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Effectiveness of cardiac resynchronization therapy in mild congestive heart failure: systematic review and meta-analysis of randomized trials

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Aims Cardiac resynchronization therapy (CRT) improves echocardiographic parameters, symptoms, hospitalizations, and mortality in patients with New York Heart Association (NYHA) Class III or IV symptoms with left ventricular systolic dysfunction, sinus rhythm, and a prolonged QRS duration. The effectiveness of CRT in patients with mild heart failure symptoms has not been systematically reviewed.

Methods and results Randomized controlled trials of CRT in patients with NYHA Class I or II heart failure were identified from MEDLINE and EMBASE. The effects of CRT on left ventricular remodelling at 1 year were systematically reviewed, and the effects of CRT on clinical outcomes at 1 year were meta-analysed. Two studies met the pre-specified search criteria, with a total of 2430 patients (REVERSE $n = 610$ and MADIT-CRT $n = 1820$). CRT was associated with a reduction in heart failure events in both trials [combined OR 0.57, 95% confidence interval (CI) 0.46–0.70], but not mortality (combined OR 0.96, 95% CI 0.67–1.36). The effect of CRT on the combined endpoint of heart failure events or death favoured CRT (OR 0.63, 95% CI 0.51–0.77). CRT was also associated with improvement in left ventricular remodelling parameters in both studies, including a greater increase in left ventricular ejection fraction in the CRT group than in the control group, at 1 year after randomization. Serious adverse events were rare with CRT.

Conclusion CRT reduces heart failure events in patients with mild heart failure symptoms, left ventricular dysfunction, sinus rhythm, and prolonged QRS duration.

Keywords Artificial cardiac pacemaker • Artificial pacemaker • Heart failure • Mortality • Cardiac resynchronization therapy

Introduction

Advanced heart failure poses a substantial clinical and economic public health burden.[1,2] In many patients, the clinical syndrome of congestion arises from electro-mechanical dyssynchrony, leading to inefficient ventricular contraction, mitral regurgitation, and worsening ventricular dilation.[3] Studies of cardiac resynchronization therapy (CRT) using a left ventricular lead implanted via the coronary sinus have demonstrated improvements in echocardiographic parameters, symptoms, hospitalizations, and mortality in individuals with systolic left ventricular dysfunction, sinus rhythm, prolonged QRS durations, and New York Heart Association (NYHA) Class III or IV heart failure symptoms.[4–8] Current guidelines support the use of CRT

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for individuals with left ventricular ejection fractions (LVEF) $\leq$35%, QRS durations $\geq$120 ms, and advanced heart failure symptoms similar to those in clinical trials, despite optimal medical therapy.[1,2]

Although improvements in left ventricular remodelling and clinical outcomes with CRT have been demonstrated in individuals with advanced heart failure, evidence of improved left ventricular remodelling has also been demonstrated in two short-term studies of individuals with NYHA Class II symptoms[9,10] as well as in one observational registry.[11] Moreover, recently published data suggest improved heart failure and survival outcomes associated with the use of CRT in either asymptomatic or only mildly symptomatic heart failure patients.[12,13] Small elevations in brain natriuretic peptide levels are likely a surrogate for mild heart failure symptoms. Interestingly, in a post hoc analysis of the Cardiac Resynchronization in Heart Failure trial, subjects with brain natriuretic peptide levels above or below the median had similar survival outcomes with CRT.[14] We performed a systematic review and meta-analysis to determine the effects of CRT on long-term left ventricular remodelling parameters and clinical outcomes in patients with mildly symptomatic heart failure.

Methods

Search strategy

An electronic search of EMBASE and MEDLINE was performed for all English articles of human studies through July 2009 using the search terms 'CRT' OR 'CRT' OR 'biventricular pacing' OR 'biventricular pacer' OR 'BiV' OR 'biventricular pacemaker'. Bibliographies from published meta-analyses and review articles were hand-searched and experts in the field were consulted to ensure inclusion of all pertinent studies for the preliminary review.

Article selection and eligibility criteria

The search strategy focused on randomized controlled trials in which an experimental arm included CRT and the control arm did not. Our analysis was restricted to those trials that included subjects with NYHA Class I or II symptoms, and reported specified outcomes of interest (see below) at 1 year of follow-up.

Data abstraction and quality assessment

Two investigators (P.L. and N.F.) independently extracted data on study and patient characteristics, outcomes, and study quality using a standardized extraction form. Disagreements were resolved by consensus with all four investigators. Study quality was assessed using the Jadad scale, which ranges from 0 to 5 with higher values indicating better study quality.[15]

Data collected included left ventricular remodelling parameters, QRS duration, and ejection fraction, as well as the clinical outcomes of heart failure events or death from any cause at 1 year. Complications associated with CRT were also ascertained.

Data analysis

Agreement between the two data extractors were assessed with the Kappa statistic. Odds ratios for the outcome of heart failure events, mortality, or heart failure events or mortality were calculated using the DerSimonian and Laird random effects method.[16] Heterogeneity was quantified using the I^2 statistic.[17] Statistical analyses were performed with Stata™ v10.1 (College Station, TX, USA).

Results

Literature search

The initial search identified 6481 citations from EMBASE and 4967 from MEDLINE. Of these 3927 were duplicates, leaving 7521 unique citations. Electronic filtering of non-English, followed by non-human, non-randomized controlled trial left 357 studies. These 357 studies were hand searched by two independent investigators to yield two randomized controlled trials. These included the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial by Linde *et al.*[12] and the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial by Moss *et al.*[13] Two sub-studies of the REVERSE trial were also identified and were not included in the main analysis.[18,19] Details of the study flow are displayed in *Figure 1*. Agreement between the two reviewers was 0.99 and the Cohen–Kappa statistic was 0.875 [95% confidence interval (CI] 0.735, 1.000]. Hand-searching of bibliographies and consultation with experts did not contribute any additional articles that met the pre-specified inclusion criteria.

Characteristics of included studies

Both the REVERSE and MADIT-CRT trials were randomized controlled trials involving patients with poor LV systolic function and a history of symptomatic heart failure (*Table 1*). REVERSE included patients with an LVEF of 40% or less, a QRS duration of at least 120 ms, a left ventricular end diastolic diameter of 55 mm or greater, and NYHA functional Class I or II, irrespective of ischaemic or non-ischaemic heart failure aetiology classification. MADIT-CRT included individuals with an LVEF of 30% or less, a QRS duration of at least 130 ms, and patients with ischaemic cardiomyopathy with NYHA functional Class I or II, or non-ischaemic cardiomyopathy with NYHA functional Class II. Both trials required that patients were treated with optimal medical therapy.

In the REVERSE trial, all subjects received a CRT device, with or without an implantable cardioverter defibrillator (ICD) in accordance with practice guidelines. The patients were then randomized to have their CRT devices turned on (CRT-ON) or off (CRT-OFF) in a 2:1 fashion. In MADIT-CRT, patients were randomized to receive an ICD with or without CRT in a 3:2 fashion.

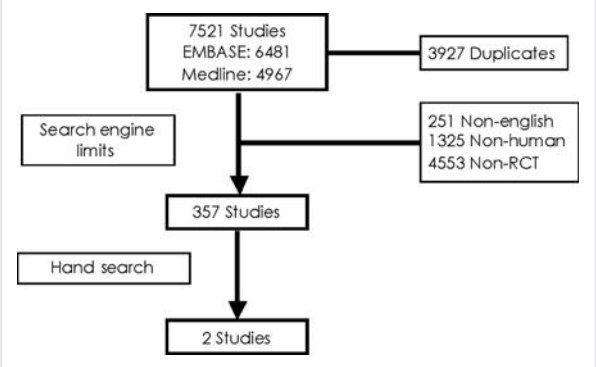

Figure 1 Study flow.

Table 1 Characteristics of included trials

Study	Design	Patients	Primary endpoint	Secondary endpoints	Blinding strategy	Location	Sponsor	Jadad score
REVERSE[12]	RCT of CRT on or off (2:1); ICD based on proper indications	NYHA I-II; LVEF ≤ 40%; QRS ≥ 120 ms; LVEDD ≥ 55 mm	Death, HF hospitalization, worsening heart failure class	LVESVI; cardiac hospitalization	Double-blind	Multi-centre, Canada, Europe, and USA	Not stated	5
MADIT-CRT[13]	RCT of CRT or no CRT (3:2); all subjects received ICDs	NYHA I-II; LVEF ≤ 30; QRS ≥ 130 ms	Death or nonfatal HF event	LVESV, LVEDV, rate of multiple HF events	None	Multi-centre, Canada, Europe, and USA	Boston Scientific	3

CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end diastolic dimension; LVESV, left ventricular end systolic volume; LVEDV, left ventricular end diastolic volume; LVESVI, left ventricular end systolic volume index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; RCT, randomized controlled trial.

The primary outcome in REVERSE was a clinical composite of worsening heart failure, which included mortality, and in MADIT-CRT the primary outcome was a composite endpoint of all-cause mortality and heart failure events.

Both studies were of high quality, with a Jadad Score of 5/5 for REVERSE and 3/5 for MADIT-CRT. Points were lost in MADIT-CRT due to lack of blinding in the patients or physicians, as CRT implantation was only performed in patients randomized to intervention. However, a blinded committee adjudicated events in both of these trials. Follow-up was excellent in both studies with primary endpoint data available for 100% of patients in REVERSE and 95% in MADIT-CRT.

The characteristics of the patients included in both studies are detailed in *Table 2*. The studies included a combined total of 2430 patients (REVERSE $n = 610$ and MADIT-CRT $n = 1820$). In each study, 55% of the subjects were classified as having ischaemic cardiomyopathy. The median age was 62 years in REVERSE and 65 years in MADIT-CRT. The majority of subjects were male (75–78%). Medical therapy for cardiac dysfunction with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and diuretics was consistent with clinical practice guidelines.[1] In the REVERSE trial, 163 (85%) of subjects in the CRT-OFF arm, and 345 (82%) of subjects in the CRT-ON arm, received ICDs. In MADIT-CRT, by protocol all subjects were treated with ICDs.

Heart failure events and mortality

The definition of heart failure events is based on that used in each of the two clinical trials.[12,13] In the REVERSE trial, heart failure events were defined as either hospitalization due to or associated with worsening heart failure, crossover to the CRT therapy arm due to worsening heart failure, and worsened patient global assessment or NYHA functional class. In MADIT-CRT, heart failure events were defined as those signs and symptoms consistent with heart failure and the requirement of decongestive therapy on an outpatient basis, or an augmented decongestive regimen as an inpatient.

In the combined meta-analysis of the REVERSE and MADIT-CRT trials, CRT was associated with a reduction in heart failure events (combined OR 0.57, 95% CI 0.46–0.70, *Figure 2*). In contrast, CRT was not associated with reductions in mortality (combined OR 0.96, 95% CI 0.67–1.36, *Figure 2*). The overall benefit of CRT on the combined endpoint of heart failure events or death (OR 0.63, 95% CI 0.51–0.77, *Figure 2*) was primarily attributable to the effects of CRT on reducing heart failure events. There was no evidence of statistical heterogeneity for each of the analysed outcomes ($I^2 = 0$).

A sub-study from the REVERSE trial reported 24-month clinical and left ventricular remodelling outcomes in the European arm of the trial.[19] The European arm was randomized throughout the 24-month period as opposed to the North American arm, which was randomized only to 12 months. CRT-ON was associated with a reduction in the odds of heart failure events or death relative to those in the CRT-OFF group (OR = 0.45, 95% CI 0.25–0.81). Notably, when compared with those patients in the North American arm of the study, patients in the European arm were younger (61 ± 10 vs. 63 ± 11 years, $P = 0.02$), less likely to have

Table 2 Baseline characteristics of patients included in the REVERSE and MADIT-CRT studies

Study	Number of subjects	Ischaemic, %	Median age	Male, %	Mean QRS, ms	ACE-I, %	ARB, %	Beta-blocker, %	Diuretic, %
REVERSE[12]	610	55	62	78	153	79	21	96	81
MADIT-CRT[13]	1820	55	65	75	NR[a]	77	21	93	75

ACE-I, angiotensin converting enzyme-inhibitor; ARB, angiotensin receptor blocker; NR, not reported.
[a]Mean QRS not reported in MADIT-CRT; ~65% of subjects had QRS durations ≥150 ms in each group.

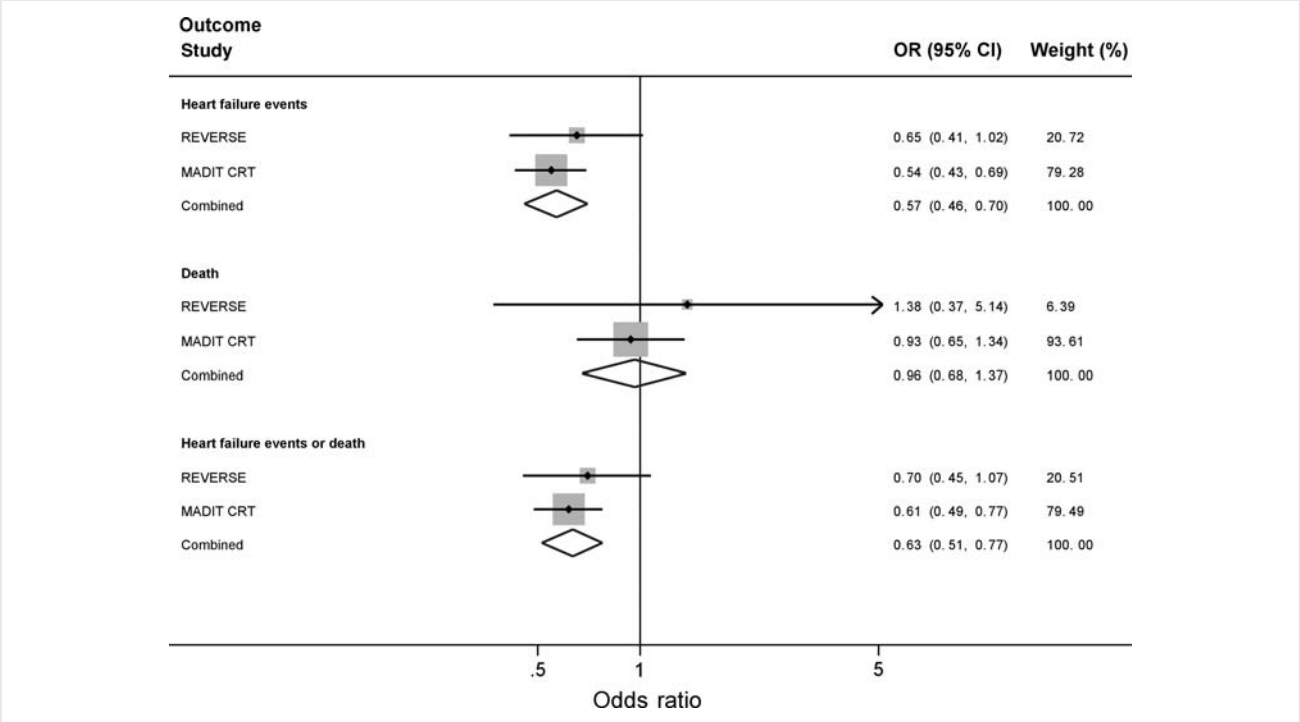

Figure 2 Forest plot demonstrating the effect of CRT on heart failure events, death, or the combined endpoint of heart failure events or death.

ischaemic cardiomyopathy (44 vs. 63%, $P < 0.001$), had a longer QRS duration (156 ± 23 vs. 151 ± 21 ms, $P = 0.008$), and had fewer comorbidities. Patients in the European arm were also less likely to have received ICDs (68 vs. 95%, $P < 0.001$). Due to the smaller study sample, we used the 12-month outcomes reported for both the North American and European arms in our meta-analysis.

Reverse left ventricular remodelling

Both trials evaluated the impact of CRT therapy on left ventricular remodelling as assessed by baseline and 12-month echocardiographic parameters. The two trials differed in their approach to CRT programming status during follow-up echocardiography. In REVERSE, echocardiographic measurements were made with CRT turned off, irrespective of treatment assignment. For CRT-ON subjects these measurements were recorded after waiting for a 10 min period. In MADIT-CRT, echocardiography was initially performed with CRT turned off for subjects who received CRT–ICD, as required by the Food and Drug Administration; however, this requirement was later reversed, and the 1-year echocardiograms were subsequently performed with CRT turned on for the duration of the study. The initial 201 CRT–ICD subjects in whom CRT was turned off were excluded from the final analysis of LV remodelling parameters reported in MADIT-CRT.

CRT significantly improved LV remodelling parameters in both studies (*Table 3*). In REVERSE, CRT-ON subjects experienced a significantly greater reduction in LV end systolic volume index when compared with CRT-OFF subjects (−18.4 ± 29.5 vs. −1.3 ± 23.4 mL/m^2, respectively, $P = <0.001$). The difference in left ventricular end systolic volume index significantly favoured CRT-ON for all subgroups assessed. A similar improvement in LV end systolic volume was observed with CRT in MADIT-CRT (−57 and −18 mL, respectively, $P < 0.001$). Significant improvement in LVEF was observed with CRT in both studies, with a greater benefit demonstrated in MADIT-CRT (*Table 3*). Superior improvements

Table 3 Assessment of left ventricular remodelling after 1-year follow-up in REVERSE and MADIT-CRT

Study group	No. subjects	LVESVI (mL/m^2)		IVCD (ms)		LVEDV (mL)		LVESV (mL)		LVEF (%)	
		Change	*P*-value	Change	*P*-value	Change	*P*-value	Change	*P*-value	Change	*P*-value
REVERSE											
CRT-ON	324	−18.4 ± 29.5	<0.001	−13.0 ± 43.2	<0.001					3.8	<0.001
CRT-OFF	163	−1.3 ± 23.4		−0.2 ± 34.0						0.6	
MADIT-CRT											
CRT-ICD	746					−52	<0.001	−57	<0.001	11	<0.001
ICD-only	620					−15		−18		3	

Data presented as mean ± standard deviation, if reported.
IVCD, interventricular conduction delay; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVESVI, left ventricular end systolic volume index.

in left ventricular end diastolic volume index, left ventricular end systolic and diastolic diameter, and interventricular conduction delay were also demonstrated with CRT in REVERSE, and in left ventricular end diastolic volume in MADIT-CRT (*Table 3*).

Two sub-studies of REVERSE also reported on the left ventricular remodelling parameters.[18,19] In a sub-study analysis including 487 of the 610 patients in the trial, improvements in left ventricular remodelling parameters with CRT immediately after implantation did not correlate with long-term improvement in parameters (left ventricular end systolic volume index $r = 0.11$, $P = 0.31$, left ventricular end diastolic volume index $r = 0.10$ $P = 0.38$, LVEF $r = 0.07$, $P = 0.72$). Favourable effects of CRT on remodelling were greatest in subjects with more prolonged interventricular mechanical delay (>40 ms), longer QRS duration (>160 ms), and for those with a non-ischaemic HF aetiology.[18] Additionally, no differences in changes of diastolic function measurements were noted between CRT-ON and CRT-OFF groups. In a separate sub-study of the 262 patients in the European arm of the REVERSE study, improvement in left ventricular remodelling parameters was also greater for patients in the CRT-ON rather than CRT-OFF arm at the 24-month follow-up period.[19]

Detailed results of left ventricular remodelling according to subgroup in MADIT-CRT have not yet been released.

Complications

The success rate of CRT implantation was 97% in the REVERSE trial and 99% in MADIT-CRT. One death was reported during the peri-implantation period in a patient receiving CRT in the MADIT-CRT trial as a result of a pulmonary embolism. Peri-implantation mechanical complications, including pneumothorax, coronary dissection, and pericardial tamponade occurred with a 1% frequency in the REVERSE trial, and 2% frequency in MADIT-CRT. Left ventricular lead problems following implantation were reported in ~7% of participants in the REVERSE trial during the 12-month follow-up period, and 4% in MADIT-CRT during a reported 30-day period. Device related infections occurred in 1% of subjects with CRT in the MADIT-CRT trial within 30 days of implantation.

No significant difference in the rate of complications was detected during the 12 months of follow-up between the CRT-ON and CRT-OFF groups in the REVERSE trial. During follow-up in the REVERSE trial, one case of heart failure occurred that resolved after turning CRT off. During follow-up beyond 30 days in the MADIT-CRT trial, adverse events defined as serious device-related events were reported with an incidence of 4.5 per 100 device-months in the CRT−ICD group, when compared with 5.2 per 100 device-months in the ICD-only group.

Discussion

This meta-analysis of prospective randomized controlled trials comparing CRT in patients with Class I or II heart failure symptoms, left ventricular systolic dysfunction, and a prolonged QRS interval in sinus rhythm demonstrated that CRT is associated with an ~40% reduction in the odds of heart failure events, but no differences in all-cause mortality at 1 year following implantation. CRT also reverses the negative remodelling effects of

heart failure in patients with mild HF symptoms receiving optimal medical therapy.

Neither REVERSE nor MADIT-CRT demonstrated a reduction in mortality with CRT. This may be related to the fact that ICD therapy was widely used in both trials. In REVERSE, over 80% of individuals in both arms received ICDs. In MADIT-CRT, all of the patients received ICD therapy. ICDs have been shown to reduce mortality in primary prevention trials of individuals with left ventricular systolic dysfunction either of ischaemic,[20–23] or non-ischaemic aetiology.[24] Furthermore, the benefit of ICD therapy has been observed in patients with mild or moderate heart failure.[22,25,26] When examined in individuals with moderate or severe heart failure symptoms, CRT alone has been associated with improved survival in one randomized controlled trial,[7] a finding further supported in a previously published meta-analysis of randomized controlled trials of CRT.[27]

CRT has been previously demonstrated to cause reversal of left ventricular structural and functional remodelling changes that occur in chronic heart failure for patients with NYHA functional Class III and IV symptoms.[4,5,7] Improvements in LV structure and function with CRT have also been observed in smaller studies of patients with NYHA Class II symptoms with 6 months of follow-up[9,10] and long-term in an observational registry.[11] Our findings extend these observations to 1 year of follow-up, and suggest that CRT may prevent the natural progression and clinical consequences of left ventricular dysfunction observed in patients with heart failure.[28]

These data demonstrate that patients with mild heart failure symptoms despite optimal medical therapy, severe left ventricular dysfunction, and QRS prolongation may benefit from CRT. Observations that the benefit of CRT also applies to those with only mild heart failure symptoms may result in an expansion of existing guideline recommendations for the use of CRT. It is difficult to assess the potential clinical and economic impact of any such change in indications for CRT, however, as it has been estimated that up to 22% of patients currently receiving CRT have NYHA Class I or II symptoms and up to 17% have LVEF above 35%.[29] Moreover, substantial differences across countries have been noted in the prescription of CRT.[30] Future studies are necessary to understand the reasons underlying disparities in the application of CRT, as well as the cost-effectiveness of CRT in patients with mild heart failure symptoms.

Limitations

The analysis is limited in that only two randomized trials evaluated the long-term effects of CRT on left ventricular remodelling or death in patients with mild heart failure symptoms. In both of these trials, the vast majority of subjects were also treated with ICDs, thereby perhaps masking any potential benefit of CRT on mortality reduction. Additionally, the absence of patient-level data limits our ability to assess subgroup effects of CRT on clinical or functional outcomes.

Conclusions

CRT is associated with an improvement in left ventricular remodelling parameters and a substantial reduction in heart failure events among individuals with NYHA Class I or II heart failure symptoms, left ventricular systolic dysfunction, and a prolonged QRS duration in sinus rhythm. These findings add to the array of therapies available for improving clinical outcomes among patients with mild heart failure symptoms.

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