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The efficacy and safety of cardiac resynchronization therapy combined with implantable cardioverter defibrillator for heart failure: a meta-analysis of 5674 patients

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Aims The purpose of this study was to evaluate the efficacy and safety of cardiac resynchronization plus implantable cardioverter defibrillator (CRT-D) therapy and implantable cardioverter defibrillator (ICD) therapy in treating heart failure by systematically reviewing randomized controlled trials.

Methods and results Databases of Medline, Embase, and Cochrane Library were searched for published studies up to 31 May 2012. Clinicaltrials.gov and US Food and Drug Administration websites were searched as well. Only randomized controlled trials comparing the efficacy of CRT-D therapy with ICD therapy were enrolled in meta-analysis. Eight randomized controlled trials characterizing 5674 patients were finally included. Meta-analysis found that CRT-D therapy was associated with significant improvement in clinical conditions [odds ratio (OR): 1.66; 95% confidence interval (CI):1.33–2.07] and a reduction in hospitalization (OR: 0.7; 95% CI: 0.6–0.81) and all-cause mortality (OR: 0.8; 95% CI: 0.67–0.95). Although advantages of CRT-D therapy over ICD therapy were obvious, the peri-implantation adverse events of CRT-D therapy remained to be concerns.

Conclusion Compared with ICD therapy, patients receiving CRT-D therapy have favourable outcomes regarding improvement in clinical conditions, hospitalization rate, and overall survival, but at a significantly higher risk of peri-implantation adverse events. Future studies are warranted to optimize the clinical application of CRT-D.

Keywords Cardiac resynchronization therapy • Heart failure • Outcomes

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Introduction

Heart failure (HF) is the most common cardiovascular syndrome around the world. In developed countries, the prevalence of HF is 2.5% among adults in the community and the costs of HF exceed $33 billion per year.[1] Although in the last two decades we have seen great advances in pharmacological interventions, many HF patients remain highly symptomatic and have poor prognoses.[2,3]

Cardiac resynchronization therapy (CRT) is designed to eliminate the desynchronization of cardiac contraction among many patients with HF, and this therapy has brought improvements in cardiac performance and decrease in overall mortality.[4–7] Meanwhile, patients with HF are at high risk of sudden death. Although remarkable progresses have been achieved in medical management for this group of patients, the mortality rate remains unsatisfactorily high.[8,9] Implantable cardioverter defibrillator (ICD) is designed to detect and correct high-risk arrhythmias, and a number of clinical trials are in favour of ICDs over antiarrhythmic drugs in the prevention of sudden death caused by malignant arrhythmias.[10–15]

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What's new?

- Current evidence of the efficacy and safety of cardiac resynchronization therapy and implantable cardioverter defibrillator (ICD) therapy is limited. This meta-analysis characterizing 5674 patients systematically evaluated the role of cardiac resynchronization plus implantable cardioverter defibrillator and ICD therapy in the treatment of heart failure patients regarding patients' clinical status, mortality, and rate of hospitalization, as well as peri-implantation adverse events.

Whether the combination of CRT and ICD would create a synergistic effect has been an object of debate for many years. Recently, some meta-analyses have suggested that the cardiac resynchronization plus implantable cardioverter defibrillator (CRT-D) therapy could reduce mortality more significantly among patients with HF relative to ICD therapy alone.[16–19] However, the results are limited due to incomplete selection of clinical trials, or inadequate subset analyses, or a lack of safety assessment. So as far as we are aware, there are no synthesized studies focusing on the comparisons of outcomes such as improvement in clinical conditions, rate of hospitalization, and adverse events between CRT-D therapy and ICD therapy. Therefore, we performed a meta-analysis to systematically assess the efficacy and safety of CRT-D and ICD therapy in treating patients with HF.

Methods

Data sources and search strategy

To perform a systematic review and meta-analysis of open clinical trials remains challenging due to different study design and intrinsic biases. We conducted this study according to the guideline of PRISMA Statement.[20] Literature searches in the database of Medline, Embase, The Cochrane Library, and clinicaltrials.gov and US Food and Drug Administration websites were performed for eligible studies. English articles relevant to 'cardiac resynchronization therapy' and 'clinical trial' were identified for further assessment. The literature search was updated on 31 May 2012.

Inclusion criteria

We established the inclusion criteria according to the following requirements: (i) randomized controlled clinical trials; (ii) enrolled patients with HF, left ventricular ejection fraction (LVEF) $\leq$35%, and QRS duration $\geq$120 ms; (iii) compared CRT-D therapy with ICD therapy; (iv) included $>$50 participants; and (v) reported data about mortality, hospitalization, or improvement of clinical conditions, or peri-implantation adverse events.

Quality assessment and study outcome

The qualities of included studies were assessed according to the guideline of PRISMA Statement.[20] The key points were summarized as follows: (i) clear definition of study population? (ii) clear definition of outcomes and outcome assessment? (iii) independent assessment of outcome measurements? (iv) sufficient duration of follow-up (defined as at least 12 months)? (v) no selective loss of follow-up? and (vi) important confounders and prognostic factors identified? Each yes for these questions scored one point, and each no scored zero. The discrepancy was resolved by consensus. The studies characteristics, including study design, study population, treatment intervention, follow-up, outcome report, and adverse events, were extracted and recorded in our original information table. The outcomes of this study were improvement of clinical conditions, hospitalization rate, overall mortality, and peri-implantation adverse events. The improvement of clinical conditions was defined as the proportion of patients whose HF symptoms or New York Heart Association (NYHA) functional class were improved during follow-up in each group.

Statistical analysis

The significance between two groups was estimated by odds ratio (OR) with a two-tailed 95% CIs. A fixed-effect model was used for homogenous studies, whereas a random-effect model was used for heterogeneous studies. Statistic I^2 was used to describe the percentage of total across-studies variation due to study-to-study heterogeneity. A two-sided P value $<$0.05 was considered statistically significant. Subgroup analyses were performed to explore and control potential confounders. The statistical analyses were conducted by employing Review Manager Software Package (Version 5.0, The Cochrane Collaboration).

Results

Studies selection

The study selection process is illustrated in *Figure 1*. A total of 1561 literature was retrieved by our preliminary search. Two hundred and seventy-eight of them were excluded because 267 reports were non-English articles, and 11 studies were not human researches. After screening titles and abstracts, we excluded 1227 studies due to irrelevance. The remaining 56 studies relevant to our subject were selected for further assessment. During this process, 48 studies were excluded. Of these studies, 20 studies were systematic reviews and meta-analyses; 9 studies compared conventional pacing with biventricular pacing; 7 studies compared CRT with pharmacotherapy; 8 studies were cost-effectiveness researches; 3 studies enrolled $<$50 participants; and 1 study enrolled patients with narrow QRS complex. Consequently, eight randomized controlled trials were finally selected in this meta-analysis.[21–28]

Baseline characteristics of included studies

The baseline characteristics of eight included studies are shown in *Table 1*. All included studies were designed with randomized controlled method and conducted in multi-centre manner. Two of the eight included studies were cross-over designed trials,[21,22] and the other six studies applied parallel design.[23–28] Four studies primarily enrolled patients with NYHA class I–II (enrolling patients with NYHA class I–II $>$60%),[24,26–28] whereas the other four studies primarily enrolled patients with NYHA class III–IV (enrolling patients with NYHA class III–IV $>$60%).[21–23,25] One study had a 3-month follow-up,[21] three studies had a mean follow-up of 6 months,[22–24] and the other four studies had a mean follow-up of 12 months or more.[25–28] The mean ages of each included studies were comparable. Male patients were predominantly enrolled in these studies. More than 60% patients were diagnosed as ischaemic cardiomyopathy at baseline. Two studies partly

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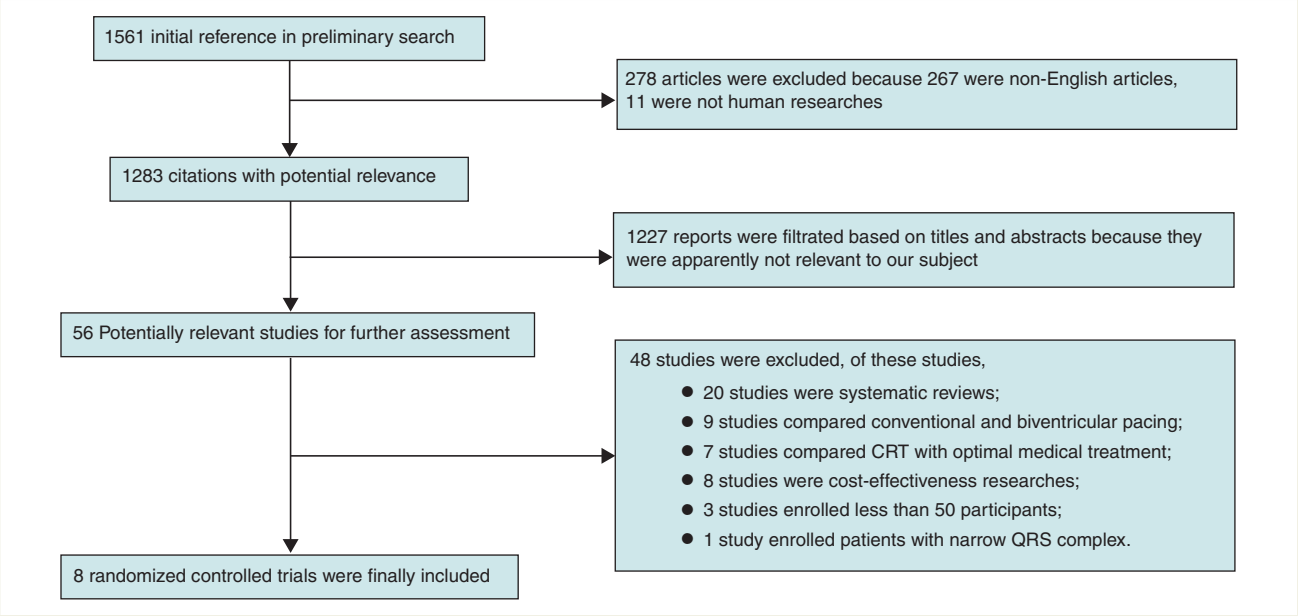

Figure 1 Flow diagram of study selection.

included patients with atrial fibrillation (12–13%),[27,28] whereas five studies recruited a small proportion of patients with right bundle branch block.[22–24,27,28] The mean LVEF at baseline ranged from 22 to 27%, and the baseline QRS duration ranged from 150 to 168 ms. More than 88% patients in these studies received angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. A <65% use of β-blockers was observed in four earlier studies,[21–24] whereas a >90% patients receiving β-blockers was observed in three recent studies.[26–28] The study size differed from 179 patients in RHYTHM-ICD trial[25] to 1820 patients in MADIT-CRT trial.[27] Ultimately, a total of 5674 patients were included in this meta-analysis, 3147 of them were assigned in the CRT-D group and 2527 patients in the ICD group.

Quality assessment and outcome report

The quality assessment for included studies is shown in *Table 2*. Except four studies had a relatively insufficient follow-up period,[21–24] the quality schema were fulfilled by all included studies. Ultimately, four studies scored five points,[21–24] and the other four studies had full scores.[25–28]

Among included studies, four of them reported the outcome of clinical conditions improvement,[22–24,26] five studies reported the data of hospitalization,[22,23,26–28] and all included studies assessed the outcome of mortality.[21–28] The above outcome data are summarized in *Table 3*.

Comparison of improvement in clinical conditions

When pooling data from four studies together (1390 patients),[22–24,26] CRT-D therapy showed to significantly improve clinical conditions by 66% (OR: 1.66; 95% CI: 1.33–2.07) with respect to ICD therapy alone. The clinical conditions of 414 patients (51.8%) in the CRT-D group were improved, compared with 227 patients (38.5%) in the ICD group, representing an absolute increased benefit of 13.3%. No evidence of significant heterogeneity was observed between studies regarding this effect ($I^2 = 18\%$; $P = 0.3$) (*Figure 2*).

Different study designs may have different impact on the pooled results of meta-analysis. Subgroup analysis for studies with parallel design[23,24,26] still showed a significantly greater improvement of clinical conditions in the CRT-D group as compared with the ICD group (OR: 1.77; 95% CI: 1.39–2.25), and without evidence of heterogeneity ($I^2 = 0\%$; $P = 0.37$).

Considering variations in the follow-up period may affect the results of meta-analysis, when we only included studies with a follow-up period of 6 months,[22–24] the significantly greater improvement in clinical conditions was maintained in the CRT-D group (OR: 1.57; 95% CI: 1.18–2.09), with test for heterogeneity ($I^2 = 39\%$; $P = 0.2$). This benefit was consistent with the result of REVERSE trial,[26] which had a mean follow-up of 12 months.

The category of NYHA functional class at baseline may also contribute to the heterogeneity between studies. When studies that predominantly enrolled patients with NYHA class I–II were included,[24,26] a significantly greater improvement in clinical conditions was observed in the CRT-D group (OR: 1.95; 95% CI: 1.45–2.64), without evidence of heterogeneity ($I^2 = 0\%$; $P = 0.38$). When we included studies that predominantly enrolled patients with NYHA class III–IV,[22,23] a borderline benefit of improvement in clinical conditions was observed in the CRT-D group (OR: 1.36; 95% CI: 0.98–1.89), and there was no evidence of heterogeneity ($I^2 = 0\%$; $P = 0.55$).

Comparison of hospitalization

When hospitalization data from five studies (5087 patients) were combined,[22,23,26–28] CRT-D therapy showed to significantly

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Table 1 Baseline characteristics of eight included randomized controlled trials

Study	Study design	Study size (n)	NYHA class (%)	Mean follow-up	Mean age (years) (SD)	Male (%)	ICM (%)	AF (%)	RBBB (%)	ACEI or ARB/ β-blocker/ diuretic (%)	Mean ejection fraction (%) (SD)	QRS width (ms) (SD)
Lozano *et al.*[21]	RCT cross-over	CRT-D:109 ICD:113	I, II: 35 III, IV: 65	3 months	65 (10)	83	68	NR	NR	98/42/90	22 (0.007)	NR
CONTAK-CD 2003[22]	RCT cross-over	CRT-D:245 ICD:245	II: 33 III, IV:67	6 months	66 (11)	84	69	0	32	88/47/86	22 (7)	158 (26)
MIRACLE-ICD 2003[23]	RCT parallel	CRT-D:187 ICD:182	III, IV:100	6 months	67 (10)	77	70	0	13	91/60/94	24 (6.2)	163 (22)
MIRACLE-ICD II 2004[24]	RCT parallel	CRT-D:85 ICD:101	II:100	6 months	63 (12)	89	57	NR	16	96/64/83	24.5 (6.7)	165 (24)
RHYTHM-ICD 2004[25]	RCT parallel	CRT-D:119 ICD:60	I, II:8 III, IV:92	12 months	NR	NR	NR	0	NR	NR	24.8 (7.7)	168
REVERSE 2008[26]	RCT parallel	CRT-D:419 ICD:191	I, II:100	12 months	62 (11)	79	55	0	NR	97/95/79	27 (7)	153 (22)
MADIT-CRT 2009[27]	RCT parallel	CRT-D:1089 ICD:731	I, II:100	2.4 years	65 (11)	75	55	12	13	97/93/74	24 (5)	65% patient >150 ms
RAFT 2010[28]	RCT parallel	CRT-D:894 ICD:904	II:80 III:20	40 months	66 (9)	83	67	13	9	97/90/84	23 (5)	158 (24)

RCT, randomized controlled trial; CRT-D, cardiac resynchronization therapy plus implantable cardioverter defibrillator (group); ICD, implantable cardioverter defibrillator (group); NYHA, New York Heart Association; ICM, ischaemic cardiomyopathy; AF, atrial fibrillation; RBBB, right bundle branch block; ACEI , angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SD, standard deviation; NR, not reported.

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Table 2 Assessment of the methodological quality for eight included randomized controlled trials

Quality schema[a]	Lozano et al.[21]	CONTAK-CD[22]	MIRACLE-ICD[23]	MIRACLE–ICD II[24]	RHYTHM-ICD[25]	REVERSE[26]	MADIT-CRT[27]	RAFT[28]
Clear definition of study population?	1	1	1	1	1	1	1	1
Clear definition of outcomes and outcome assessment?	1	1	1	1	1	1	1	1
Independent assessment of outcomes?	1	1	1	1	1	1	1	1
Sufficient duration of follow-up? (defined as at least 12 months)	0	0	0	0	1	1	1	1
No selective of loss during follow-up?	1	1	1	1	1	1	1	1
Prognostic factors and confounders identified?	1	1	1	1	1	1	1	1
Total score	5	5	5	5	6	6	6	6

[a]The quality assessment for included randomized controlled trials was performed according to the PRISMA Statement.[20] Each 'yes' to the question scored one point, each 'no' scored zero. The full score is six points, representing high methodological quality of study.

reduce hospitalization rate by 30% (OR: 0.7; 95% CI: 0.6–0.81) as compared with ICD therapy alone. Four hundred and forty-four patients (15.7%) in the CRT-D group experienced hospitalization, as compared with 508 patients (22.5%) in the ICD group, suggesting an absolute reduction of 6.8%. There was no significant heterogeneity at this comparison ($I^2 = 45\%$; $P = 0.12$) (*Figure 3*).

When we performed subset analysis for studies with parallel design,[23,26–28] the CRT-D group still showed a significant benefit in reducing hospitalization as compared with the ICD group (OR: 0.69; 95% CI: 0.59–0.8), with no significant heterogeneity regarding this effect ($I^2 = 57\%$; $P = 0.07$).

When subgroup analysis was conducted in studies with 6 months follow-up,[22,23] a neutral effect of CRT-D or ICD therapy on hospitalization was observed (OR: 0.97; 95% CI: 0.71–1.34), without significant heterogeneity between studies ($I^2 = 3\%$;
$P = 0.31$). Whereas the subgroup analysis for studies with follow-up ≥12 months was performed,[26–28] a significant benefit in reducing hospitalization was observed in the CRT-D group (OR: 0.64; 95% CI: 0.54–0.75), without evidence of heterogeneity ($I^2 = 0\%$; $P = 0.59$).

When performing subgroup analysis in studies predominantly enrolling patients with NYHA class I–II,[26–28] CRT-D therapy exhibited a significantly lower hospitalization as compared with ICD therapy (OR: 0.64; 95% CI: 0.54–0.75), and no evidence of heterogeneity was observed ($I^2 = 0\%$; $P = 0.59$). When subgroup analysis was performed in studies predominantly enrolling patients with NYHA class III–IV,[22,23] there was no statistical difference between both groups (OR: 0.97; 95% CI: 0.71–1.34), without significant heterogeneity ($I^2 = 3\%$; $P = 0.31$).

Comparison of all-cause mortality

All studies included in this meta-analysis reported the data of mortality. When we pooled data from eight studies (5674 patients),[21–28] CRT-D therapy showed to significantly reduce mortality by 20% (OR: 0.8; 95% CI: 0.67–0.95), as compared with ICD therapy alone. Three hundred and seven patients (9.8%) in the CRT-D group reach this endpoint, compared with 337 patients (13.3%) in the ICD group, and the absolute benefit in the reduction of mortality was 3.5%. No evidence of heterogeneity between studies was observed during this effect ($I^2 = 0\%$; $P = 0.83$). When studies with cross-over design were excluded, subset analysis for studies with parallel design[23–28] still showed a significant effect on reducing mortality in the CRT-D group as compared with the ICD group (OR: 0.81; 95% CI: 0.68–0.97), without evidence of heterogeneity ($I^2 = 0\%$; $P = 0.76$) (*Figure 4*).

Subgroup meta-analysis in studies with a 3- or 6-month follow-up[21–24] showed that CRT-D therapy decreased the mortality as compared with the ICD group, but this reduction effect was not significant (OR: 0.73; 95% CI: 0.46–1.18), and no evidence of heterogeneity was observed ($I^2 = 0\%$; $P = 0.79$). When studies with follow-up ≥12 months were included,[25–28] CRT-D therapy exhibited a significant advantage in reducing mortality as compared with the ICD group (OR: 0.81; 95% CI: 0.67–0.97), with no appreciable heterogeneity ($I^2 = 0\%$; $P = 0.5$).

When studies predominantly enrolling patients with NYHA class I–II were included,[24,26–28] the mortality in the CRT-D group was

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Table 3 Outcomes reported from included randomized controlled trials

Study	Improvement of clinical condition (*n*/*N*)	Hospitalization (*n*/*N*)	Overall mortality (*n*/*N*)
Lozano *et al.*[21]	NR	NR	CRT-D: 5/109 ICD: 10/113
CONTAK-CD 2003[22]	CRT-D: 39/109 ICD: 37/116	CRT-D: 32/245 ICD: 39/245	CRT-D: 11/245 ICD: 16/245
MIRACLE-ICD 2003[23]	CRT-D: 98/187 ICD: 78/182	CRT-D: 85/187 ICD: 78/182	CRT-D: 14/187 ICD: 15/182
MIRACLE-ICD II 2004[24]	CRT-D: 49/85 ICD: 36/101	NR	CRT-D: 2/85 ICD: 2/101
RHYTHM-ICD 2004[25]	NR	NR	CRT-D: 6/119 ICD: 2/60
REVERSE 2008[26]	CRT-D: 228/419 ICD:76/191	CRT-D: 17/419 ICD: 15/191	CRT-D: 9/419 ICD: 3/191
MADIT-CRT 2009[27]	NR	CRT-D: 136/1089 ICD: 140/731	CRT-D: 74/1089 ICD: 53/731
RAFT 2010[28]	NR	CRT-D: 174/894 ICD: 236/904	CRT-D: 186/894 ICD: 236/904

CRT-D, cardiac resynchronization therapy plus implantable cardioverter defibrillator (group); ICD, implantable cardioverter defibrillator (group); NR, not reported.

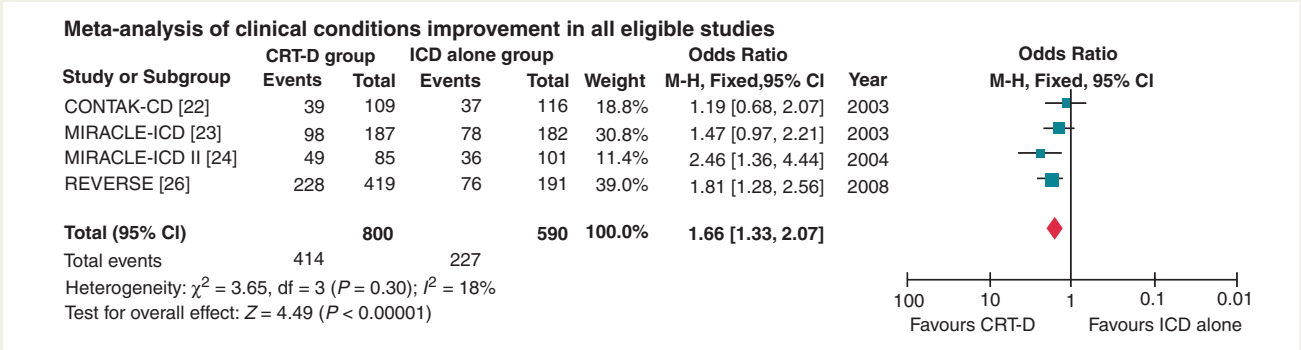

Figure 2 Meta-analysis of clinical conditions improvement.

significantly lower as compared with the ICD group (OR: 0.8; 95% CI: 0.67–0.96), accompanying no evidence of heterogeneity ($I^2 = 0\%$; $P = 0.59$). When studies predominantly enrolling patients with NYHA class III–IV were included,[21–23,25] a statistically insignificant effect was found (OR: 0.76; 95% CI: 0.48–1.21), and no evidence of heterogeneity was observed ($I^2 = 0\%$; $P = 0.66$).

Success rates and complication of device implantation

The success rates of device implantation and peri-implantation adverse events are summarized in *Table 4*. The implantation success rate ranged from 88.3% in MIRACLE-ICD study[23] to 98.4% in MADIT-CRT study[27] and the overall success rate of pooled studies (involving 5671 patients) could achieve up to 95.3%.

A percentage of 0.4% overall peri-implantation mortality was observed in the pooled data (involving 4581 patients). About 5.5% of included patients (involving 5044 patients) experienced lead problems like dislodgement or lead reposition. Device-related infections occurred at 1.4% of included patients (involving 3823 patients). Mechanical damages (consisting of pneumothorax or haemothorax, pericardial effusion or tamponade, and coronary sinus dissection or perforation) occurred at 4.4% of included patients (involving 5044 patients).

Based on the available data from MADIT-CRT[27] and RAFT study,[28] the pooled results including 3618 patients showed that 239 adverse events (12.1%) occurred in the CRT-D group, whereas 86 adverse events (5.3%) occurred in the ICD group during the first 30 days of device implantation. The pooled results revealed that the CRT-D group had a statistically higher complication rate than the ICD group (OR: 2.57; 95% CI: 1.98–3.32; *Figure 5*). Of these adverse events, such as pneumothorax, haemothorax, pocket haematoma, pocket required revision, infections, lead dislodgement and reposition, and coronary sinus

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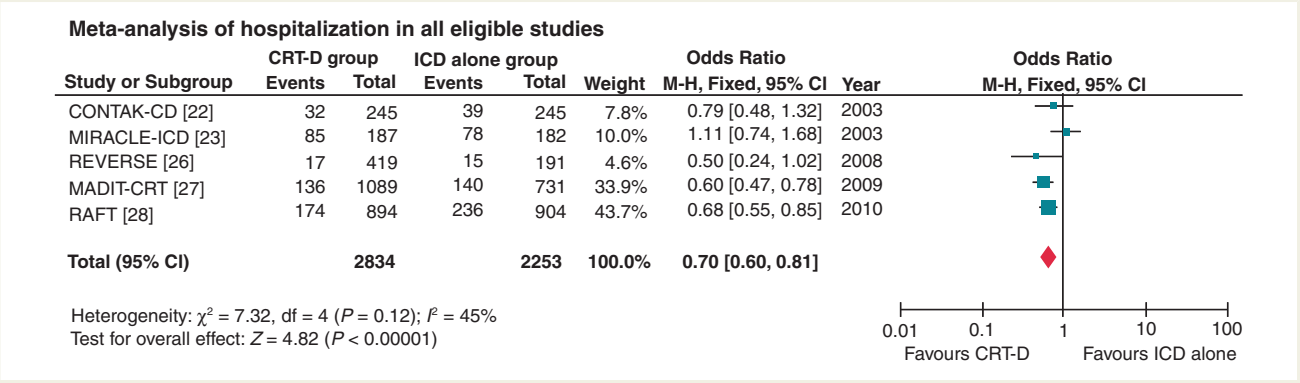

Figure 3 Meta-analysis of hospitalization.

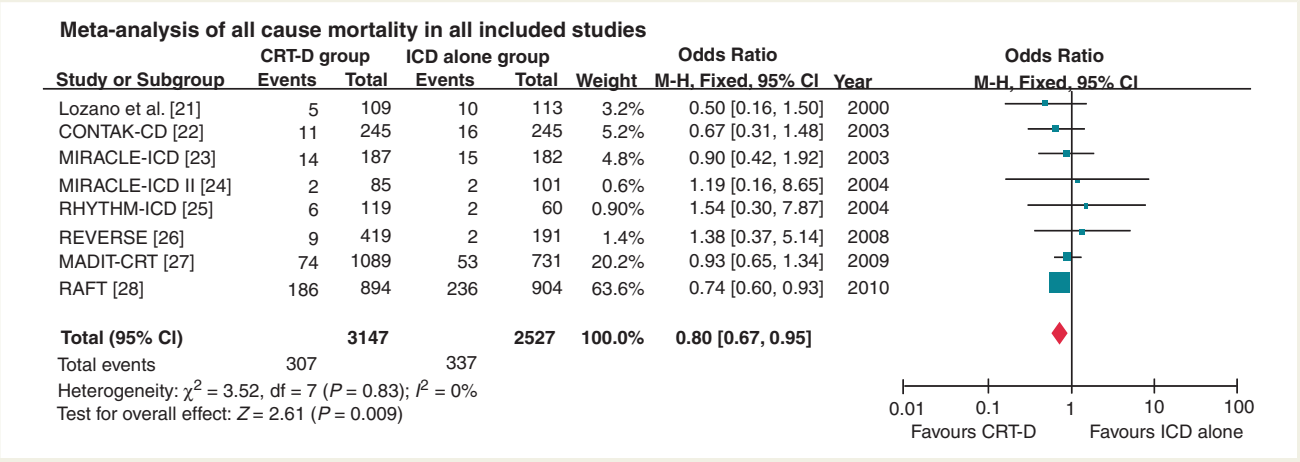

Figure 4 Meta-analysis of mortality.

dissection, all were observed to occur more frequently in the CRT-D group, particularly the risks of lead problems and coronary sinus dissection were significantly higher among patients assigned to the CRT-D group.

Discussion

Despite many advances in pharmacotherapy, the clinical outcomes seems not to improve parallely among patients with HF. Implantable cardioverter defibrillator implantation has been proved to improve the survival rate and reduce the risk of sudden death among high-risk patients, but ICD therapy alone is shown to be associated with recurrent HF events.[29] On the other hand, as an effective adjunctive therapy for pharmacological management, CRT has been found to improve the short-term and long-term outcomes of patients with HF. Therefore, it is reasonable to expect that CRT plus ICD therapy could slow down the progression of HF and provide additional benefits in reducing morbidity and mortality among patients.

Efficacy of CRT

A series of clinical trials has been performed to compare the benefits of CRT-D with ICD therapy among patients with HF. Lozano *et al.*[21] conducted the first multi-centre randomized study, and their results demonstrated that combination of biventricular pacing with ICD therapy did not improve survival rate. Later, the CONTAK-CD study,[22] which enrolled 490 patients with NYHA class II–IV, also observed an insignificant difference in clinical conditions, rate of hospitalization, and mortality between CRT-D and ICD therapy groups. However, there were major changes halfway during the process of this trial, therefore, the results of this study should be interpreted with caution.

The results of the MIRACLE-ICD series studies (MIRACLE-ICD and MIRACLE-ICD-II)[23,24] did not show a significant improvement in survival and reduction of hospitalization in CRT-D therapy as compared with ICD therapy alone. Noteworthy, the aforementioned four studies had a follow-up period of only 6 months. The results from our subset meta-analyses of studies with a follow-up $\leq$6 months were consistent with the MIRACLE-ICD series studies. Possible explanations may be the inadequate pharmacotherapy (the

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Table 4 Implantation success rate, and peri-implantation complication rates in the included randomized controlled trials

Study	Implantation success rate *n/N* (%)	Peri-implantation death *n/N* (%)	Lead dislodgement or reposition *n/N* (%)	Infection *n/N* (%)	Mechanical damage[a] *n/N* (%)
CONTAK-CD 2003[22]	501/567(88.4)	12/567(2.1)	NR	NR	NR
MIRACLE-ICD 2003[23]	379/429(88.3)	NR	47/369(12.7)	NR	25/369(6.8)
MIRACLE-ICD II 2004[24]	191/210(91.0)	1/191(0.5)	16/210(7.6)	NR	7/210(3.3)
RHYTHM-ICD 2004[25]	182/205(88.8)	5/205(2.4)	22/205(10.7)	1/205(0.5)	31/205(15.1)
REVERSE 2008[26]	621/642(96.7)	NR	66/642(10.3)	NR	13/642(2.0)
MADIT-CRT 2009[27]	1790/1820(98.4)	1/1820(0.1)	44/1820(2.4)	17/1820(0.9)	84/1820(4.6)
RAFT 2010[28]	1740/1798(96.8)	1/1798(0.1)	81/1798(4.5)	37/1798(2.1)	60/1798(3.3)
Total success or complication rates	5404/5671(95.3)	20/4581(0.4)	276/5044(5.5)	55/3823(1.4)	220/5044(4.4)

[a]Mechanical damage consisted of peri-implantation adverse events such as pneumothorax or haemothorax, pericardial effusion or tamponade, and coronary sinus dissection or perforation.
NR, not reported.

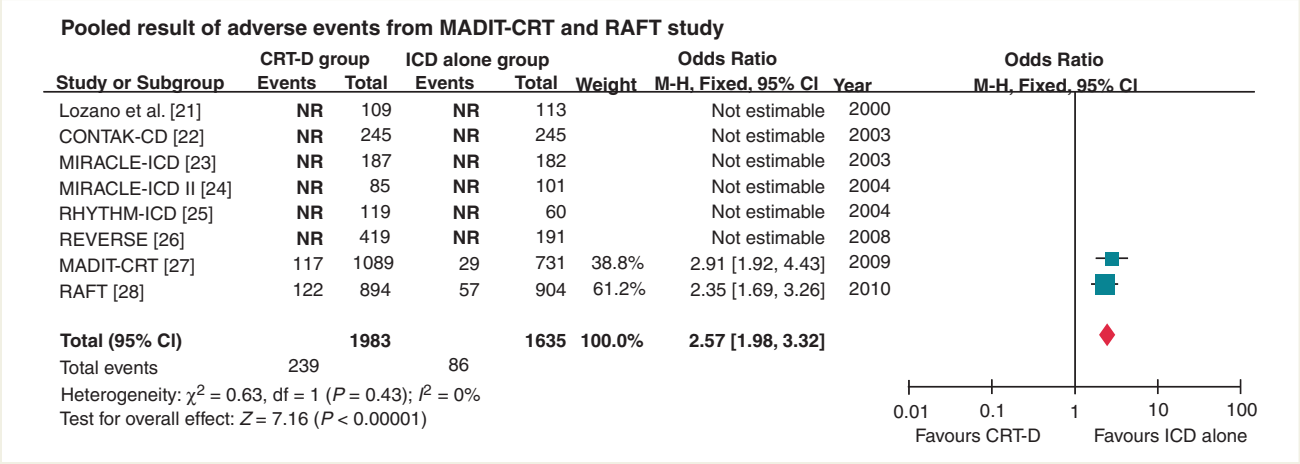

Figure 5 Meta-analysis of adverse events.

percentage of patients who received β-blockers was <60%) in earlier studies,[21–23] and a relatively short follow-up period for CRT to take full effect. Moreover, in MADIT-CRT[27] and RAFT studies,[28] same results have been observed in Kaplan–Meier analysis during the early stage of follow-up, although their final results showed that CRT-D had more benefits than ICD. It should also be interpreted that CRT can correct the cardiac desynchrony and increase the cardiac pump efficiency within a short time, thus patients who began to present HF symptoms may be alleviated quickly, which could partly explain why our subset meta-analysis of studies within a 6-month follow-up showed significant improvements in clinical status among patients who received CRT-D therapy.

Recently, there are three major clinical studies concerning the comparison of CRT-D and ICD therapy. Conducted in 2008, REVERSE study[26] recruited 610 patients with NYHA functional class I–II and demonstrated that compared with ICD therapy, CRT-D therapy significantly improved the clinical conditions and showed a borderline significance in the reduction of hospitalization during a 12-month follow-up. Although the patients in the REVERSE study showed better compliance to pharmacological treatment guidelines than those in previous clinical trials, this study failed to detect a between-group difference in mortality. Another study, MADIT-CRT trial,[27] which involved 1820 patients, showed that significant reduction in non-fatal HF events was achieved in the CRT-D group during an average follow-up of 2.4 years. However, a neutral effect on overall mortality between CRT-D and ICD groups was observed, which may be attributed to the enrollment of less severe patients. The most recent study RAFT[28] enrolled 1798 mild-to-moderate HF patients and followed them up to an average of 40 months. It concluded that long-term hospitalization and overall mortality can be substantially reduced by CRT combined with ICD therapy as compared with ICD

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therapy alone. In another extent, patients indicated to CRT-D therapy could receive a maximal benefit in survival and reduction of HF events if they had a relatively longer life expectance.

The results of our meta-analysis may add important information to previous studies. Eight randomized controlled trials focusing on CRT-D and ICD therapy were included in our study, where not only efficacy but also safety of the two therapies was systematically reviewed. Besides, studies were subjected to subgroup analyses with regard to the study design, follow-up period, and NYHA functional category. The pooled results show that patients in the CRT-D group experience a greater improvement in clinical status and reduction in hospitalization than those in the ICD group. When comparing all-cause mortality among studies, our results show similar results to previous meta-analysis. The subgroup analyses revealed a beneficial effect in favour of CRT-D therapy on survival rate, particularly among patients when a sufficient follow-up period was taken into account.

Subgroup analyses for the efficacy of CRT-D therapy among patients with bundle branch blocks, near-normal QRS interval, and atrial fibrillation were not performed in our study due to a lack of data. Recently, a meta-analysis including four randomized controlled trials found that CRT was effective in reducing HF events in patients with left bundle branch block, but the efficacy of CRT was not so evident among patients with other kinds of conduction blocks.[30] Another meta-analysis showed similar results, suggesting that CRT provided no benefits for patients with right bundle branch block.[31] There were several studies focusing on the association between QRS duration and the efficacy of CRT therapy. Their results demonstrated that among the patients who had received CRT therapy those with a QRS $\geq$ 150 ms had significantly less HF events than those with a QRS $<$150 ms.[32,33] So far, current studies contradict each other as to whether CRT-D therapy could improve the clinical conditions of patients with atrial fibrillation as compared with those with sinus rhythms.[34,35] Future researches may be needed to give a clear picture of CRT-D-treating patients with these particular characteristics.

Safety of cardiac resynchronization therapy

Although the benefit of CRT therapy is evident among published studies, potential adverse events relating to CRT should be taken into account. Our analysis revealed an overall successful implantation rate to be around 95%; however, it should be noted that the peri-implantation mortality, prevalence of lead problems, and device-related infection was 0.4, 5.5, and 1.4%, respectively (*Table 4*). With respect to the adverse events of CRT-D therapy, MADIT-CRT study[27] and RAFT study[28] showed that pneumothorax, pocket haematoma, device-related infection, and lead problems occurred more frequently among patients in the CRT-D group than those in ICD group. Our study demonstrated consistent results when these adverse events were considered, especially lead dislodgement and coronary sinus dissection remained significant problems. Although most of the adverse events may not be fatal, they could indeed increase the duration of hospitalization and thus reduce patients' life quality.[36,37] On the other hand, it should be mentioned that this meta-analysis included studies over a relatively wide time range (since year 2000), and we do believe that the results of implantation success rates and complications can be improved by technical improvements over time.

Another concern remains that the efficacy of CRT-D therapy might be overestimated due to the fact that patients enrolled in trials were relatively younger than those in real-world clinical practice, given that older patients carry a larger burden of concurrent diseases.[38] Moreover, evidence exists that CRT implantations among the population are performed by general clinicians, considering that most of the included studies are from large clinical centres, it would not be difficult to speculate a lower success implantation rate and a higher incidence of adverse events peri-implantation in hospitals that are more under qualified.[39,40] Therefore, clinicians need to balance the advantages and disadvantages of CRT-D therapy meticulously during the process of decision-making.

Summary

This systematic review and meta-analysis collected data from randomized controlled studies in order to fully evaluate the efficacy and safety of CRT-D therapy in treating patients with HF accompanied by LVEF $\leq$ 35% and QRS $\geq$ 120 ms. Our results show that CRT-D therapy may provide more benefits to HF patients from a long-term perspective with respect to clinical conditions, hospitalization, and all-cause mortality. It should be noted that CRT-D therapy was associated with significantly higher risk of peri-implantation adverse events. The pros and cons of CRT-D therapy need to be weighed carefully during the exploration of an optimized strategy to treat patients with HF.

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