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Comparison of clinical trials evaluating cardiac resynchronization therapy in mild to moderate heart failure

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Abstract

Recently, three large randomized clinical trials: REVERSE, MADIT-CRT, and RAFT were completed aiming to determine the effects of cardiac resynchronization therapy (CRT) or CRT with defibrillator (CRT-D) in less advanced, predominantly NYHA class II heart failure (HF) patients. The REVERSE trial, significantly smaller than the other two trials, could be considered as a phase II study indicating that mild-to-moderate HF patients show symptomatic and hemodynamic improvement in response to CRT. The MADIT-CRT and RAFT are considered as definitive trials with large patient populations of about 1,800 patients each, and HF event/ /hospitalization or death as the primary endpoint. Both trials showed a significant reduction in the risk of primary endpoints: a 34% reduction in MADIT-CRT and 25% reduction in RAFT. However, RAFT also showed a significant reduction in mortality which was not observed in MADIT-CRT. The clinical characteristics of patients studied in both trials were different despite somewhat similar entry criteria. RAFT enrolled more advanced HF patients (including 20% NYHA class III patients) than MADIT-CRT. In the CRT-D arm, RAFT patients had about 20% two-year mortality in comparison to approximately 6% two-year mortality in MADIT-CRT. Mortality in RAFT was in similar to those observed in CRT-D patients in the COMPANION trial (estimated 25% two-year mortality), and in the CRT arm of the CARE-HF trial (estimated 18% two-year mortality), both older studies which enrolled NYHA class III and IV HF patients. Based on the above comparison, one could conclude that RAFT enrolled moderate-to-advanced HF patients whereas MADIT-CRT enrolled truly mild- -to-moderate patients. (Cardiol J 2010; 17, 6: 543–548)

Key words: heart failure, cardiac resynchronization therapy

Introduction

Heart failure (HF) patients with decreased ejection fraction (EF), New York Heart Association (NYHA) class III or IV, and a wide QRS (≥ 120 ms) derive significant benefit from cardiac resynchronization therapy (CRT) measured by HF hospitalization and death as the primary endpoints [1–3]. CRT improves functional status and quality of life but even more importantly decreases the risk of HF hospitalization and mortality.

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial enrolled 1,520 HF patients with an EF ≤ 35%, NYHA class III or IV, QRS ≥ 120 ms who were randomized to conventional pharmacologic therapy or CRT with either a pacemaker (CRT-P) or a pacemaker-defibrillator (CRT-D) [1]. CRT-P decreased the risk of death or hospitalization for any cause by 19% (hazard ratio: 0.81; p = 0.014) and CRT-D by 20% (hazard ratio: 0.80; p = 0.01). Hospitalization for HF or death was reduced respectively by 34%

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Table 1. Comparison of clinical trials evaluating clinical effects of cardiac resynchronization therapy in mild to moderate heart failure.

Trial	REVERSE	REVERSE European	MADIT-CRT	RAFT
Number of patients	610	262	1,820	1,798
Design of trial				
Inclusion criteria:				
NYHA class	I/II	I/II	I/II	II/III
EF	≤ 40%	≤ 40%	≤ 30%	≤ 30%
QRS	≥ 120 ms	≥ 120 ms	≥ 130 ms	≥ 120 ms/ /≥ 200 ms paced
Primary endpoint	HF clinical composite score	HF clinical composite score	HF event or death	HF hospitalizations or death
Intervention	CRT-D or CRT *vs* no CRT (2:1)	CRT-D or CRT *vs* no CRT (2:1)	CRT-D *vs* ICD (3:2)	CRT-D *vs* ICD (1:1)
Results of trial				
Follow-up	12 months	24 months	28 months	40 months
NYHA class:				
I	18%	17%	15%	–
II	82%	83%	85%	80%
III	–	–	–	20%
Mean EF	27%	28%	24%	23%
Mean QRS	153 ms	153 ms	158 ms	158 ms
Left bundle branch block	NR	NR	70%	72%
HF or death:				
Comparison arm	NR	24%*	25.3%	40.3%
CRT/CRT-D arm	NR	12%*	17.2%	33.2%
Hazard ratio (p value)	NR	0.38 (0.003)	0.66 (0.001)	0.75 (< 0.001)
HF hospitalization:				
Comparison arm	7%	18.4%	22.8%	26.1%
CRT/CRT-D arm	3%	7.8%	13.9%	19.5%
Hazard ratio (p value)	0.47 (0.03)	0.39 (0.01)	0.59 (< 0.001)	0.68 (< 0.001)
Death:				
Comparison arm	2.2%	8.6%	7.3%	26.1%
CRT/CRT-D arm	1.6%	5.7%	6.8%	20.8%
Hazard ratio (p value)	NR (0.63)	0.40 (0.09)	1.00 (0.99)	0.75 (0.003)

*Estimated from the figure; CRT — cardiac resynchronization therapy; ICD — implantation cardioverter-defibrillator; NR — not reported; NYHA — New York Heart Association class; EF — ejection fraction; HF — heart failure

($p < 0.002$) and by 40% ($p < 0.001$). Mortality was decreased by 24% by CRT-P ($p = 0.059$) and by 36% by CRT-D ($p = 0.003$).

The Cardiac Resynchronization-Heart Failure (CARE-HF) Study involved 813 HF NYHA class III or IV patients with an EF ≤ 35% who were randomized to conventional medical therapy or CRT-P (without defibrillator) [2]. The primary endpoint was a composite of death from any cause or an unplanned hospitalization for a major cardiovascular event. The use of CRT-P significant reduced this primary endpoint by 37% (hazard ratio: 0.63; $p < 0.001$) and mortality by 36% (hazard ratio: 0.64; $p < 0.002$). Both of these studies formed the basis for clinical indications for CRT, thus recommending that HF patients with NYHA class III or IV, EF ≤ 35% and QRS ≥ 120 ms should be treated with CRT-D devices.

However, the vast majority of HF patients with depressed EF remain in less advanced stages of HF. Therefore it is even more important to prevent progression of HF in patients mild to moderate HF, namely NYHA class I and II. The question regarding the benefits of CRT therapy in such less advanced patients was raised by investigators designing and conducting three large randomized clinical trials: REVERSE, MADIT-CRT, and RAFT (Table 1).

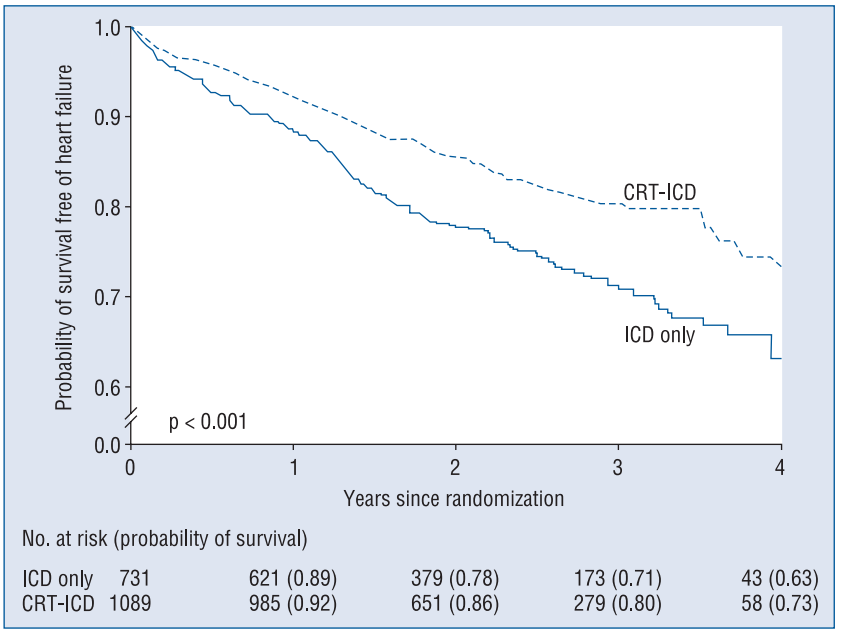

Figure 1. Kaplan-Meier estimates of the probability of survival free of heart failure in CRT-D *vs* ICD in the MADIT-CRT (reproduced from reference [6] with permission).

REVERSE

Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial enrolled 610 NYHA class II patients and class I patients with previous HF symptoms, with QRS ≥ 120 ms and EF ≤ 40% [4]. This trial did not use classical HF hospitalization or death endpoint due to its limited sample size. Instead, the primary endpoint was the HF clinical composite response that scored patients as improved, unchanged, or worsened over a relatively short follow-up of 12 months. The study did not meet the primary endpoint: 16% of patients worsened in the CRT-ON compared with 21% in the CRT-OFF ($p = 0.10$) group. In secondary analyses, the time-to-first HF hospitalization during 12-month follow-up was significantly delayed in the CRT-ON group (hazard ratio: 0.47, $p = 0.03$).

European investigators of this trial followed 262 of the patients up to 24 months and the primary endpoint of worsening was found to be significantly lower in the CRT-ON group than in the CRT-OFF group (19% *vs* 34%, respectively, $p = 0.01$) [5]. Time to first HF hospital stay or death in the European cohort was significantly delayed by CRT (hazard ratio: 0.38; $p = 0.003$). The REVERSE trial was not designed to answer the question about the effect of CRT on HF hospitalization or death. Furthermore, it allowed for both CRT-P and CRT-D therapy making the applicability of findings more difficult regarding effects of this therapy on mortality.

MADIT-CRT

The Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) trial was the first large randomized trial that was designed to determine whether CRT-D therapy *vs* ICD only therapy will reduced the risk of the clinical endpoint of a HF event or death in mild to moderate HF patients [6]. A HF event was defined as HF hospitalization (accounting for 87% of HF events) or outpatient HF management (accounting for the remaining 13% of HF events). The trial enrolled 1,820 ischemic (NYHA class I or II) and nonischemic (class II) cardiomyopathy patients with EF ≤ 30% and QRS ≥ 130 ms. The primary endpoint occurred in 17.2% of patients randomized to CRT-D and 25.3% to ICD only therapy: a 34% reduction in the risk of HF event or death (hazard ratio in the CRT-D group: 0.66; $p = 0.001$). Figure 1 shows Kaplan-Meier estimates of the probability of survival free of HF in CRT-D *versus* ICD in the MADIT-CRT trial. This effect was dominated by a significant 41% reduction in the risk of HF events whereas there was no significant difference in mortality between the CRT-D and ICD-only arms.

Patients with a wide QRS duration ≥ 150 ms as well as females had significantly more benefit from CRT-D than patients with QRS < 150 ms and males [6]. Further analyses revealed that patients with left bundle branch block (LBBB), accounting

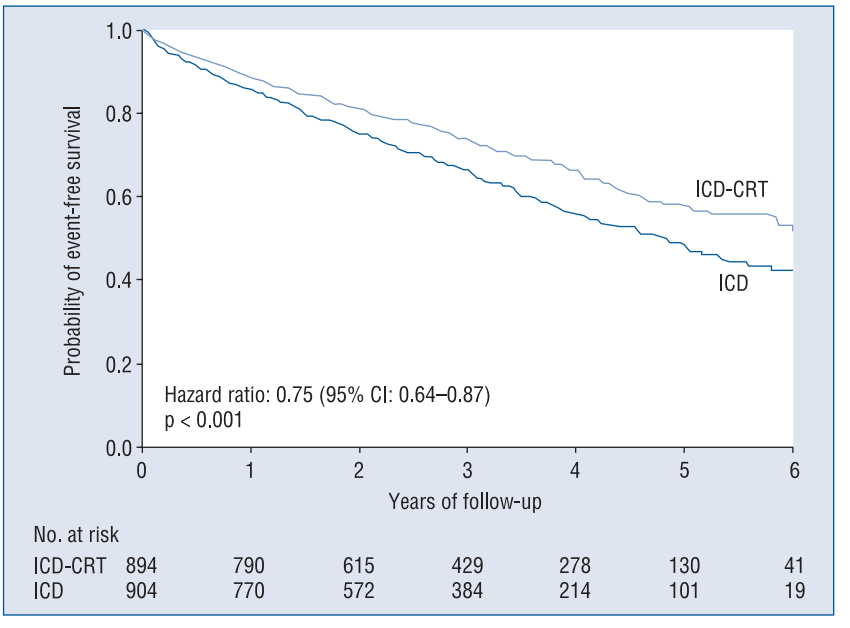

Figure 2. Kaplan-Meier estimates of hospitalization for heart failure or death in the RAFT (reproduced from reference [10] with permission).

for 70% of the enrolled patients, derived a significant benefit from CRT-D whereas patients with a wide QRS complex and right bundle branch block (RBBB) or indeterminate ventricular conduction disturbances (IVCD) (regardless of QRS duration) did not demonstrate reduction in primary events [7, 8]. Hazard ratios for comparing CRT-D *vs* ICD only groups regarding the primary endpoint were significantly ($p < 0.001$) lower in LBBB patients (hazard ratio: 0.47; $p < 0.001$) than in non-LBBB (RBBB or IVCD) patients (hazard ratio: 1.24; $p = 0.257$) [8]. These observations led to the approval of new CRT-D indications by the Food and Drug Administration [9], which cover not only NYHA class III and IV patients but also NYHA class II or ischemic class I HF patients with QRS duration ≥ 130 ms, EF ≤ 30% and LBBB.

RAFT

The recently presented and published results of the Resynchronization/Defibrillation in Advance Heart Failure Trial (RAFT) provide further evidence supporting these new indications [10]. RAFT enrolled 1,798 NYHA class II or III HF patients with an EF ≤ 30% and an intrinsic QRS ≥ 120 ms or a paced QRS ≥ 200 ms, and randomized them 1:1 to an implantable cardioverter-defibrillator (ICD) alone or an ICD plus CRT (CRT-D). Similarly to the MADIT-CRT trial, the primary endpoint was defined as hospitalization for HF or death. The risk of primary endpoint was significantly reduced by 25% (hazard ratio: 0.75; $p<0.001$), from 40.3% in the ICD-only group to 33.2% in the CRT-D group (Fig. 2). At the same time, mortality was also reduced by 25% (hazard ratio: 0.75; $p = 0.003$), from 26.1% in the ICD-only patients to 20.8% in CRT-D patients. Since the RAFT trial enrolled 80% of patients with NYHA class II and 20% with NYHA class III, the authors performed additional analyses in these two subgroups, which showed that when the analysis was confined to just NYHA class II patients, a reduction in cardiac events was still significant: 27% reduction in primary endpoint, 29% reduction in mortality (Fig. 3). Additional subgroup analyses demonstrated significant interaction terms for QRS duration ≥ 150 ms and for QRS morphology indicating that patients with wide QRS benefit from CRT-D therapy significantly more than patients with QRS < 150 ms and that patients with LBBB benefit more than patients with RBBB, IVCD or paced QRS. Females also showed a trend toward more significant benefit than men.

Comparison of REVERSE, MADIT-CRT, and RAFT

The REVERSE trial is difficult to compare with the MADIT-CRT and RAFT trials since it is a relatively small trial with a limited number of patients and limited follow-up which did not specify cardiac

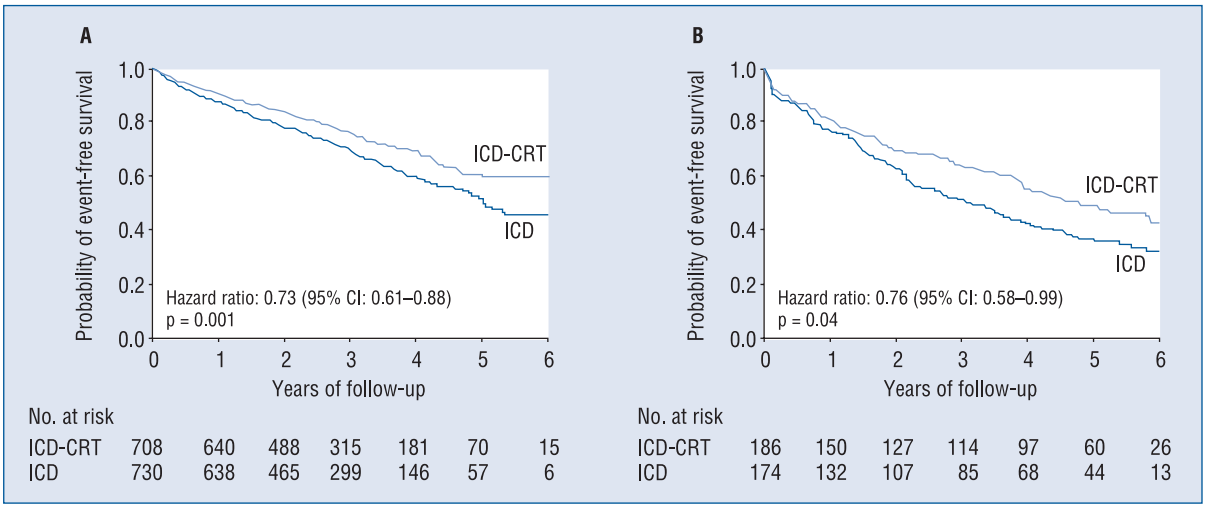

Figure 3. Kaplan-Meier estimates of hospitalization for heart failure or death among patients with NYHA class II (**A**) and class III (**B**) heart failure (reproduced from reference [10] with permission).

events (HF or death) as the primary endpoint of the study. As originally designed, REVERSE trial did not meet the primary endpoint of change in HF or clinical status. The study met the secondary endpoint: significant reduction in the left ventricular (LV) end-systolic volume index associated with CRT. Nevertheless, tertiary analyses of HF hospitalization showed a significant reduction in CRT--treated patients in comparison to non-CRT patients. The REVERSE trial should be considered as a phase II trial, designed with a short follow-up and secondary type endpoints. Follow-up extended to 24 months in the European REVERSE trial patients demonstrated that the primary endpoint of HF status improvement and reduction in LV volumes were found significant, as well as the clinical endpoint of HF hospitalization and HF hospitalization or death were also significantly reduced in CRT-ON *vs* CRT--OFF patients. It is important to stress that in comparison to the MADIT-CRT and RAFT trials, the REVERSE trial enrolled patient with less advanced LV dysfunction, with EF ≤ 40% and mean EF of 27%. Therefore, this study indicates that not only patients with mild to moderate HF and EF ≤ 30% (as in MADIT-CRT and RAFT) benefit from CRT. However, the study is too small to truly determine whether patients with EF in the range of 31–40% truly benefit from CRT regarding HF hospitalization or death. It would be extremely valuable to have the entire US and European cohorts of REVERSE patients followed for another few years to determine their long-term risk of HF or death, especially in patients with an EF of 31–40%, a subset which was not addressed by MADIT-CRT and RAFT.

The main comparison could be done between MADIT-CRT and RAFT, two large, phase III, definitive trials with a similar design evaluating the effect of CRT-D in mild-to-moderate HF patients. The MADIT-CRT was the first definitive trial completed and published in 2009 [6] and its results help establishing new Food and Drug Administration--approved expanded indications for CRT-D therapy. One could ask: what have we learned from RAFT after the publication of the MADIT-CRT trial. Both studies showed a significant reduction in HF or death with CRT-D therapy. However, MADIT-CRT showed a 34% reduction during a mean 28-month follow-up, whereas the reduction in RAFT was 25% with a 40-month follow-up. At the same time MADIT-CRT did not show a significant mortality benefit, whereas RAFT demonstrated a significant 25% reduction in mortality. The risk of a HF event in the ICD-only arm was comparable in both trials: 26% in RAFT and 23% in MADIT-CRT. But the 26% mortality was much higher in RAFT ICD-only patients when comparing to the 7% mortality in MADIT-CRT patients randomized to the ICD-only arm. This is a meaningful distinction even after adjusting for differences in the follow-up duration: roughly over twice higher mortality despite a similar risk of HF events. What are the reasons for these differences?

The trials were similar regarding some characteristics of the study population: mean EF, mean QRS duration, and percentage of patients with LBBB. However, there were several differences between these two study populations. RAFT included 20% of patients in NYHA class III and 80% in

NYHA class II, whereas MADIT-CRT included 85% of class II and 15% class I patients. RAFT included 82% men whereas MADIT-CRT enrolled 75% men, which may have contributed to a higher mortality as well. The percentage of ischemic patients was 67% *vs* 55%, respectively, and mortality is expected to be higher in ischemic than nonischemic patients. MADIT-CRT included only sinus rhythm patients whereas RAFT enrolled 13% patients with atrial fibrillation and 8% patients with a paced rhythm, factors known to characterize more advanced HF patients. Glomerular filtration rate of < 60 mL/min/1.73 m^2 was observed in 51% patients in RAFT, whereas MADIT-CRT included 41% of such patients; < 30 mL/min/1.73 m^2 in 7% and 3%, respectively. Patients in both trials were similarly treated pharmacologically. Therefore, RAFT enrolled more advanced HF patients than MADIT--CRT who were more likely to die with ICD-only therapy as well as more likely to die despite CRT-D therapy. In fact, based on the above comparison one could conclude that RAFT enrolled moderate-to--advanced HF patients whereas MADIT-CRT enrolled truly mild-to-moderate patients.

When comparing two-year mortality rates in patient treated with CRT devices (based on published Kaplan-Meier curves), RAFT showed about 20% two-year mortality in the CRT-D arm, which is comparable with about 18% two-year mortality in the CARE-HF, the trial enrolling class III and IV patients, and comparable with a 25% two-year mortality observed in the CRT-D arm in the COMPANION trial, also enrolling class III and IV patients. These rates are much higher than the 6% two-year mortality observed in MADIT-CRT patients randomized to CRT-D therapy.

Based on the above comparisons, RAFT seems to be more similar to CARE-HF or COMPANION than to MADIT-CRT, which probably explains the differences between trials regarding the magnitude of the effect of CRT-D on HF events and differences in the effect on mortality. Long-term follow-up of MADIT-CRT patients will possibly allow us to determine whether in these mild HF patients, CRT-D also reduces mortality, which would be expected after about a 40% reduction the risk of HF events.

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