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Review article

# Cardiac resynchronization therapy in patients with mild heart failure is an earlier reverse therapy

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ABSTRACT

This systematic review with meta-analysis sought to determine the efficacy, safety of implantation of cardiac resynchronization therapy (CRT) in mild heart failure (HF). Medline, Embase, Elsevier, and Sciences online database as well as Google scholar literature were used for selecting appropriate studies with randomized controlled design. The literature search of all major databases retrieved 2035 studies. After screening, a total of 10 trials were identified that reported outcomes of interest. Pooled analysis was performed on left ventricular (LV) ejection fraction ($P < 0.001$), LV end-diastolic volume ($P < 0.001$), LV end-systolic volume ($P < 0.001$), LV end-diastolic diameter ($P < 0.001$), LV end-systolic diameter ($P < 0.001$), incidence of progression of heart failure ($P < 0.001$), mortality ($P = 0.06$), infection ($P = 0.1$), and pneumothorax ($P = 0.08$). Overall, implantation of CRT in patients with asymptomatic and mild HF resulted in improved cardiac function, decreased progression of HF, trend to decrease of mortality in short to long-term follow-up.



## 1. Introduction

Heart failure (HF) is considered as an epidemic disease of the modern era nowadays.[1–3] Despite recent developments in HF management, the morbidity and mortality in this clinical syndrome remain unacceptably high and patients suffer from debilitating symptoms adversely affecting their quality of life.[1–3] Failure may be compounded in patients with intra-ventricular conduction delay possibly due to a loss of ventricular synchronization.[4] Regarding that importance of adverse events in this clinical syndrome, there is an emerging emphasis on understanding the progression from heart failure risk factors to asymptomatic ventricular dysfunction and eventually to symptomatic heart failure and death.[1–4] The placement of an implantable cardioverter-defibrillator (ICD) improves survival and reduces the risk of sudden death. However, life-prolonging defibrillator therapy is associated with an increased risk of first and recurrent HF events.[5] Cardiac resynchronization therapy (CRT) can improve symptoms of HF, quality of life, exercise capacity, and left ventricle function when used in patients suffered from symptomatic HF with New York Heart Association (NYHA) functional class III or ambulatory class IV with a wide QRS complex.[6,7] Recently, the ACCF/AHA guidelines limited the Class I indication for CRT to patients with a QRS duration ≥150 ms.[8,9] However, a QRS duration of 120–150 ms is still recommended as the Class I indication in the European Society of Cardiology (ESC) guidelines if the patient has an LBBB pattern and depressed LVEF.[9] Also, according to Tracey et al., CRT can be useful (Class IIa indication) for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class III/ambulatory class IV symptoms on GDMT.[8] Regarding that progression of clinical symptoms from mild to severe HF partially resulting from insufficient and inappropriate treatments, current investigations focus on introducing treatments with ability of earlier reverse of HF symptoms. Several studies have reported the efficacy and safety of implantation of CRT in asymptomatic or mild HF. However, data from RCTs are limited and so far largely inconclusive. This systematic review with meta-analysis sought to

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determine the strength of evidence for the effects of CRT on changes in left ventricular ejection fraction (LVEF), left ventricular end diastolic (LVEDV) and end systolic volumes (LVESV), left ventricular end diastolic (LVEDD) and end systolic diameters (LVESD), left ventricular end systolic volume index (LVESVI), and impact on incidence of HF, mortality, infection, pneumothorax, and hematoma required intervention.

## 2. Methods and materials

### 2.1. Literature search

A comprehensive literature search was conducted in major electronic databases (Medline/Pubmed, Embase, Elsevier, Web of Knowledge, Sciences online database and Google Scholar) from their inception through July 25, 2014 to identify the RCTs reporting the effects of CRT on echocardiographic results and clinical outcomes in patients with mild HF. Predefined search terms included: "cardiac resynchronization therapy", "CRT", "biventricular pacing", "biventricular pacemaker", and "heart failure", "HF", "mild HF". No language restrictions were applied. All retrieved references of the included RCTs were also reviewed to determine additional studies not indexed in the common databases. Studies were included into the analysis when they met the following criteria: (1) RCT, (2) comparison of CRT with a control group, and (3) reporting data on the echocardiographic results and clinical outcomes according to our review-checklist. In addition, abstracts without peer-review publications of manuscripts were not included.

### 2.2. Data extraction and outcome measures

Two investigators (S.A.-H.-S. and A.A.K.-B.) extracted the data independently, and discrepancies were resolved via a consensus standardized abstraction checklist used for recording data in each study. Data retrieved from the trials included: author's name, mean age, gender, sample size, study design, type of controls, duration of follow-up, primary and secondary endpoints, NYHA class, consumption of beta blocker, diuretics, angiotensin converting enzyme inhibitors and angiotensin receptor blockers, Jadad score. For each group the following data were recorded: LVEF, LVESV, LVEDV, LVEDD, LVESD, LVESVI, incidence of heart failure, mortality, infection, pneumothorax, and hematoma required intervention. For exploration of heterogeneity among trials, a subgroup analysis of disparities in the patients' characteristics was performed for (1) average age ($<$65 years vs. $\geq$65 years), (2) percentage of male gender ($<$80% vs. $\geq$80%), (3) follow-up duration ($\leq$6 months vs. $>$6 months), (4) sample size ($\leq$500 vs. $>$500).

### 2.3. Statistical analysis, publication bias and quality assessment

Data were analyzed by STATA version 11.0 utilizing METAN and METABIAS modules. The effect sizes measured were odds ratio (OR) with 95% confidence interval (CI) for categorical variables. Regarding non-categorical data, weighted mean difference (WMD) with 95% CI was used for calculating differences between intervention and control groups. OR $<$1 favored CRT and OR $>$1 favored control. RCTs with no events in the 2 arms were discarded from pooled analysis. Forest plots were created for each outcome. A value of $P < 0.1$ for $Q$ test or $I^2 > 50\%$ indicated significant heterogeneity among the studies. Heterogeneity among trials was accounted for by applying a random effect model when indicated. The presence of publication bias was evaluated using the Begg and Egger tests. Quality assessment of RCTs was performed using the Jadad score. The Jadad score assesses 3 items including randomization (0–2 points), blinding of study (0–2 points) and withdrawals and dropouts (0–1 points). Higher scores indicate better reporting ("high" quality: 5; "good" quality: 3–4; "poor" quality: 0–2). Results were considered statistically significant at a $P$-value $< 0.05$.

## 3. Results

### 3.1. Literature search strategy and included trials

Literature search retrieved 2035 studies from screened databases of which 1769 (86.9%) were excluded after initial review. Of 266 primarily included studies, 256 were excluded after detailed evaluation due to insufficient reporting of endpoints of interest. The final analysis included 10 RCTs.

### 3.2. Study characteristics, effect measures and clinical outcomes

#### 3.2.1. Left ventricular ejection fraction

A total of 2582 patients were included from 5 RCTs reporting data on LVEF. Patient population of RCTs ranged from 36 to 1820 patients (Table 1). From all patients, 1463 were allocated to CRT and 1119 to the control group. Mean increase in LVEF for all trials were $5.1 \pm 5.6$ with $6.78 \pm 6.14$ for CRT and $3.42 \pm 5.24$ for the control group (Table 2). Applying a random effect model, pooled analysis revealed that CRT succeeded in increasing ejection fraction mildly with a WMD of 2.88 (95% CI: 2.77–3; $P < 0.001$) (Fig. 1). There was a significant heterogeneity among the studies (chi-squared = 857.25, $I^2$ = 99.5%, $P < 0.001$). The subgroup analysis is presented in Table 3.

#### 3.2.2. Left ventricular end diastolic and end systolic volume

A total of 2042 cases were included from 3 RCTs reporting data on LVEDV and LVESV. Patient population of RCTs ranged from 36 to 1820. From all patients, 1193 were allocated to CRT and 849 to the control group (Table 1). Mean decrease in LVEDV for all trials was $-29.31 \pm 52.2$ with $-44.6 \pm 59.9$ for CRT and $-14.5 \pm 44.5$ for the control group, and mean decrease in LVESV for all RCTs was $-32.1 \pm 49.6$ with $-46.7 \pm 56.4$ for CRT and $-15.7 \pm 42.8$ for the control group, respectively (Table 2). Applying a random effect model, pooled analysis reported that CRT therapy could significantly decrease LVEDV (WMD of −37.31; 95% CI: −39.53 to −35.1; $P < 0.001$) and LVESV (WMD of −39.02; 95% CI: −41.2 to −36.84; $P < 0.001$). There was no significant heterogeneity among the studies for LVEF and LVESV analyses ($I^2$ = 0.0% for both).

#### 3.2.3. Left ventricular end diastolic diameter and end systolic diameter

A total of 2346 cases were included from 3 RCTs reporting data on LVEDD and LVESD. Patient population of RCTs ranged from 36 to 1820. From all patients, 1353 were allocated to CRT and 993 to the control group (Table 1). Mean decrease in LVEDD for all trials was $-2.4 \pm 3.4$ with $-4.1 \pm 3.7$ for CRT and $-0.8 \pm 3.1$ for the control group, and mean decrease in LVESD for all RCTs was $-3.6 \pm 4$ with $-5.7 \pm 4.4$ for CRT and $-1.6 \pm 3.6$ for the control group, respectively (Table 2). Applying a random effect model, pooled analysis reported that CRT could significantly decrease LVEDD (WMD of −2.98; 95% CI: −3.1 to −2.85; $P < 0.001$) and LVESD (WMD of −3.35; 95% CI: −3.48 to −3.22; $P < 0.001$). There was a significant heterogeneity among the studies for LVEDD and LVESD ($I^2$ = 99.1% for LVEDD and $I^2$ = 99.6% for LVESD).

#### 3.2.4. Left ventricular end systolic volume index

A total of 2082 patients were included from 2 RCTs reporting data on LVEF; 1269 were allocated to CRT and 813 to the control group. Applying a random effect model, pooled analysis revealed that CRT succeeded in significantly decreasing LVESV index with a