. Forest plot depicting the sensitivity analysis of all-cause mortality event.

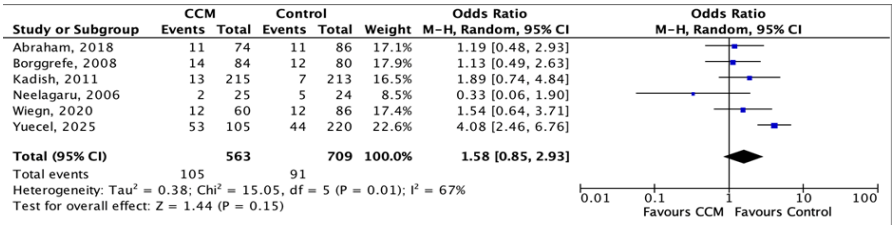

Figure 7. Forest plot depicting the major adverse cardiovascular event.

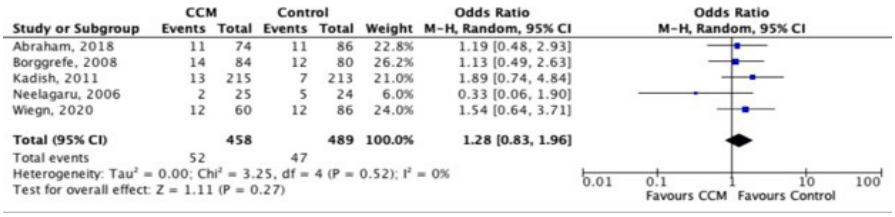

Figure 8. Forest plot depicting the sensitivity analysis of major adverse cardiovascular event.

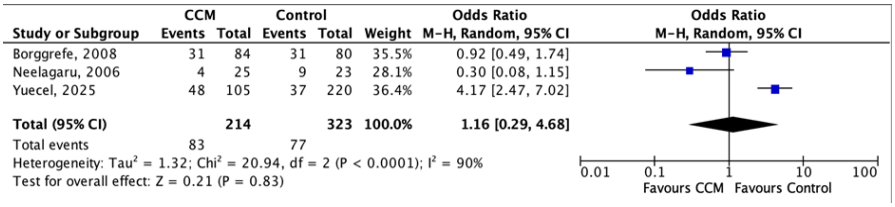

Figure 9. Forest plot depicting the analysis of the rehospitalization event.

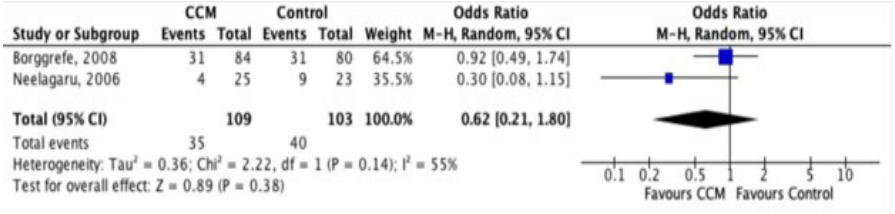

Figure 10. Forest plot depicting the sensitivity analysis of the rehospitalization event.

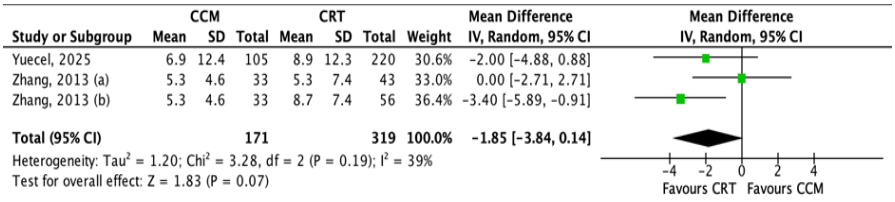

Figure 11. Forest plot depicting the left ventricular ejection fraction.

Rehospitalization

The heart failure-related rehospitalization analysis included two RCTs and one cohort study, comprising 323 patients in the control group and 214 in the CCM group. CCM was associated with a 16% higher risk of rehospitalization compared with the control group, according to a pooled OR of 1.16 (95% CI of 0.29 to 4.68). With an I^2 value of 90% ($\tau^2 = 1.32$; $p < 0.0001$), significant heterogeneity was observed among trials, indicating substantial variation in impact estimates. However, $p = 0.83$ indicated that this was not statistically significant. The corresponding forest plot result is shown in Figure 9.

Further sensitivity analysis was conducted, which included 2 RCTs along with 109 patients in the CCM group and 103 patients in the control group. CCM here showed a different direction of effect, where it is associated with a lower rehospitalization compared to the control group, with a pooled OR of 0.62 and a 95% CI of 0.21 to 1.80 ($p = 0.38$). Heterogeneity here is lower than the previous result, with an I^2 score of 55% ($\tau^2 = 0.36$; $p < 0.14$). Both the summary effect and the heterogeneity in this analysis, however, have failed to reach statistical significance. The corresponding forest plot result is shown in Figure 10.

Left Ventricular Ejection Fraction

The analysis of left ejection fraction improvement included three cohort studies, including 319 patients in the OMT+CRT group and 171 patients in the CCM group. A decreased LVEF in CCM was shown by the random-effects meta-analysis, with a pooled mean difference of -1.85 and a 95% CI of -3.84 to 0.14. With an I^2 score of 39% ($\tau^2 = 1.20$; $p = 0.19$), there was little between-study heterogeneity. This result was not statistically significant ($p = 0.07$). The corresponding forest plot is shown in Figure 11.

6-Minute Walk Distance

The study of 6MWD improvement included four RCTs with 339 patients in the OMT group and 360 in the CCM group. A positive improvement in 6MWD with CCM over control was shown by the random-effects meta-analysis; the pooled mean difference was +17.95 meters, with a 95% CI of 5.45 to 30.45. There was no evidence of between-study heterogeneity (I^2 = 0%; τ^2 = 0.00; p = 0.63). A statistically significant overall impact was seen (p = 0.005). The corresponding forest plot is shown in Figure 12.

Peak Oxygen Consumption (VO_2 Max)

Peak oxygen consumption was analyzed from five RCTs, including 408 patients in the OMT group and 401 patients in the CCM group. The CCM group had a greater peak oxygen consumption, according to the random-effects meta-analysis, with a mean difference of +0.91 mL/kg/min and a 95% CI of 0.44 to 1.37. The I^2 score was 61% (τ^2 = 9.93; p = 0.08), indicating low between-study heterogeneity. A statistically significant overall impact was seen (p = 0.01). The corresponding forest plot is shown in Figure 13.

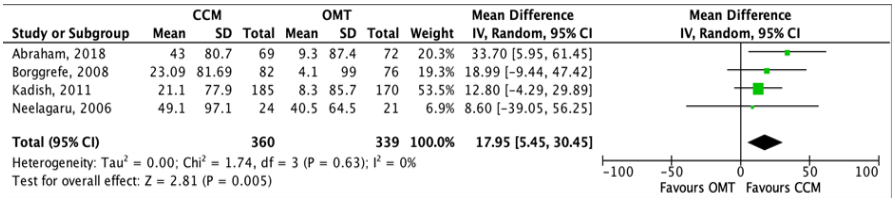

Figure 12. Forest plot depicting the 6-minute walk distance.

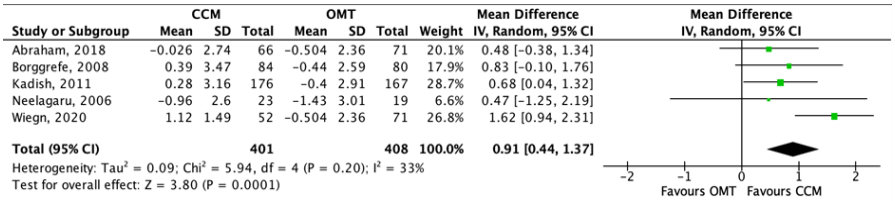

Figure 13. Forest plot depicting the VO_2 Max.

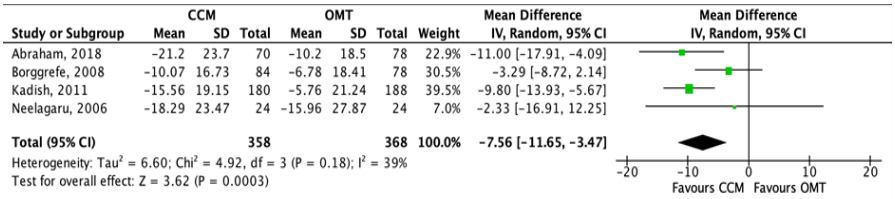

Figure 14. Forest plot depicting the MLHFQ score

Minnesota Living with Heart Failure Questionnaire

The MLHFQ analysis included four RCTs, with 358 patients in the CCM group and 363 patients in the OMT group. The pooled mean difference was -7.56 points, with a 95% CI of -11.65 to -3.47. This indicates that the CCM group had a lower questionnaire score on average than the control group, which is indicative of a higher quality of life. The I^2 score was 39% (τ^2 = 6.60; p = 0.18), indicating minimal between-study heterogeneity. The heterogeneity results were not statistically significant, even though the total impact was (p = 0.0003). The corresponding forest plot is shown in Figure 14.

Funnel Plot

Overall, asymmetry can be observed for most, if not all, efficacy outcomes. This can be explained by the low number of studies that were included and an even smaller number of included studies for some of the variables. However, the risk of small study bias is low due to most studies having large samples, even if they are clustered in favor of certain outcomes. Risk of publication bias, on the other hand, is still very much a possibility; this is supported by the overwhelming agreement between most, if not all, the studies in their respective variables. Funnel plots mentioned are presented in Figure 15.

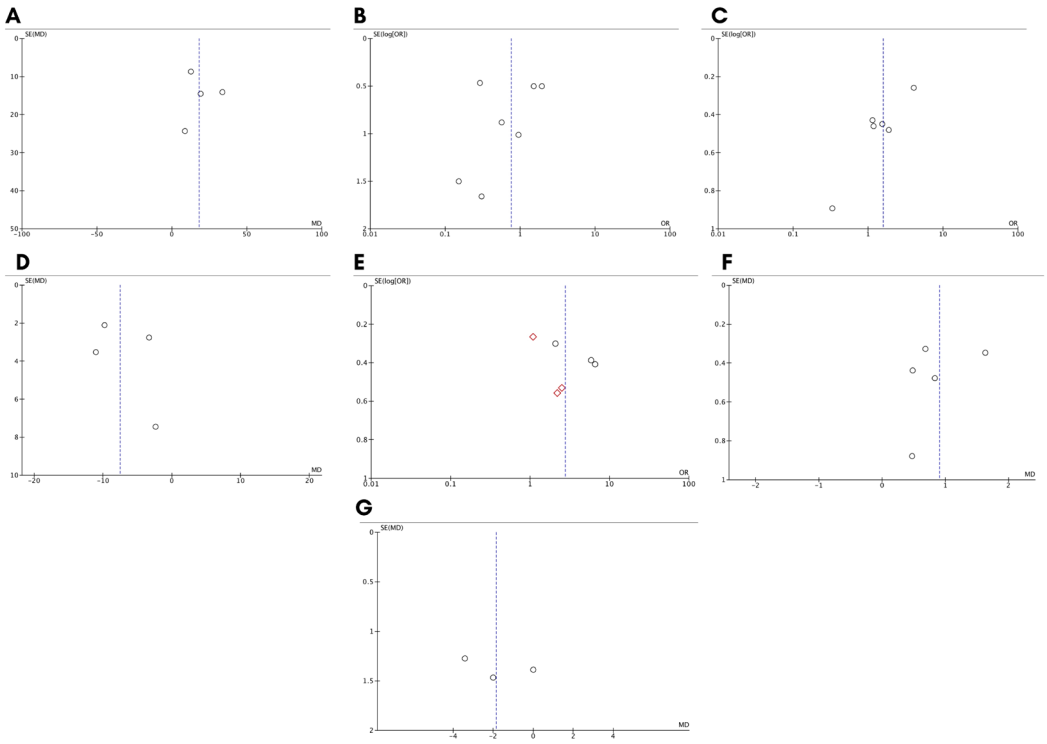

Figure 15. Corresponding funnel plots for 6-minute walk distance (A), all-cause mortality (B), major adverse cardiovascular event (C), Minnesota Living with Heart Failure Questionnaire (D), NYHA functional class (E), VO2 MAX (F), and LVEF (G).

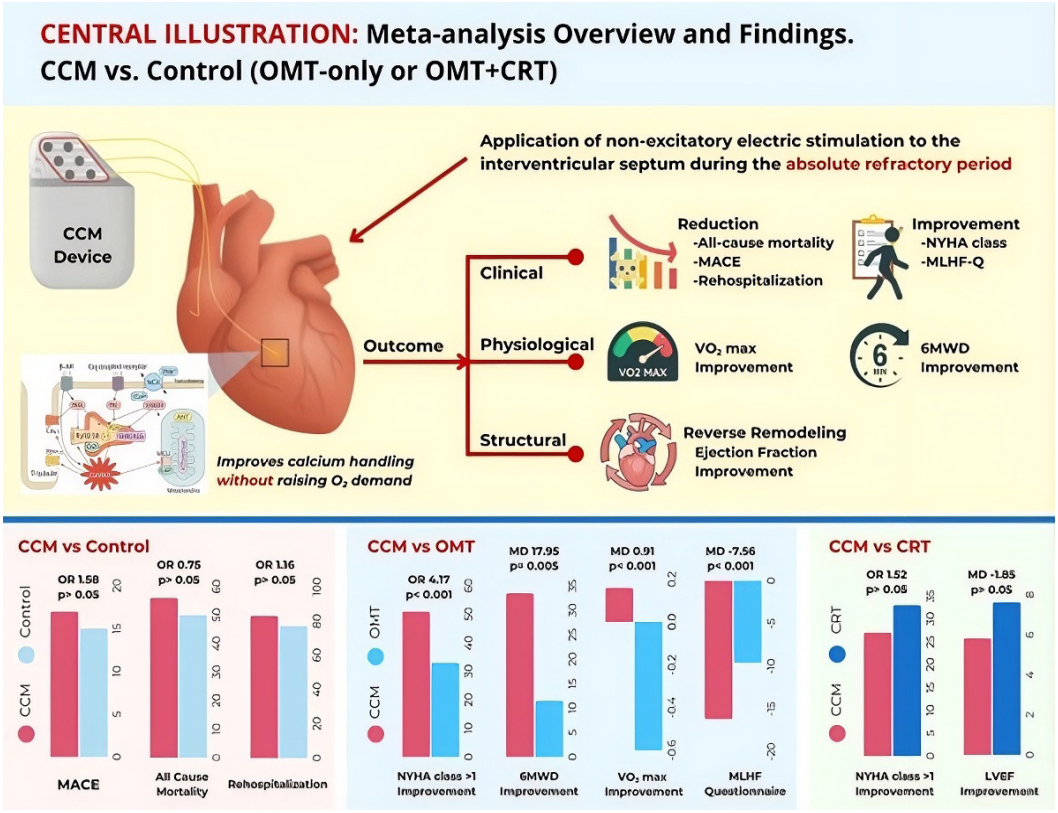

Figure 16. Overview of different comparators and their respective findings.

Discussion

This meta-analysis shows that CCM consistently improves clinical and physiological outcomes in heart failure, with statistically significant gains across NYHA functional class, 6MWD, peak oxygen consumption, and quality of life. CCM demonstrates no statistically significant difference when compared to CRT in improving functional status, with both therapies performing comparably. The significant improvement observed in the overall analysis is primarily driven by comparisons with OMT, as seen in Figure 16, whereas no statistically significant difference was observed between CCM and CRT. This finding suggests that CCM effectively improves symptoms to a degree similar to CRT in appropriately selected patients, particularly those who are not candidates for resynchronization therapy.

Physiological capacity and quality of life consistently favored CCM. CCM improved exercise tolerance to a significant degree, as reflected by better performance on the 6MWD test and increased peak oxygen consumption compared with OMT alone. In addition, CCM improved the quality of life, with patients reporting better scores on validated heart failure questionnaires by around eight points. These findings were generally consistent across studies, supporting the robustness of CCM's effect on functional and patient-reported outcomes.

In contrast, all-cause mortality, MACE, and rehospitalization were not significantly reduced with CCM. Notably, the point estimate for MACE trended in an unfavorable direction, and rehospitalization demonstrated extreme between-study heterogeneity, limiting interpretability. Heterogeneity in the MACE analysis was largely driven by the study by Yuecel et al.[6], in which the CCM group experienced worse outcomes compared with CRT-D. Importantly, this study enrolled a population with lower baseline ejection fraction and a higher burden of ventricular arrhythmias, both of which are strongly associated with poorer prognosis.[14] When this study was excluded, heterogeneity resolved and the MACE point estimate attenuated, yet the overall effect remained non-significant, suggesting that population differences rather than a deleterious effect of CCM accounted for the observed signal.

A further consideration of fundamental importance is that CCM and CRT are not applied to identical patient populations, and direct comparative interpretation must account for this distinction. CRT is an established device therapy with a primary indication in patients with wide QRS complexes, where the underlying pathophysiology is one of electrical dyssynchrony. CCM, by contrast, is typically indicated in patients with narrow QRS duration who are not candidates for CRT, a population in which heart failure is driven predominantly by intrinsic myocardial contractile impairment rather than dyssynchrony. Viewed in this context, the clinical significance of our findings is that CCM achieves comparable structural outcomes to CRT despite being applied in a population that is inherently less responsive to resynchronization-based interventions, reinforcing the value of CCM as a complementary therapy targeting a distinct and underserved patient population.

The differential roles of CCM and CRT are further clarified when considered within the framework of electrical conduction. In patients with wide QRS duration, mechanical dyssynchrony is the dominant abnormality, and CRT improves outcomes by restoring coordinated ventricular contraction. In contrast, patients with narrow QRS duration typically have preserved electrical synchrony, with heart failure driven primarily by impaired myocardial contractile strength[18], as illustrated in Figure 17. Current guidelines provide strong indications for CRT in patients with reduced ejection fraction and prolonged QRS duration, whereas patients with narrow QRS are often limited to implantable cardioverter-defibrillator therapy for sudden death prevention, which does not address symptoms or myocardial dysfunction. In this context, CCM may fill an important role, particularly in patients with narrow QRS duration and ejection fraction above traditional CRT thresholds.[19]

Regarding structural outcomes, ejection fraction alone is an incomplete surrogate for structural recovery in the context of CCM. Unlike CRT, which improves Ejection Fraction (EF) partly through geometric resynchronization of a dyssynchronous ventricle, CCM acts on calcium handling and myocyte contractility globally, a mechanism that may produce meaningful structural benefit without necessarily driving large shifts in ejection fraction. The comparable LVEF between CCM and CRT observed in this analysis should therefore be interpreted not as evidence of a failure of CCM to achieve structural benefit, but as evidence that CCM achieves equivalent structural outcomes in a population in which CRT's geometric advantage does not apply. This interpretation is supported by echocardiographic data demonstrating uniform augmentation of LV systolic function, reduction in functional mitral regurgitation, and favorable

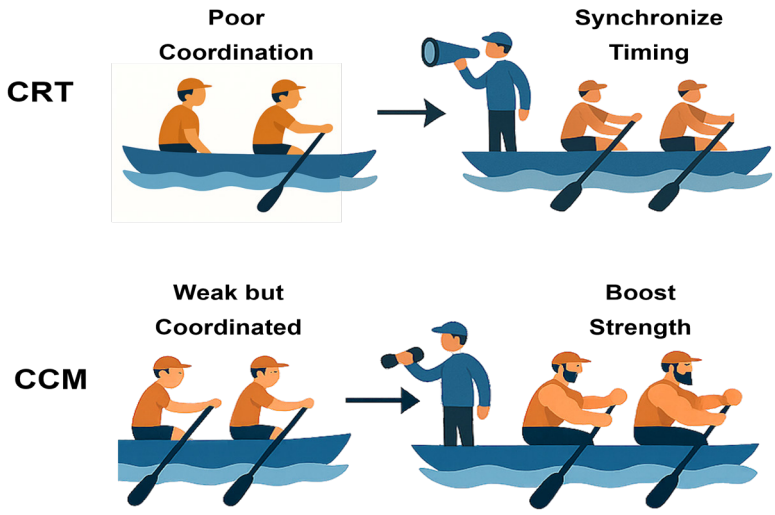

Figure 17. A comparison of the mechanism of action between CCM and CRT.

structural adaptation — effects not fully captured by ejection fraction alone and that collectively reflect meaningful myocardial recovery.[16]

These structural and functional effects align with the underlying mechanisms of CCM. In heart failure, impaired calcium handling due to reduced Sarco/Endoplasmic Reticulum Calcium ATPase (SERCA) activity, persistent phospholamban inhibition, downregulation of L-type calcium channels, and altered mitochondrial function contribute to depressed contractility and progressive myocardial dysfunction. CCM, delivered during the absolute refractory period, favorably modulates these pathways, restoring calcium cycling and myocardial energetics and thereby improving contractile function without increasing myocardial oxygen demand.[17] This mechanistic profile, targeting intrinsic myocyte contractile performance rather than electrical synchrony, explains both the functional gains observed across trials and the structural improvements that extend beyond what ejection fraction alone would suggest.

The observed outcome pattern can be explained by baseline characteristics and study design. Among the included trials, the study by Kadish et al.[10] contributed the largest proportion of patients and therefore exerted substantial influence on pooled estimates. Follow-up duration varied widely across studies, with some trials having relatively short observation periods —particularly relevant for clinical endpoints such as mortality and rehospitalization, as myocardial recovery and its translation into improved survival are time-dependent processes that may not be captured within limited follow-up.

Approximately forty percent of the study population had non-ischemic cardiomyopathy, an important determinant of response to CCM. Long-term observational data indicate that patients with non-ischemic cardiomyopathy experience greater and more sustained improvement in systolic function compared with those with ischemic cardiomyopathy, despite similar baseline ejection fraction, a difference that is biologically plausible and likely reflecting a lower burden of irreversible myocardial scar and a greater proportion of reversible interstitial fibrosis. Although etiology-based subgroup analyses in the present meta-analysis did not reach statistical significance, limited follow-up duration and variability across studies are the more plausible explanations.[15]

Differences in QRS stratification further contributed to heterogeneity, particularly in comparisons between CCM and CRT. Some studies, such as Zhang et al.[9], categorized patients into multiple QRS-duration groups, whereas others, such as Yuecel et al.[6], used a single cutoff around 130 ms. These differences are clinically relevant because CRT efficacy is highly dependent on QRS duration and morphology, whereas CCM acts independently of electrical synchrony, meaning the two therapies target fundamentally different pathophysiological substrates, a distinction that must be considered when interpreting comparative outcomes.

Emerging evidence suggests that the therapeutic effects of CCM may extend beyond traditional HFrEF populations. Abraham et al.[8] demonstrated that patients with ejection fraction ≥35% derived greater benefit from CCM across exercise capacity, quality of life, and NYHA functional class. These observations have prompted the ongoing AIM

HIGHer trial, which is evaluating CCM in patients with ejection fraction between 40% and 60% — a population with limited device-based treatment options, and its results will be important in defining the future scope of CCM therapy.

Finally, safety considerations are critical when interpreting the neutral findings on clinical endpoints. Despite concerns that CCM might provoke ventricular arrhythmias, available evidence does not support an increased arrhythmic risk. Studies assessing autonomic function have demonstrated reductions in sympathetic activity following CCM therapy, and ambulatory monitoring has consistently shown similar arrhythmic burden between CCM-treated patients and controls. These findings support the electrophysiological safety of CCM and suggest that the lack of observed mortality benefit is more likely related to patient selection and follow-up duration rather than adverse effects of the therapy itself.[20]

It should be noted that this is the first meta-analysis to directly compare CCM not only with OMT but also with CRT. Included studies were generally of good quality and allowed subgroup insights towards ejection fraction strata, ischemic vs non-ischemic cardiomyopathy, and QRS duration. Nevertheless, several limitations warrant consideration. The included cohort studies enrolled populations that were predominantly male (comprising up to 70-80% of participants) and with a mean age of approximately 65 years, limiting generalizability to women and younger patients. Patients with permanent Atrial Fibrillation (AF) were largely excluded due to early device requirements for P-wave sensing, despite AF being highly prevalent in heart failure, a restriction that meaningfully narrows the applicability of these findings to real-world populations. Follow-up durations were also relatively short across most studies, which may have been insufficient to capture the full extent of myocardial recovery and its downstream effects on survival. Finally, most included studies were conducted prior to the widespread adoption of Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors, meaning the incremental benefit of CCM within the context of contemporary guideline-directed medical therapy may be underestimated.

Conclusion

In conclusion, this meta-analysis demonstrates the safety and efficacy of CCM as a device therapy that reliably improves symptoms, exercise capacity, and quality of life in patients with heart failure. CCM provides structural and functional benefits comparable to CRT, despite acting through a fundamentally different mechanism, and offers a meaningful therapeutic alternative for patients ineligible for resynchronization therapy, particularly those with narrow QRS duration, mildly reduced or even preserved ejection fraction. While no significant reduction in mortality or rehospitalization was observed, this likely reflects study design limitations, patient selection, and insufficient follow-up rather than an absence of clinical effect. CCM should therefore be viewed as a complementary, not competing, therapy to CRT, one that fills an important treatment gap by targeting impaired myocardial contractility rather than electrical dyssynchrony. Larger, longer, and more contemporary trials incorporating current guideline-directed medical therapy are needed to fully establish CCM's role in the modern heart failure treatment landscape.

List of Abbreviations

6MWD	6-Minute Walk Distance
AF	Atrial Fibrillation
CCM	Cardiac Contractility Modulation
CI	Confidence Intervals
CRT	Cardiac Resynchronization Therapy
HFrEF	Heart Failure with reduced Ejection Fraction
HFmrEF	Heart Failure with mildly reduced Ejection Fraction
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Event
MD	Mean Differences
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NOS	Newcastle Ottawa Scale
NYHA	New-York Heart Association
OMT	Optimal Medical Therapy
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trials
SGLT2	Sodium-Glucose Cotransporter-2

Ethical Clearance

Not applicable.

Publication Approval

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