Chapter 23

Critical appraisal of the use of cardiac resynchronization therapy beyond current guidelines

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J Am Coll Cardiol 2010;56(10):754-62

ABSTRACT

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with drug-refractory, chronic heart failure. Multiple single- and multi-center studies have shown significant reductions in left ventricular (LV) volumes and an increase in LV systolic function. More importantly, CRT reduces mortality and morbidity during long-term follow-up. Current guidelines consider CRT as a class I indication for heart failure patients in New York Heart Association (NYHA) functional class III-IV, with depressed LV ejection fraction (LVEF) ≤35%, and a wide QRS complex (≥120 ms). However, the benefits of this therapy could possibly be extended to selected sub-groups of patients who do not fulfill these criteria. These sub-groups include patients with mildly symptomatic heart failure and patients with a narrow QRS complex (<120 ms). Results from recent multi-center controlled clinical trials including heart failure patients in NYHA functional class I-II or with a narrow QRS complex are equivocal. While expanding CRT to patients with a narrow QRS complex seems currently not likely, the benefits of CRT in mildly symptomatic patients are more evident. Perhaps attenuation of disease progression will prove to be a successful new treatment strategy in heart failure patients in the future. In addition, multi-modality cardiac imaging will allow optimizing responder rate in patients undergoing CRT according to current guidelines.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with drug-refractory, chronic heart failure. Multiple single- and multi-center studies have shown significant reductions in mortality and morbidity in heart failure patients after CRT implantation.[1-5] In addition, CRT improved left ventricular (LV) performance by restoring the synchronicity of the electromechanical activation, inducing reverse remodeling, and reducing mitral regurgitation.[6-9] Accordingly, current guidelines consider CRT as a class I indication for heart failure patients in New York Heart Association (NYHA) functional class III-IV, with LV ejection fraction (LVEF) ≤35%, and a wide QRS complex (≥120 ms).[10] Recently, the benefit of CRT has been explored in selected sub-groups of patients who do not fulfill these criteria. These sub-groups include patients with mildly symptomatic heart failure and patients with a narrow QRS complex (<120 ms). Results from recent multi-center controlled clinical trials including heart failure patients in NYHA functional class I-II or with a narrow QRS complex may provide evidence to expand the indications of CRT.[11-13] The present article reviews these trials and discusses the role of CRT in heart failure patients in NYHA functional class I-II or with narrow QRS complex.

CRT IN PATIENTS WITH NARROW QRS COMPLEX

Prolonged QRS complex duration (≥120 ms) indicates the presence of cardiac dyssynchrony that can be corrected with CRT. The landmark trials that demonstrated the efficacy of CRT included heart failure patients with QRS complex durations >120 ms. Therefore, current guidelines recommend CRT only in heart failure patients with QRS complex duration ≥120 ms.[10] However, data from the CONQUEST (Congestive Heart Failure and QRS Duration: Establishing Prognosis) study, including more than 3000 heart failure patients, demonstrated that 42% of the patients with systolic heart failure had a QRS duration <120 ms.[14] Based on these data and according to current guidelines, a significant percentage of heart failure patients would not be amenable for CRT. The assessment of LV mechanical dyssynchrony with different imaging modalities may identify heart failure patients who could benefit from CRT, despite having a narrow QRS complex. Indeed, several echocardiographic studies have demonstrated that 40-50% of heart failure patients with a narrow QRS complex may also exhibit LV dyssynchrony.[15] This sub-group of patients with a narrow QRS complex, but with presence of LV mechanical dyssynchrony, may also benefit from CRT. To elucidate the effects of CRT on heart failure patients with a narrow QRS complex, several single-center studies were performed providing encouraging results (Table 1).[16-19] In these trials, patients with a narrow QRS complex exhibited similar improvements in clinical parameters and LVEF as patients with a wide QRS complex. Comparable observations were made in the Evaluation

of CRT in Narrow QRS Patients with Mechanical Dyssynchrony from a Multi-center Study (ESTEEM-CRT). This study included 68 patients with NYHA functional class III heart failure symptoms QRS <120 ms, LVEF ≤35% and LV mechanical dyssynchrony as defined by the standard deviation of time to peak systolic velocity of 12 segments (Ts-SD) >28.7 ms. All patients received CRT with defibrillator (CRT-D) and underwent invasive dP/dtmax testing for AV optimization at implantation. Preliminary results of this trial were presented at the Heart Rhythm Society congress in 2008.[20] After 6 months follow-up, a significant reduction in NYHA functional class (-0.7±0.7, p<0.01) was observed, accompanied by an improvement in quality of life score (-23±21, p<0.01). In contrast however, no significant changes in peak VO2 or LVEF were noted. The authors concluded from these results that patients with narrow QRS complex and LV dyssynchrony (using tissue Doppler imaging, Ts-SD) did not improve as measured by exercise performance and LV reverse remodeling.

Table 1. Benefits of CRT on symptomatic heart failure patients with a narrow QRS complex: results from single- and multi-center trials

	Achilli et al.[16]	Bleeker et al.[17]	Yu et al.[19]	ESTEE[20]	RethinQ[11]
No. patients	14	33	51	68	87
Age (years)	68 ± 8	63 ± 11	63 ± 11	58 ± 14	60 ± 12
Male gender (%)	71%	85%	78%	68%	71%
Ischemic etiology (%)	29%	70%	49%	60%	54%
QRS duration (ms)	110 ± 11	110 ± 8	103 ± 13	102 ± 10	107 ± 12
LV dyssynchrony (ms)	43 ± 17	102 ± 32	36 ± 14	45 ± 21	81 ± 39
Effects of CRT on clinical and echocardiographic parameters at follow-up					
Reduction in NYHA class	1.6 ± 0.1	0.9 ± 0.6	0.7 ± 0.4	0.7 ± 0.7	54% improved
Reduction in quality of life score	NA	13 ± 16	8 ± 19	23 ± 21	8 (1-10)*
Improvement in 6-MWD (m)	94 ± 19	89 ± 107	46 ± 88	NA	26 (0-46)*
Reduction in LV end-systolic dimensions: diameter (mm)[1]/volume (ml)[2]	5.8 ± 0.2[1]	39 ± 34[2]	17 ± 19[2]	5 ± 40[2]	19 (12-34)*[2]
Improvement in LVEF (%)	9 ± 1	8 ± 8	7 ± 6	0.8 ± 8.2	1.2 (0.4-4.4)*

6-MWD = 6-minute walk distance; CRT = cardiac resynchronization therapy; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

* 95% Confidence Intervals

RETHINQ:

The Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ) trial is the first randomized multi-center study in patients with narrow QRS complex (<130 ms), and included a total of 172 heart failure patients in NYHA functional class III with an indication for an implantable cardioverter-defibrillator (ICD).[11] All patients showed LV mechanical dyssynchrony as assessed by echocardiographic techniques (96% as assessed with tissue Doppler imaging and 4% as assessed with M-mode echocardiography). After implantation of a CRT device with cardioverter-defibrillator capability, patients were randomized to the CRT group or the control group (no CRT). The study failed to demonstrate a significant dif-

ference in the primary end-point (increase in peak oxygen consumption ≥1.0 ml per kilogram of body weight per minute during exercise testing at 6 months) between the CRT group and the control group. Secondary end-points included change in quality of life score and change in NYHA class at 6 months follow-up. Change in quality of life score was similar between the CRT group and the control group (-7 vs. -8, p = 0.91). However, at 6 months follow-up, a significantly larger proportion of patients in the CRT group improved in NYHA functional class by ≥1 point compared to the control group (54% vs. 29%, p = 0.006), although no differences in change in 6-minute walk distance and LV volumes were noted between the 2 groups. When the analyses were performed according to baseline QRS complex duration, those patients with a QRS complex between 120-130 ms exhibited significant improvements in peak oxygen consumption and NYHA functional class whereas those patients with a QRS <120 ms showed a significant improvement only in NYHA functional class (Figure 1).[11]

Although RethinQ could not demonstrate conclusive evidence to support CRT in narrow QRS patients by its primary end-point of peak myocardial oxygen consumption, there was a significant improvement in NYHA functional class in the CRT group as compared to the control group. The limited benefits of CRT in patients with narrow QRS complex may be explained by the presence of short LV electrical activation delays as recently demonstrated.[21, 22] The time delay between onset of the QRS complex to the latest activated area of the left ventricle may indicate the amount of global LV dyssynchrony amenable to be corrected through CRT. In patients with LBBB morphology, the LV activation delays are usually longer than those observed in patients with narrow QRS complex or RBBB. Indeed, patients with QRS duration >150 ms and LBBB morphology showed the highest response rates in recent multi-center trials.[12, 13] In contrast, patients with short LV activation delays or with the latest activated areas located far away from the vein targeted by the LV pacing lead (patients with RBBB or anterior myocardial scar) may show less clinical and echocardiographic improve-

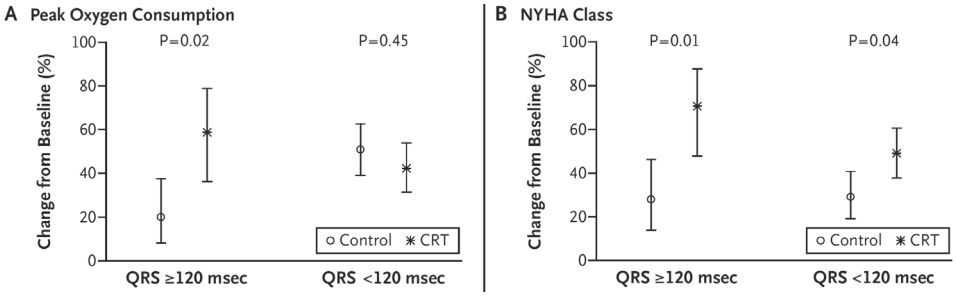


Figure 1. Effects of CRT in patients with narrow QRS complex in RethinQ.
At 6 months follow-up, those patients with a QRS between 120-130 ms showed a significant improvement in peak oxygen consumption (A) and NYHA functional class (B) as compared to controls. However, patients with a QRS duration <120 ms showed only a significant improvement in NYHA functional class.
Adapted with permission from Beshai et al. *N Engl J Med* 2007;357:2461-71.

ment at mid- or long-term follow-up after CRT.[23, 24] In this regard, accurate identification of the latest mechanically activated areas to guide the LV lead positioning may help to improve the response rates to CRT. The use of non-invasive imaging techniques to evaluate either the electrical or mechanical substrate of LV dyssynchrony will help to identify the patients with narrow QRS complex or RBBB who will benefit from CRT.

It should be emphasized that the current 2 trials (ESTEEM and RethinQ) included few patients, had limited follow-up (up to 6 months) and did not focus on re-hospitalization and long-term survival. Currently, there is a large prospective randomized trial ongoing that will focus on exactly these issues. The EchoCRT (Echocardiography guided Cardiac Resynchronization Therapy) trial will include over 1000 patients, carefully selected by novel advanced echo techniques, evaluated by a single core laboratory before entrance in the study.[25] Patients are randomized to CRT or no CRT and patients in both study arms will receive an ICD. The primary end-point is all-cause mortality or hospitalization for cardiovascular events during long-term follow-up.

There are several other ongoing studies evaluating the effects of CRT in heart failure patients with narrow QRS complex. The CRT-Narrow (Cardiac Resynchronization Therapy - Narrow-dp/dt) is a non-randomized study that evaluates acute and mid-term effects of CRT on LV function by invasive measures of LV performance and LV reverse remodeling.[26] Finally, the EARTH (Evaluation of Resynchronization Therapy for Heart Failure) trial,[27] will investigate the impact of LV mechanical dyssynchrony on clinical outcome of symptomatic heart failure patients with a narrow QRS complex (<130 ms). The results of these trials may determine the subsequent dissemination of CRT in this specific group of patients.

CRT IN MILD HEART FAILURE

To date, the vast majority of patients in the large CRT trials were in NYHA functional class III and IV. The 2 largest trials that showed a survival benefit for CRT over optimal medical therapy alone included patients only in NYHA functional class III and IV. As a result, current guidelines consider CRT as a class I indication only for heart failure patients in NYHA functional class III-IV.[10]

Much less is known about the effects of CRT in patients with mild symptoms of heart failure. Some studies have hypothesized that CRT in mildly symptomatic heart failure patients might prevent heart failure worsening. In the Multicenter InSync Randomized Clinical Evaluation II (MIRACLE ICD II) trial, 186 patients in NYHA functional class II, a LVEF ≤35%, a QRS complex ≥130 ms and a class I indication for an ICD were randomized to CRT-ON (n = 85) or CRT-OFF (n = 101).[28] At 6 months follow-up, the CRT-ON group had a greater reduction in LV diastolic and systolic volumes (p = 0.04 and p = 0.01 respectively). In addition, CRT-ON recipients showed statistically significant improvement in NYHA functional class and clinical

composite[29] response (p = 0.05 and p = 0.01 respectively). There were no significant differences in improvement in peak oxygen consumption, 6-minute walking distance or quality of life scores.[28] Similar results were reported by the CONTAK-Cardiac Defibrillator (CONTAK-CD) trial, with significant reductions in LV dimensions.[5]

The results of CONTAK-CD and MIRACLE ICD II, together with the observation that LV reverse remodeling was a better predictor of long-term survival than clinical improvement,[30] led to the use of LV reverse remodeling as an end-point in clinical randomized CRT trials . Since patients with mild heart failure symptoms may also exhibit depressed LV function and wide QRS complex, 2 large clinical trials were conducted to investigate whether CRT could prevent or attenuate disease progression and induce LV reverse remodeling in this group (Table 2).[31, 32]

Table 2. Comparison of the MADIT-CRT and REVERSE trials

	REVERSE[12, 31]	MADIT-CRT[13, 32]
Inclusion criteria		
• LVEF	• ≤40%	• ≤30%
• QRS duration	• ≥120 ms	• ≥130 ms
• NHYA class	• I / II	• I / II
Study design		
• Randomization (CRT vs. control)	• 2 : 1	• 3 : 2
• ICD	• Yes / No	• Yes
• Primary end-point	• HF CCS	• All-cause mortality or HF event
Results		
• No. of patients	• 610	• 1820
• NHYA class II	• 503 (82%)	• 1555 (85%)
• Ischemic heart disease	• 333 (55%)	• 999 (55%)
• Outcome summery	• No less worsening in CCS (16% in CRT-ON vs. 21% in CRT-OFF, p = 0.10)	• Significant reduction in all-cause mortality or HF event (HR 0.66, p = 0.001)

CCS = clinical composite score; HF = heart failure; ICD = implantable cardioverter-defibrillator; other abbreviations as in Table 1

REVERSE:

REsynchronization reVErses Remodeling in Systolic left vEntricular

dysfunction (REVERSE) was a randomized, double-blind trial, investigating the effects of CRT in patients with asymptomatic and mildly symptomatic heart failure and a prolonged QRS interval.[12] The study hypothesized that CRT might delay disease progression in heart failure patients with less severe symptoms by inducing LV reverse remodeling. Eligible patients were in NYHA functional class I or II for at least 3 months before enrollment. Patients were required to be in sinus rhythm with a QRS duration ≥120 ms, to have LVEF ≤40%, and an LV end-diastolic diameter (LVEDD) ≥55 mm (Table 2).

The primary end-point of the study was the heart failure clinical composite response.[29] Main secondary end-point was the absolute change in left ventricular end-systolic volume index (LVESVi) between baseline and 12 months follow-up. A total of 610 patients were included between September 2004 and September 2006. After enrollment, 419 were randomized to CRT-ON and 191 randomized to CRT-OFF. In the CRT-ON group, 16% worsened in their heart failure clinical composite response at 1 year, as compared with 21% of patients in the CRT-OFF group (p = 0.10, Figure 2). The LVESVi decreased significantly in the CRT-ON group (-18.4±29.5 ml/m2), while no change in LVESVi (-1.3±23.4 ml/m2) was observed in the CRT-OFF group (p<0.0001). This decrease in LVESVi was even more evident in patients with a QRS duration ≥152 ms as compared to patients with a QRS duration <152 ms. Also, a significant increase in LVEF was observed in the CRT-ON group (+3.8%), whereas no significant change (+0.6%) was noted in the CRT-OFF group (p<0.0001). Finally, CRT reduced the risk of heart failure hospitalization (hazard ratio [HR] 0.46, p = 0.03). Although REVERSE failed to show a difference in the primary end-point, the results indicate that CRT can reverse LV remodeling and reduce the risk for heart failure hospitalization in mildly symptomatic heart failure patients (NYHA functional class I and II), hereby delaying disease progression in these patients.

Recently, Daubert et al. reported the results from the 24-month follow-up of the European cohort of REVERSE.[33] In this sub-group, the 262 European patients in REVERSE were followed for 24 months (in contrast to the 12-month follow-up in the main trial). Over this 24-month follow-up period, CRT resulted in less clinical worsening and an improvement in LV function. There was a significant reduction in the clinical composite end-point in the CRT group (19% worsened in the CRT-ON group as compared to 34% of patients in the CRT-OFF group, p = 0.01). In addition, LVESVi decreased significantly in the CRT-ON group (decrease of 27.5±31.8 ml/m2 in the CRT-ON group vs. 2.7±25.8 ml/m2 in the CRT-OFF group, p<0.0001). Finally, a significant reduction in time to first heart failure hospitalization or death was observed in the

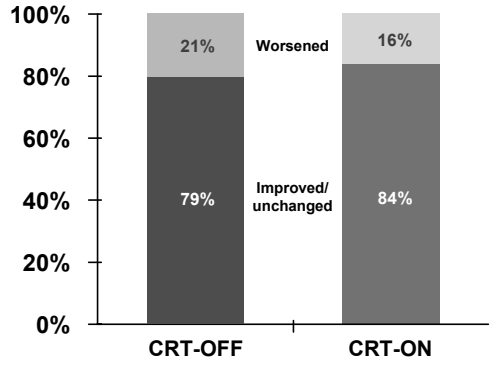


Figure 2. The heart failure clinical composite score response (primary end-point) in REVERSE. Comparison of proportion of worsened patients at 12 months, p = 0.10. Adapted with permission from Linde et al. *J Am Coll Cardiol* 2009;52:1834-43.

CRT-ON group (HR 0.38, p = 0.003, Figure 3). These results provide further evidence that CRT might be useful in delaying heart failure worsening.

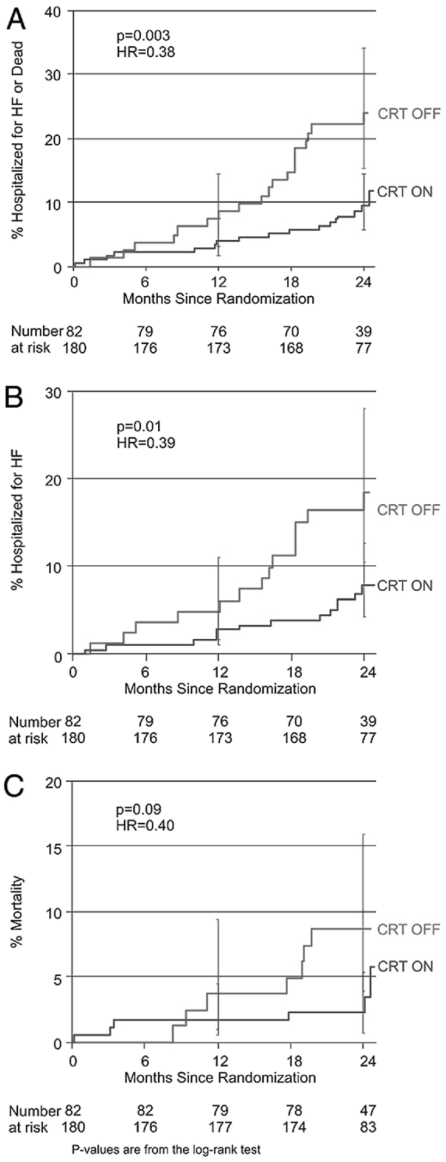


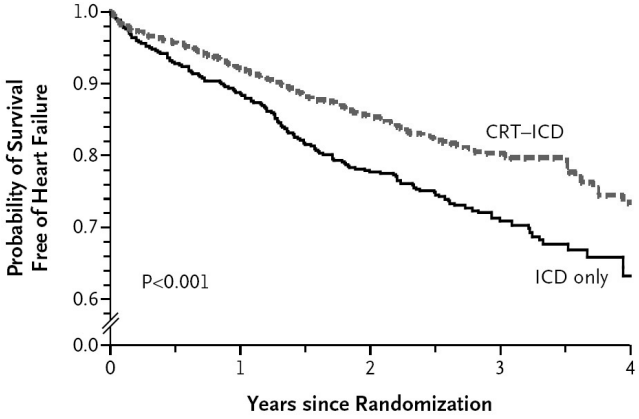
Figure 3. Long-term follow-up in the European REVERSE patients. Time to first hospitalization for heart failure or death from any cause (Panel A), time to first hospitalization for heart failure (Panel B), and time to death from any cause (Panel C).
Adapted with permission from Daubert et al. *J Am Coll Cardiol* 2009;54:1837-46.

MADIT-CRT:

The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) enrolled 1820 patients between December 2004 and April 2008.[13] It was designed to determine whether CRT with defibrillator (CRT-D) would reduce the risk of mortality and heart failure events as compared to ICD-only, in subjects with NYHA I-II heart failure, LVEF ≤30% and QRS duration ≥130 ms. Other end-points included: changes in LVESV at 1-year follow-up, changes in LV end-diastolic volume (LVEDV) at 1-year follow-up, and subject-specific rates of multiple heart failure events.

During follow-up, 187 of 1089 patients (17.2%) in the CRT-D group reached the primary end-point, as compared to 185 of 731 patients (25.3%) in the ICD-only group (HR 0.66, 95% confidence interval [CI] 0.52-0.84, p = 0.001, Figure 4). This superiority of CRT-D over ICD-only was driven by a 41% reduction in the risk of heart failure events. There was no difference in mortality between the groups, with a 3% annual mortality in both groups. Interestingly, the beneficial effect of CRT on the primary end-point was greater in patients with a QRS duration ≥150 ms than in patients with a QRS duration <150 ms (HR 0.48, 95% CI 0.37-0.64 vs. HR 1.06, 95% CI 0.74-1.52; p = 0.001 for interaction). In addition to these findings, a reduction of 52 ml in LVEDV was observed at 1-year follow-up in the CRT-D group, compared to a 15 ml reduction in the ICD-only group, p<0.001 (Figure 5). Finally, a reduction of 57 ml in LVESV was observed in the CRT-D group, as compared to 18 ml in the ICD-only group, p<0.001 (Figure 5). The results of MADIT-CRT provide evidence that preventive therapy with CRT-D in heart failure patients with minimal heart failure symptoms, but a wide QRS complex and a low LVEF, decreases the risk of heart failure events.

Currently, there is another large trial ongoing in patients with mild heart failure symptoms. The Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT) will include 1800 subjects in NYHA class II, LVEF ≤30% and QRS duration ≥120 ms.[34] Patients are then randomized to receive either ICD or CRT-D in a 1:1 fashion. The primary end-point is a composite of total mortality and heart failure hospitalization during long-term follow-up. The results of this large randomized trial are eagerly awaited.



No. at Risk (Probability of Survival)

ICD only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT–ICD	1089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

Figure 4. Long-term follow-up in MADIT-CRT. There was a significant difference in survival free of heart failure between the group that received cardiac-resynchronization therapy plus an implantable cardioverter–defibrillator (CRT–ICD) and the group that received an ICD only (unadjusted $p < 0.001$ by the log-rank test).
Adapted with permission from Moss et al. *N Engl J Med* 2009;361:1329-38.

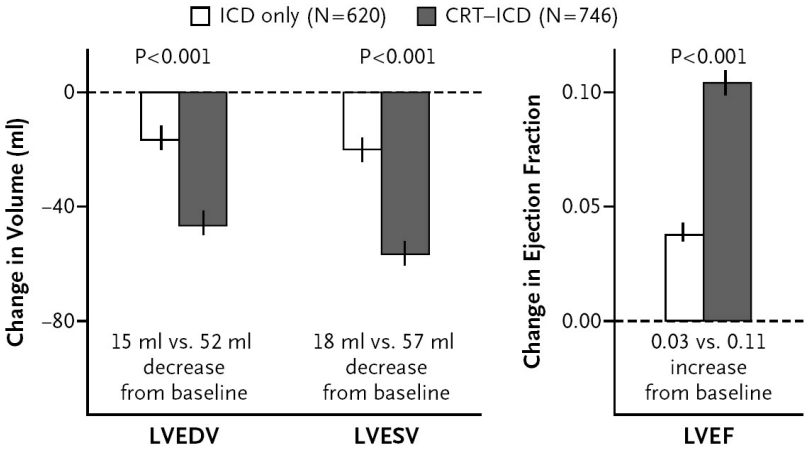


Figure 5. Changes in mean echocardiographic left ventricular volumes and ejection fraction between baseline and 1-year follow-up in MADIT-CRT. There were significant differences in changes in LV volumes and LVEF between the 746 patients who received cardiac-resynchronization therapy plus an implantable cardioverter–defibrillator (CRT–ICD) and the 620 patients who received an ICD only.
Adapted with permission from Moss et al. *N Engl J Med* 2009;361:1329-38.

FUTURE PERSPECTIVE

The future of CRT might be heading towards 2 separate directions; 1) to improve the responder rate in patients undergoing CRT according to current guidelines, and 2) to expand treatment to patient groups that might also benefit from CRT.

Improving response rate

In order to optimize CRT response rate, numerous studies have focused on identifying possible responders before implantation by means of echocardiography. A recent sub-analysis of the PROSPECT trial revealed that patients with more extensive LV dyssynchrony had more pronounced reduction in LVESV at 6 months follow-up.[35] This finding emphasizes the relation between pre-implantation LV dyssynchrony and outcome after CRT. Conversely, it remains currently unclear which measure of dyssynchrony should be used, and which cut-off value for dyssynchrony should be considered to select patients for CRT implantation. In addition to the use of echocardiographic measurements to predict response to CRT, a more recent study identified several ECG patterns as potential determinants of CRT response.[36] In particular, longer LV activation times, lower QRS scar score and evidence of wavefront fusion after CRT initiation, as measured from the surface ECG, were potent markers of significant LV reverse remodeling at 6 months follow-up. Using an algorithm based on these specific ECG parameters may also further optimize patient selection for CRT.

Furthermore, the extent and location of myocardial scar and the presence of a suitable venous anatomy to place the LV pacing lead at the latest activated area of the left ventricle are crucial determinants of a favorable response to CRT.[37] Therefore, an integrated approach evaluating LV dyssynchrony, total myocardial scar burden and cardiac venous anatomy may refine the selection of potential responders to CRT. Currently, magnetic resonance imaging, nuclear imaging and multi-detector row computed tomography constitute valuable imaging techniques to evaluate all these parameters.[37]

Finally, the LV pacing lead location may be of importance. Several studies have indicated that positioning the LV lead outside the region of latest activation may reduce the response rate after CRT.[38, 39] In addition, (transmural) scar at the location of the LV pacing lead may also result in non-response after CRT, making scar assessment of significant importance in ischemic heart failure patients before device implantation.[40] Taking all this into consideration, an integrated approach on these factors may improve response to CRT, rather than relying on any single measure (Figure 6).[41]

After CRT device implantation, cardiac imaging plays a central role in the evaluation of response to CRT. Among several parameters proposed to define response to CRT, reduction in LVESV ≥15% has demonstrated to be independently related to improved long-term clinical

outcome.[30, 42] Accordingly, current single-center and multi-center trials include this end-point as definition of response to CRT. Echocardiography is the most frequently used imaging technique to evaluate changes in LV volumes. However, the use of 3-dimensional imaging modalities such as real-time 3-dimensional echocardiography or magnetic resonance imaging may provide a more accurate estimation of LV volumes and ejection fraction.[43] Particularly the development of CRT devices compatible with magnetic resonance systems is important, so that LV volumes can be assessed with this modality after CRT implantation.[44] Finally, a multidisciplinary evaluation of heart failure patients treated with CRT including further adjustments of the device settings and medical treatment may improve the response rate to CRT as recently demonstrated by Mullens et al.[45]

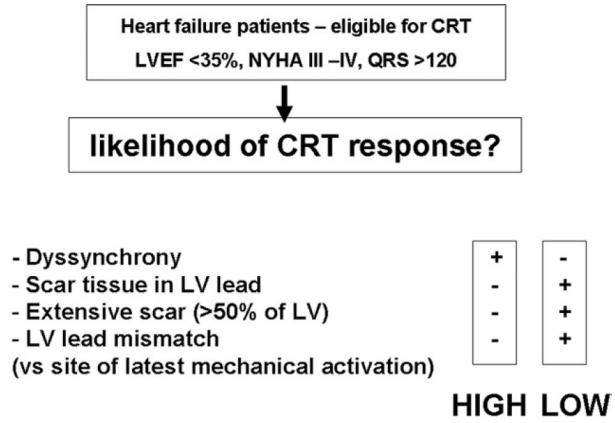


Figure 6. Algorithm to help determine whether the patient has a high or low likelihood of response to CRT.
Integrating information on various factors for prediction of response to CRT may improve response rates. Important issues are: LV dyssynchrony, scar tissue in the region where the LV pacing lead is positioned, the total extent of scar in the LV, and whether the LV lead is positioned in the site of latest mechanical activation.
Adapted with permission from Bax et al. *J Am Coll Cardiol* 2009;53:1933-43.

Expanding treatment to other patient groups, outside current guidelines

Perhaps the most important issue raised by the results of these recent large trials is whether the current indications for CRT should be expanded. The performance of current inclusion criteria for CRT implantation may be suboptimal as they may exclude some groups of patients who may benefit from CRT. Indeed, definitions of heart failure are imprecise and the majority includes typical symptoms and objective evidence of LV dysfunction. Currently, only heart failure patients in NYHA functional class III-IV and LVEF ≤35% are considered candidates for CRT implantation. However, these inclusion criteria exclude patients in NYHA functional class I-II who may benefit from CRT by preventing progression of the disease, as recently observed in the MADIT-CRT and REVERSE trials.[12, 13]

Both trials have demonstrated the effect of CRT to improve LV function and prevent heart failure progression in mildly symptomatic heart failure patients[12, 13], and expansion of guidelines for CRT selection may be considered. Perhaps attenuation of disease progression, rather than reversing severe heart failure will prove to be a successful new treatment strategy in heart failure patients in the future, although more data on survival benefit in these patients may be needed before definitive conclusions can be drawn.

Conversely, the results from ESTEEM-CRT and RethinQ[11, 20] make the expansion of CRT to heart failure patients with a narrow QRS complex currently unlikely. However, the results of the ongoing EchoCRT trial will determine whether CRT is an effective treatment option in this specific group of patients.[25] The last mentioned trial will be the first to use the newly proposed speckle-tracking echocardiographic technique for evaluation of LV mechanical dyssynchrony. This novel methodology permits the assessment of active myocardial deformation and provides accurate information on LV dyssynchrony and permits identification of the area of latest mechanical activation. This more robust method of dyssynchrony assessment may improve selection of suitable candidates for CRT.

Finally, there are a few other cardiac conditions where CRT indication is still controversial. It has been suggested that atrial fibrillation may convey a lower response rate to CRT.[46, 47] A recent meta-analysis including 1146 heart failure patients compared the clinical and echocardiographic response to CRT in patients with sinus rhythm (n = 797) or atrial fibrillation (n = 367).[48] Both patient groups showed significant improvement in NYHA functional class, LVEF and long-term survival after CRT; the need for atrioventricular junction ablation in atrial fibrillation is still not entirely clear.[46, 47, 49]

Other clinical conditions such as upgrading from right ventricular pacing, right-sided heart failure and congenital heart disease, have also demonstrated clinical benefit from CRT.[50-52] Patients with drug-refractory heart failure but preserved LVEF (>35%) and impaired LV filling may also benefit from CRT.[53] However, more data are needed in these subpopulations.

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