



Meta-analysis

Cardiac resynchronization therapy in patients with mild heart failure is a reversal therapy



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ARTICLE INFO

Article history:

Received 1 July 2015

Accepted 8 August 2016

Available online 25 August 2016

Keywords:

Cardiac resynchronization therapy

Heart failure

Mildly symptomatic

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.

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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 Considering the 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 Since progression of clinical symptoms from mild to severe HF may result from insufficient and inappropriate treatments, current management focuses on introducing treatments with ability of reversing 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 determine the

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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. ≥65 years), (2) percentage of male gender (<80% vs. ≥80%), (3) follow-up duration (≤6 months vs. >6 months), (4) sample size (≤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 was 5.1 ± 5.6 with 6.78 ± 6.14 for CRT and 3.42 ± 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 ± 52.2 with -44.6 ± 59.9 for CRT and -14.5 ± 44.5 for the control group, and mean decrease in LVESV for all RCTs was -32.1 ± 49.6 with -46.7 ± 56.4 for CRT and -15.7 ± 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 ± 3.4 with -4.1 ± 3.7 for CRT and -0.8 ± 3.1 for the control group, and mean decrease in LVESD for all RCTs was -3.6 ± 4 with -5.7 ± 4.4 for CRT and -1.6 ± 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

Table 1
Demographic data of included studies.

Author (references)	N		Mean age (yrs)		Male (%)		Mean LVEF (%)		Mean LVEDV (ml)		Mean LVESV (ml)		ORS (ms)	
	CRT	C	CRT	C	CRT	C	CRT	C	CRT	C	CRT	C	CRT	C
MADIT CRT ¹⁰	1089	791	65	64	74.7	75.6	24	24	245	251	175	179	699	476
Greater-earth trial ¹¹	61	60	61	61	75	75	24	24	211	211	161	161	155	155
Gierula ¹²	25	25	77	77	64	64	39	41	N.D.	N.D.	N.D.	N.D.	168	159
REVERSE trial ¹³	180	82	61.7	60.4	79	85	28.1	27.8	256	257	186	186	155	157
CONTACT trial ¹⁴	245	245	66	66	85	83	21	22	N.D.	N.D.	N.D.	N.D.	160	156
Van Geldorp ¹⁵	19	17	64	67	78.9	76.4	36	36	163	147	109	98	193	196
RAFT trial ¹⁶	894	904	66.1	66.2	84.8	81	22.6	22.6	N.D.	N.D.	N.D.	N.D.	157	158
Narrow-CRT trail ¹⁷	60	60	65	68	88	83	28	29	201	194	148	136	107	104
MIRACLE trial ¹⁸	85	101	63	63.1	88.2	90.1	24.4	24.6	337	329	260	252	166	165
CARE-HF trial ¹⁹	86	89	64	64	77	77	24.8	24.8	122	122	N.D.	N.D.	160	160
Author (references)	Beta-blocker		Diuretic		Design		Follow-up		Jadad					
	CRT	C	CRT	C	CRT	C	CRT	C	CRT	C				
MADIT CRT ¹⁰	93.3	93.2	75.7	72.9	ICD + CRT vs. ICD		2.4 years		4					
Greater-earth trial ¹¹	94	94	N.D.	N.D.	ICD + CRT vs. ICD + LV		6 months		4					
Gierula ¹²	56	52	N.D.	N.D.	CRT vs. RV		6 months		4					
REVERSE trial ¹³	95	90	84	87	ICD + CRT (on) vs. ICD + CRT (off)		24 months		4					
CONTACT trial ¹⁴	48	46	88	83	ICD + CRT (on) vs. ICD + CRT (off)		6 months		4					
Van Geldorp ¹⁵	N.D.	N.D.	N.D.	N.D.	ICD + CRT vs. ICD + RV		6 months		3					
RAFT trial ¹⁶	90.4	89	84.7	83.6	ICD + CRT vs. ICD + RV		40 months		4					
Narrow-CRT trail ¹⁷	87	92	85	87	CRT defibrillator vs. ICD		12 months		4					
MIRACLE trial ¹⁸	63.5	63.5	87.1	80.2	ICD + CRT (on) vs. ICD + CRT (off)		6 months		4					
CARE-HF trial ¹⁹	81	81	54	54	CRT vs. no CRT		50 months		4					

Table 2
Clinical outcomes of included studies.

Author	LVEF (%)		LVEDV		LVESV		LVEDD		LVESD			
	CRT	C	CRT	C	CRT	C	CRT	C	CRT	C		
MADIT CRT ¹⁰	11 ± 5	3 ± 3	-52.2 ± 33.2	-14.7 ± 14.4	-57.3 ± 31.2	-18.1 ± 16.3	-6 ± 3.4	-1.5 ± 1.5	-8.9 ± 4.4	-2.5 ± 2.2		
Greater-earth ¹¹	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.		
Gierula ¹²	9 ± 6	-1.5 ± 5.3	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.		
REVERSE trial ¹³	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.		
CONTACT trial ¹⁴	5.1 ± 0.7	2.8 ± 0.7	N.D.	N.D.	N.D.	N.D.	-2.4 ± 0.8	0 ± 0.8	-3.2 ± 0.8	-0.5 ± 0.8		
Van Geldorp ¹⁵	5 ± 11	12 ± 11	-39 ± 70.5	-13 ± 57.3	-41 ± 61	-15 ± 55.3	-4 ± 7	-1 ± 7	-5 ± 8	-2 ± 8		
RAFT trial ¹⁶	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.		
Narrow-CRT trail ¹⁷	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.		
MIRACLE trial ¹⁸	3.8 ± 8	0.8 ± 6.2	-41 ± 76	-16 ± 62	-42 ± 77	-14 ± 57	N.D.	N.D.	N.D.	N.D.		
CARE-HF trial ¹⁹	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.		
Author (references)	LVESV index		HF		Mortality		Infection		Pneumothorax		Hematoma required intervention	
	CRT	C	CRT	C	CRT	C	CRT	C	CRT	C	CRT	C
MADIT CRT ¹⁰	-28.7 ± 15.5	-9.1 ± 8.2	136	140	36	18	12	5	19	6	36	18
Greater-earth ¹¹	N.D.	N.D.	8	4	2	2	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Gierula ¹²	N.D.	N.D.	0	2	1	2	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
REVERSE trial ¹³	-27.5 ± 31.8	-2.7 ± 25.8	13	14	10	7	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
CONTACT trial ¹⁴	N.D.	N.D.	32	39	11	16	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Van Geldorp ¹⁵	N.D.	N.D.	N.D.	N.D.	0	0	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
RAFT trial ¹⁶	N.D.	N.D.	174	236	130	162	21	16	11	8	14	11
Narrow-CRT trail ¹⁷	N.D.	N.D.	5	11	4	5	2	1	N.D.	N.D.	1	1
MIRACLE trial ¹⁸	N.D.	N.D.	7	19	2	2	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
CARE-HF trial ¹⁹	N.D.	N.D.	N.D.	N.D.	23	27	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Long-term follow-up												
Author	Follow-up	Design	Conclusion									
MADIT trial ²⁰	7 years	ICD + CRT vs. ICD	This study indicated that in patients with mild heart-failure symptoms, left ventricular dysfunction, and left bundle-branch block, early intervention with CRT-D was associated with a significant long-term survival benefit									
REVERSE trial ²¹	5 years	ICD + CRT (on) vs. ICD + CRT (off)	This study indicated that in patients with mild HF, CRT produced reverse LV remodeling accompanied by very low mortality and need for heart failure hospitalization. These effects were sustained over 5 years. Cardiac resynchronization therapy in addition to optimal medical therapy produces long-standing clinical benefits in mild heart failure.									

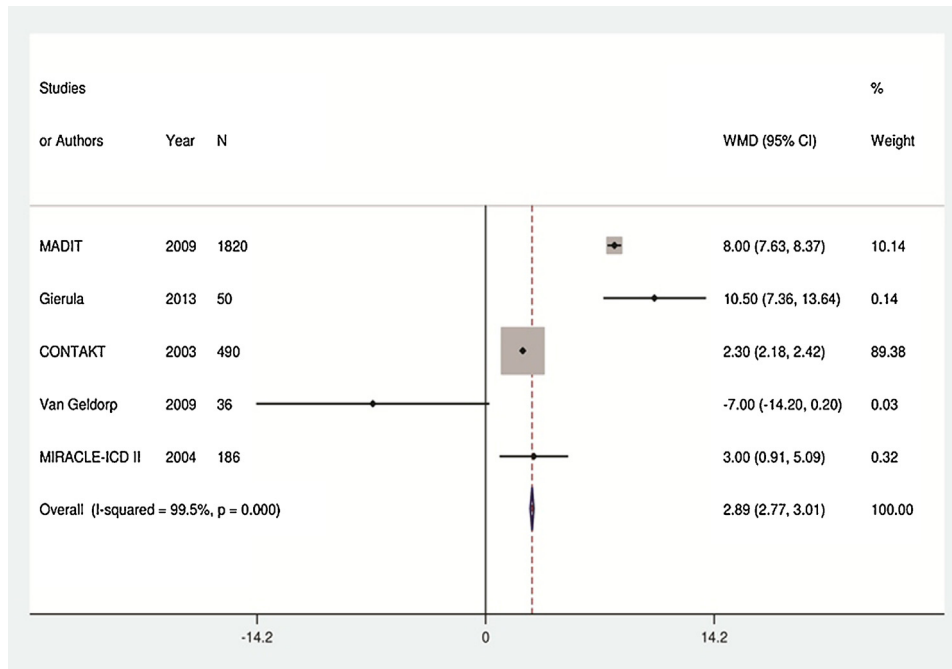


Fig. 1. Forest plot of weighted mean differences (WMD) for treatment with cardiac resynchronization therapy on left ventricle ejection fraction.

WMD of -19.71 (95% CI: -20.79 to -18.63 ; $P < 0.001$). There was no significant heterogeneity among the studies (chi-squared = 1.92, $I^2 = 48\%$, $P = 0.1$).

3.2.5. Incidence of progression of heart failure

A total of 4847 patients were included from 8 RCTs reporting data on the incidence of progression of HF. Patient population of RCTs ranged from 50 to 1820 subjects (Table 1). From all cases,

2639 were allocated to CRT and 2208 to the control group (Tables 1–2). The overall incidence of heart failure was 17.33% ranging from 4% to 22.8%. Progression of heart failure occurred in 14.2% in CRT group and 21.05% in control group (Table 2). Pooled treatment effect analysis revealed that CRT could significantly decrease the incidence of progression of heart failure with an OR of 0.64 (95% CI: 0.55–0.74; $P < 0.001$) using a fixed model (Fig. 2). No significant heterogeneity was observed among the RCTs (Chi-squared = 8.76, $I^2 = 20.1\%$, $P = 0.2$). Begg and Egger tests showed no potential publication bias among the included RCTs (Begg test, $P = 1.0$; Egger test, $P = 1.0$).

Table 3
Subgroup analysis for clinical outcomes.

Subgroup	Studies (N)	Odd ratio or SMD (95% CI)	P-value
S.G.A for left ventricle ejection fraction (LVEF) according to SMD			
<i>Age (years)</i>			
≤65	2	1.67 (1.57 to 1.77)	<0.001
>65	3	2.62 (2.38 to 2.86)	<0.001
<i>Male (%)</i>			
≤80	4	1.99 (1.89 to 2.09)	<0.001
>80	1	0.42 (0.13 to 0.71)	0.004
<i>Follow up</i>			
≤6 months	4	1.75 (1.57 to 1.93)	<0.001
>6 months	1	1.85 (1.74 to 1.96)	<0.001
<i>Sample size</i>			
≤500	4	1.75 (1.57 to 1.93)	<0.001
>500	1	1.85 (1.74 to 1.96)	<0.001
S.G.A for left ventricle end diastolic and systolic diameter (LVEDD and LVESD) according to SMD			
<i>Age (years)</i>			
≤65	1	-1.60 (-1.71 to -1.50)	<0.001
>65	2	-0.26 (-2.90 to -2.41)	<0.001
<i>Male (%)</i>			
All studies have male percentage less than 80%			
<i>Follow up</i>			
≤6 months	2	-2.66 (-2.90 to -2.41)	<0.001
>6 months	1	-1.60 (-1.71 to -1.50)	<0.001
<i>Sample size</i>			
≤500	2	-2.66 (-2.90 to -2.41)	<0.001
>500	1	-1.60 (-1.71 to -1.50)	<0.001

3.2.6. Mortality

Ten RCTs (5058 patients) reported data on death. Mortality occurred in 7.98% in CRT group and 10.41% in control group (Table 2). In fact 1 out of 10 comparisons did not present any postoperative death events in 2 comparative arms, therefore, the

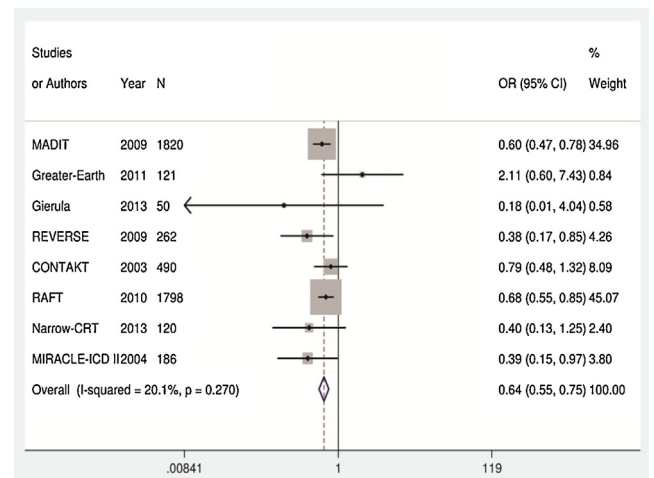


Fig. 2. Forest plot of odds ratio (OR) for treatment with cardiac resynchronization therapy on progression of heart failure.

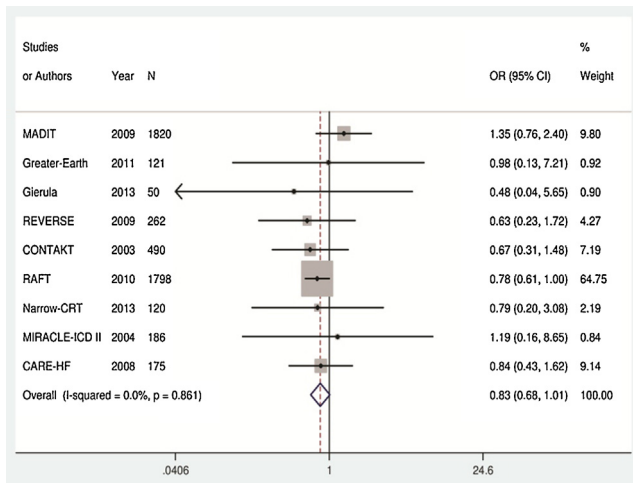


Fig. 3. Forest plot of odds ratio (OR) for treatment with cardiac resynchronization therapy on incidence of mortality.

remaining 9 RCTs (5022 cases) were used to perform the meta-analysis. Pooled treatment effect analysis revealed that CRT had a statistical trend toward reduction in mortality with an OR of 0.83 (95% CI: 0.68–1.01; $P = 0.06$) using a fixed model (Fig. 3). No significant heterogeneity was observed among the RCTs (chi-squared = 3.95, $I^2 = 0.0\%$, $P = 0.8$). Begg and Egger tests showed no potential publication bias among the included RCTs (Begg test, $P = 0.655$; Egger test, $P = 0.655$).

3.2.7. Infection

Three RCTs (3738 cases) reported data on the occurrence of infection. Overall incidence of infection was 1.54%: 1.71% in CRT group and 1.29% in control group (Tables 1–2). Pooled analysis indicated that CRT group was associated with a trend toward increased incidence of infections with an OR of 1.44 (95% CI: 0.83–2.47; $P = 0.1$) using a fixed model (Fig. 4). No significant heterogeneity was observed among the RCTs (chi-squared = 0.18, $I^2 = 0.0\%$, $P = 0.9$). Begg and Egger tests found no potential publication bias among the included RCTs (Begg test, $P = 0.117$; Egger test, $P = 0.117$).

3.2.8. Pneumothorax

Two RCTs (3618 cases) reported data on the occurrence of pneumothorax. Overall incidence of pneumothorax was 1.21%;

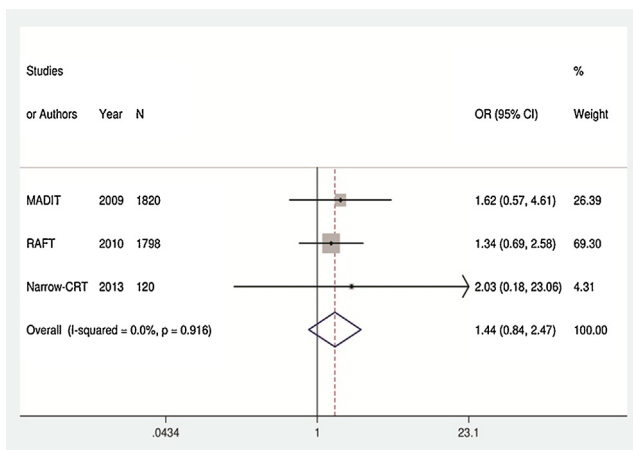


Fig. 4. Forest plot of odds ratio (OR) for treatment with cardiac resynchronization therapy on incidence of infection.

1.51% in CRT group and 0.85% in control group. Pooled analysis revealed that CRT group had trend toward increased incidence of pneumothorax with an OR of 1.75 (95% CI: 0.91–3.33; $P = 0.08$) using a fixed model. No significant heterogeneity was observed among the RCTs (chi-squared = 0.42, $I^2 = 0.0\%$, $P = 0.5$).

3.2.9. Hematoma required intervention

A total of 3738 patients were included from 3 RCTs reporting data on the incidence of hematoma. From these cases, 2043 were allocated to CRT and 1695 to the control group. The overall incidence of hematoma was 2.16% ranging from 1.3% to 2.9%. Hematoma occurred in 2.49% in CRT group and 1.76% in control group. Pooled analysis indicated that CRT did not significantly increase the incidence of hematoma with an OR of 1.32 (95% CI: 0.83–2.09; $P = 0.2$) using a fixed model. No significant heterogeneity was observed among the RCTs (chi-squared = 0.05, $I^2 = 0.0\%$, $P = 0.9$).

4. Discussion

Early diagnosis and appropriate treatment are of critical importance in HF: if the disease is controlled at earlier stages, survival and quality of life in patients are more likely to improve.^{1–3} According to guidelines, CRT when used in patients with moderate and severe HF, will be able to significantly improve clinical symptoms, quality of life, return to work, physical activities, and left ventricular function.^{2–4} Therefore, beneficial effects of CRT implantation in patients with NYHA class III and IV resulted in effective and efficient treatment before the patient required heart transplant.^{2–4} It is obvious that in HF, decreased left ventricular function results in increasing residual blood volume at the end of systole and diastole with consequently increasing left ventricular diameters and decreasing LVEF. Therefore, the more this vicious cycle continues, the higher the failure grade and more the clinical symptoms appear.

The main findings of our study are that CRT could significantly reduce residual blood volume and diameters of the left ventricle at the end of systole and diastole, and also increase LVEF. Given the fact that the follow-up period might be an important factor to detect an improvement in patients with mild HF, another noted difference is that we used extended follow-up of the REVERSE Trial: 24 months clinical and left ventricle remodeling which were reported by the European cohort.¹³ REVERSE Trial suggested that clinical outcomes and LV function were improved and LV dimensions were decreased in a patient population in NYHA class I or II.¹³

Our findings revealed that CRT could considerably prevent progression of HF, therefore, in patients with mild HF, CRT implantation at earlier stages of HF could be used in order to prevent worsening of clinical signs and decrease the cases of severe HF requiring heart transplant, thus being considered as reversal therapy. Lubitz et al. reported that CRT in patients with mild HF symptoms, left ventricular dysfunction, sinus rhythm and prolonged QRS duration could decrease HF events.²⁶ In the current study, CRT was also shown to have a strong tendency toward decreasing mortality (although not statistically significant). A study by Tu et al. also stated that CRT could significantly decrease all-cause mortality which confirms our deduction.²⁷ MADIT-CRT showed that CRT combined with ICD decreased the risk of heart failure events in relatively asymptomatic patients with LVEF less than 30% and wide QRS complex. The absence of an observed mortality benefit in this trial was probably due to a very low annual mortality rate (3%) throughout the course of the study period.¹⁰

A foreign material in the body may develop complications including hemorrhage related to implant placement, such as hematoma requiring intervention and infection.^{25–27} The results of

our study revealed that the patients with CRT were more prone to develop infection and pneumothorax, however the incidence of hematoma requiring intervention was comparable to the control group. The importance of this issue lies in the fact that for using beneficial effects of CRT, other treatments managing CRT complications should be considered for the patients, such as appropriate prophylactic antibiotics along with CRT implant placement in order to decrease the risk of infection, accurate radiographic and clinical investigations looking for pneumothorax, and opportune intervention when such complications appear. Previous studies have revealed that CRT could significantly increase the incidence of LV lead repositioning, infection, pneumothorax, hematoma, and coronary venous dissection. Although many of these adverse events did not have substantial long-term consequences, they may cause substantial morbidity and increase the overall costs to health care system.^{28–30}

Burri et al. argued that although CRT improved patients' outcome, this was at the expense of a greater rate of device-related complications such as infections and stimulation of phrenic nerve and lead repositioning compared with ICD implantation.³¹ RAFT reported that patients with NYHA class II or III heart failure, a wide QRS complex, and left ventricular systolic dysfunction, the addition of CRT to an ICD reduced rates of death and hospitalization for heart failure. This improvement was accompanied by more adverse events such as left ventricular lead dislodgment and infection.¹⁶ MADIT-CRT showed that CRT was associated with a significant decrease of mortality and HF events during 7 years follow-up in patients with mild HF symptoms, left ventricular dysfunction and left bundle-branch block.²⁰ Also the results of a 5-year-follow-up (REVERSE study) indicated that in patients with mild HF, CRT produced reverse LV remodeling, accompanied by very low mortality and need for HF hospitalization. CRT in addition to optimal medical therapy produced long-term clinical benefits in mild HF.²¹ On the other hand, several studies examined medical costs in patients with mild HF, strongly emphasizing that CRT reduced total medical costs in patients with asymptomatic and mild HF compared to optimal medical therapy.^{22–24}

5. Limitation

Our study is associated with several limitations. Data from some end-points of interest were not available for all studies, and we did not contact the authors to obtain unpublished data. Additionally, the absence of patient-level data limits our ability to assess sensitive patient-based subgroup analysis about effects of CRT on clinical or functional outcomes.

6. Conclusion

Implantation of CRT in patients with asymptomatic and mild HF can result in improved cardiac function, decreased progression of HF from mild to severe, reduced mortality in short to long-term follow-up. Although risk of complications such as infection, and pneumothorax increased after implantation of CRT, it is recommended to recognize the complications at earlier stages and use supplementary treatments and appropriate controls. As CRT also reduces medical costs in patients with mild HF compared with optimal medical therapy we strongly recommend this treatment strategy for patients with mild HF as an economical treatment with high efficiency.

Conflicts of interest

The authors have none to declare.

Acknowledgments

We would like to thank for their assistance Dr. Fatemeh Haddad, and Dr. Arezoo Shahidzadeh to writing of manuscript, and Dr. Elham Rahimizadeh, Dr. Zahra Sarrafan, Dr. Zahra Ghodrati-pour, and Dr. Ali Mohammad Dehghan for their assistance to collecting data and statistical analysis. The authors are indebted to Al-Majed et al. for their interesting article entitled "Meta-analysis: cardiac resynchronization therapy for patients with less symptomatic heart failure".³²

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