REVIEW

Cardiac Resynchronization Therapy: Who Benefits?

Jason S. Chinitz, MD, Andre d'Avila, MD, PhD, Martin Goldman, MD, Vivek Reddy, MD, and Srinivas Dukkipati, MD

ABSTRACT

Background: Cardiac resynchronization therapy (CRT) has been well established in multiple large trials to improve symptoms, hospitalizations, reverse remodeling, and mortality in well-selected patients with heart failure when used in addition to optimal medical therapy. Updated consensus guidelines outline patients in whom such therapy is most likely to result in substantial benefit. However, pooled data have demonstrated that only approximately 70% of patients who qualify for CRT based on current indications actually respond favorably. In addition, current guidelines are based on outcomes from the carefully selected patients enrolled in clinical trials, and almost certainly fail to include all patients who might benefit from CRT.

Findings: The identification of patients most likely to benefit from CRT requires consideration of factors beyond these standard criteria, QRS morphology with particular consideration in patients with left bundle-branch block pattern, extent of QRS prolongation, etiology of cardiomyopathy, rhythm, and whether the patient requires or will eventually need antibradycardia pacing. In addition, the baseline severity of functional impairment may influence the type of benefit to be expected from CRT; for example, New York Heart Association class I patients may derive long-term benefit in cardiac structure and function, but no benefit in symptoms or hospitalizations can be reasonably expected. In contrast, certain New York Heart Association class IV patients may be too sick to realize long-term mortality benefits from CRT, but improvements in hemodynamic profile and functional capacity may represent vital advances in this population.

Conclusion: This review evaluates the evidence regarding the various factors that can predict positive or even detrimental responses to CRT, to help better determine who benefits most from this evolving therapy.

Key Words: biventricular pacing, cardiac resynchronization therapy, cardiomyopathy, dyssynchrony, heart failure, implantable cardioverter defibrillator

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INTRODUCTION

Cardiac resynchronization therapy (CRT) is an effective therapy to correct impaired ventricular electromechanical coupling, or dyssynchrony. In many, but not all, patients with heart failure (HF), it can produce benefitial hemodynamic effects and improved outcomes. Identification of the subset of patients most likely to respond favorably to CRT is the primary clinical challenge. Several large clinical trials have established the efficacy of CRT to improve peak oxygen consumption (VO_2), 6-minute walking distance (6MWD), quality of life (QoL) scores, left ventricular (LV) size and function, mitral regurgitation severity, and functional capacity in most HF patients with New York Heart Association (NYHA) class III to IV symptoms, severely impaired LV function, sinus rhythm, and significant QRS prolongation. The Comparison of Medical Therapy, Pacing, and Defibrillation on Heart Failure (COMPANION)[1] and the Cardiac Resynchronization-Heart Failure (CARE-HF)[2] trials subsequently established significant improvements in hospitalizations for HF and mortality from CRT, either alone (CRT-P) or in combination (CRT-D) with an implantable cardioverter defibrillator (ICD), in these selected patients. This overall benefit is similar to the efficacy reported for angiotensin-converting enzyme inhibitor[3] or β-blocker treatment[4] in patients with HF, and is additive to this medical therapy.

Professional societies in the United States and Europe have adopted strong recommendations in support of CRT. Both the 2008 American College of

From the Mount Sinai School of Medicine, New York, NY. Received March 7, 2013; final revision received March 12, 2014. Address correspondence to J.S.C.; e-mail: jason.chinitz@mountsinai.org

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Cardiology Foundation/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS) Guidelines for Device-based Therapy,[5] and the 2010 European Society of Cardiology (ESC) Guidelines on Device Therapy in Heart Failure,[6] gave CRT a class I indication for NYHA class III and ambulatory class IV patients in sinus rhythm, with LV ejection fraction (LVEF) ≤35% and QRS duration >120 ms. In 2012, the ACCF/AHA/HRS released a focused update modifying the class I indication for CRT only to patients with NYHA class II, III, and ambulatory class IV symptoms with left bundle-branch block (LBBB) and QRS duration ≥150 ms (Table 1).[7] However, pooled data have demonstrated that only approximately 70% of patients who qualify for CRT based on current indications actually respond favorably.[8] In addition, current guidelines are based on outcomes from the carefully selected patients enrolled in clinical trials and almost certainly fail to include all patients who might benefit from CRT. Important questions remain, such as whether less symptomatic patients respond to CRT, how QRS morphology or extent of QRS delay affects response, and the effect of tachy- and brady-arrhythmias on CRT efficacy. More recently, the effect of CRT has been evaluated in more diverse populations of patients with HF to help better appreciate the various factors that can predict positive or even detrimental responses to CRT beyond currently accepted criteria and to help better determine who benefits from this evolving therapy.

ROLE OF CRT ACCORDING TO NYHA FUNCTIONAL CLASS

NYHA Class IV Heart Failure

Although the benefit of CRT in patients with HF who have advanced symptoms has been established in multiple studies, only small numbers of patients in these trials have been classified as NYHA class IV. These highly symptomatic patients generally have limited myocardial reserve and poor survival, and thus it has been suggested that they may not realize the time-dependent benefits of CRT on cardiac function, or they may be destabilized by the implant procedure resulting in worse short-term outcomes. The COMPANION trial included 217 NYHA class IV patients (14% of the total population, mean LVEF 21%), all of whom were considered "ambulatory" in that they had no hospital admissions or vasoactive therapy in excess of 4 hours in the month before enrollment.[1] A post hoc analysis of this subset of patients revealed a significant improvement compared with that from optimal medical therapy (OMT) in time to all-cause mortality or hospitalization for both CRT-P (hazard ratio [HR], 0.64; $P = 0.02$) and CRT-D (HR, 0.62; $P = 0.01$), an improvement in QoL ($P < 0.01$), as well as a significant functional improvement (NYHA class improved in 78% in the CRT group compared with 52% in OMT; $P < 0.01$). However, only a nonsignificant trend toward benefit in all-cause mortality alone was demonstrated (HR, 0.67; $P = 0.11$ for CRT-P; HR, 0.63; $P = 0.06$ for CRT-D),[9] although no NYHA class IV patients died during the implantation hospitalization.

CRT also may provide meaningful functional and hemodynamic benefits in the sickest class IV HF patients as well. In one small cohort of 10 patients with inotrope-dependent class IV HF who successfully underwent CRT implantation, NYHA functional class improved in 9 of 10 patients, intravenous inotropes were discontinued in 9 patients 15 ± 14 days after CRT implant, mean LV end systolic volume (LVESV) decreased (from 174 to 150 mL; $P < 0.01$), and mean LVEF increased (from 23% to 32%; $P < 0.05$).[10] Another recent small study evaluated the use of temporary LV pacing for patients in acute refractory cardiogenic shock and evidence of LV dyssynchrony and found acute hemodynamic improvements in 67%, with an impressive (but statistically insignificant) reduction in in-hospital mortality (30% vs 80%; $P = 0.119$) in these "responders."[11] The 2012 ACCF/AHA/HRS guidelines include ambulatory class IV patients in the class I recommendation for CRT but note that data are few in these patients and comment that the sickest patients, who are dependent on inotropic therapy, have refractory fluid retention, or have progressive renal dysfunction, are at highest risk for complications from implantation and early mortality, and also are unlikely to benefit significantly from concomitant defibrillator therapy.[7] The 2010 ESC guidelines also support CRT in ambulatory class IV patients, but recognize that the use of CRT in these patients is supported to improve morbidity, but not mortality.[6]

CRT in NYHA Class I and II Heart Failure

Recent studies have established a role for CRT in patients with less symptomatic HF. To our knowledge, the Resynchronization Reverses Remodelling in Systolic Left Ventricular Dysfunction (REVERSE) study[12] was the first to evaluate this hypothesis and included 610 patients with NYHA class I (18%, all previously symptomatic) and NYHA class II (82%) HF symptoms. It concluded that in these mildly symptomatic patients, CRT improves LV remodeling and reduces HF hospitalizations, but does not significantly improve symptoms or exercise capacity in these patients with little functional impairment at baseline.[12] The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT)[13] expanded on the REVERSE findings and compared CRT-D with ICD alone in 1820 patients with NYHA class I and II symptoms, LVEF ≤30%, and QRS interval ≥130 ms. The executive committee stopped the trial early after a mean follow-up of 2.4 years as the primary endpoint (death from any cause or nonfatal HF event) was significantly improved by CRT-D (17.2% vs 25.3%; $P = 0.001$). This benefit of CRT in these class I

Table 1. Comparison Between Updated US[7] and European (ESC)[6] Guidelines for Cardiac Resynchronization Therapy

Indication	2012 ACCF/AHA/HRS Guidelines	2010 ESC Guidelines
Symptomatic heart failure	CRT indicated for patients with NYHA class II/III/ambulatory IV symptoms, LVEF ≤35%, LBBB, QRS duration ≥150 ms, sinus rhythm (class I recommendation; class IIa if QRS duration 120-149 ms)	CRT indicated for patients with NYHA class III/ambulatory IV symptoms, LVEF ≤35%, QRS duration ≥120 ms, sinus rhythm (class I recommendation)
Minimally symptomatic heart failure	CRT may be considered for patients with NYHA class I symptoms, LVEF ≤30%, ischemic etiology, LBBB with QRS duration ≥150 ms, and sinus rhythm (class IIb recommendation)	CRT indicated for patients with NYHA class II symptoms, LVEF ≤35%, QRS duration ≥150 ms, sinus rhythm (class I recommendation)
Non-LBBB morphology	CRT may be used for patients with NYHA class III/ambulatory IV symptoms, LVEF ≤35%, non-LBBB morphology, QRS duration ≥150 ms, sinus rhythm (class IIa recommendation; class IIb if QRS 120-149 ms or NYHA class II symptoms with QRS duration ≥150 ms; class III if NYHA class I or II and QRS duration <150 ms)	No differentiation based on QRS morphology
Atrial fibrillation and heart failure	CRT may be used for patients with atrial fibrillation and LVEF ≤35%, if the patient requires ventricular pacing or otherwise meets CRT criteria and undergoes atrioventricular node ablation or pharmacological rate control to allow near 100% ventricular pacing (class IIa)	CRT may be used for patients with atrial fibrillation, NYHA class III/IV symptoms, LVEF ≤35%, QRS duration ≥130 ms, and slow ventricular rates or pacemaker dependency induced by ateriovenous nodal ablation (class IIa)
Concomitant pacemaker indication	CRT may be used for patients with LVEF ≤35% who are undergoing new or replacement device implantation with anticipated requirement for significant (>40%) ventricular pacing (class IIa)	CRT indicated for patients with NYHA class III/IV symptoms, LVEF ≤35% (class I if QRS ≥120 ms; class IIa if QRS <120 ms; class IIb if NYHA class II symptoms and QRS duration <120 ms)

ACCF/AHA/HRS, American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society; CRT, cardiac resynchronization therapy; ESC, European Society of Cardiology; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

and II patients was driven by a 41% reduction in HF events; mortality was similar between the 2 groups at about 3% per year. Extended follow-up data revealed a similar reduction in subsequent HF events as well after the initial HF event in patients receiving CRT (relative risk reduction, 38%; $P = 0.003$).[14]

A mortality benefit from CRT in patients with less symptomatic HF was finally established in the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) study.[15] After a mean follow-up of 40 months, in 1798 patients (80% NYHA class II, 20% class III), the primary outcome—death or hospitalizations for HF—was significantly reduced among recipients of CRT-D compared with those with an ICD alone (33.2% vs 40.3%; $P < 0.001$), as were the secondary outcomes of death from any cause (20.8% vs 26.1%; $P = 0.003$), and hospitalizations for HF (26.1% vs 19.5%; $P < 0.001$). Subgroup analysis showed similar reductions in primary and secondary endpoints for both NYHA class II and III patients and patients with ischemic or nonischemic cardiomyopathy, whereas the benefit of CRT-D versus an ICD was significantly more pronounced among patients with a very prolonged QRS interval ≥150 msec and patients with LBBB.[15] In addition to establishing a mortality benefit for mildly symptomatic (NYHA class II) patients, this was the first trial to show that CRT provides a survival benefit beyond that provided by OMT and an ICD in patients with established indications for an ICD and a wide QRS complex, a finding that was at least in part attributable to longer follow-up than that obtained in previous studies.

In the asymptomatic NYHA class I patients, the populations enrolled in trials have thus far been too small to draw substantial conclusions. Only 15% of patients in MADIT-CRT were class I, and in these patients CRT did not significantly reduce the combined endpoint of mortality and HF events.[13] In REVERSE, among the 18% NYHA class I patients included in the trial (n = 90), there was a significant decrease in the LVESV index at 12 months similar to that seen among NYHA class II patients.[12] However, in the European REVERSE substudy, the NYHA class I patients (n = 44) showed a trend toward worsened HF clinical composite response.[16] There are no mortality data to support CRT in class I patients; however, if reverse remodeling is used as an outcome, the response rate appears to be essentially independent of NYHA functional class as long as the QRS interval is >120 ms (Fig. 1), providing some rational for early intervention.[8]

In summary, the data in patients with less symptomatic HF support a benefit from CRT, with improved mortality evident in selected NYHA class II patients. A mortality benefit from CRT in NYHA class I patients

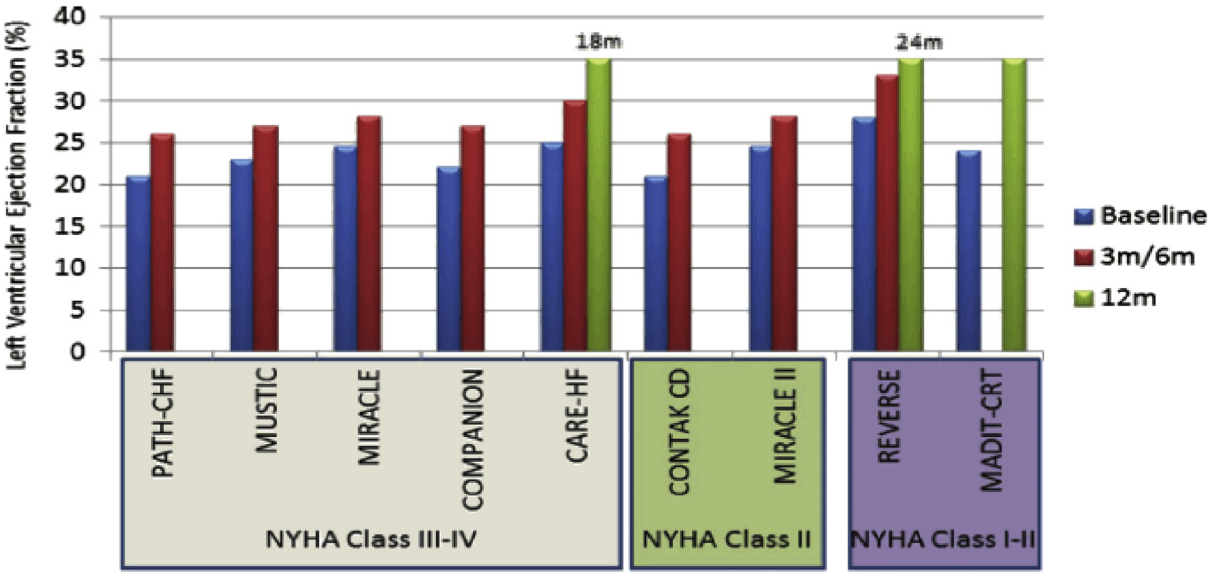

Figure 1. Left ventricular ejection fraction response to cardiac resynchronization therapy, stratified by NYHA functional class.[8] Reproduced with permission from the Japanese Circulation Society.

has not been demonstrated; however, evaluating this outcome requires longer follow-up and larger study populations because of the lower baseline mortality rate in this population. A meta-analysis of CRT trials that evaluated mortality reported significantly reduced mortality for CRT-D over ICD alone for NYHA class I and II patients (relative risk [RR], 0.80; 95% confidence interval [CI], 0.67-0.96), but not for patients in NYHA functional class III and IV (RR, 0.86; 95% CI, 0.69-1.07).[17] Interestingly, a recent post hoc analysis of MADIT-CRT demonstrated greater response to CRT (with regard to a reduction in LV end diastolic volume [LVEDV]) in patients with higher LVEFs, suggesting that the healthiest HF patients may in fact benefit the most, contrary to traditional understanding.[18] In addition to the class I indication in both the updated 2012 ACCF/AHA/HRS and 2010 ESC guidelines for patients with NYHA class II symptoms, LVEF $\leq$35%, sinus rhythm, and QRS duration $\geq$150 ms,[6,7] the US guidelines state that CRT may be considered for patients with NYHA class I symptoms with LVEF $\leq$30%, ischemic etiology of heart failure, sinus rhythm, and LBBB with QRS interval $\geq$150 ms (reflecting the population studied in MADIT-CRT). However, CRT is not recommended for patients with NYHA class I or II symptoms and non-LBBB pattern with QRS duration <150 ms (Table 1).[7]

IMPORTANCE OF QRS DURATION

Data from most CRT trials have consistently demonstrated increased benefit from CRT in patients with very prolonged QRS duration. The Pacing Therapies in Congestive Heart Failure (PATH-CHF) II study prospectively compared the benefit of CRT in patients with QRS duration between 120 and 150 ms and those with QRS duration >150 ms; it identified an improvement in VO_2, 6MWD, and QoL only in patients with QRS duration >150 ms. Only 38% of patients with QRS duration <150 ms had increased peak VO_2 by more than 1 mL/min/kg.[19] In the COMPANION trial, among patients with progressively increasing QRS intervals, there was an incrementally greater benefit among patients receiving CRT for the combined endpoint of death or hospitalization for any cause.[1] In a large registry of Medicare patients who received CRT-D with an average follow-up of 40 months, baseline QRS duration >150 ms was associated with improved short- and long-term survival compared with patients with QRS duration between 120 and 149 ms (HR, 0.77 at 1 year; HR, 0.86 at 3 years; $P < 0.001$).[20] Similarly, very prolonged QRS duration also has proved to be an important factor in the less symptomatic HF population in RAFT[15] and REVERSE.[12] The updated US guidelines therefore stratify patients by the extent of QRS prolongation, extending the strongest recommendation in support of CRT only for otherwise qualifying patients with LBBB and QRS duration $\geq$150 ms; patients with LBBB and QRS duration between 120 and 149 ms or highly symptomatic patients with non-LBBB pattern and QRS duration $\geq$150 ms are given a class IIa recommendation (Table 1).[7]

Research is ongoing to evaluate a potential role for CRT in patients with normal QRS duration who have evidence of dyssynchrony on echocardiography (20%-50% of patients with HF and narrow QRS complexes).[21] The effect of CRT among patients without dramatic QRS prolongation (<130 ms) was assessed in 172 patients in the prospective RethinQ Study, which found an improvement in VO_2 after 6 months of CRT only in patients with QRS duration >120 ms, but not in patients with QRS duration <120 ms, despite evidence of

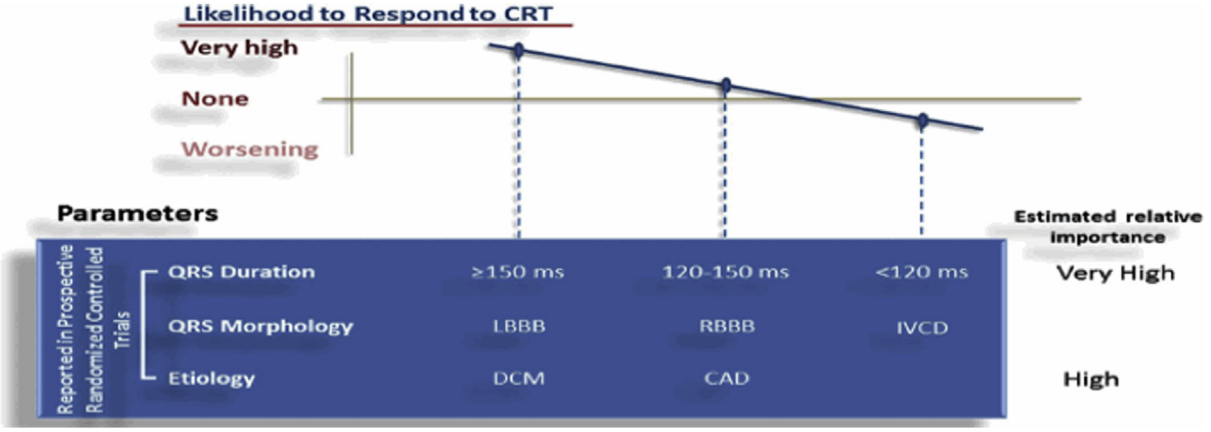

Figure 2. Relative response to cardiac resynchronization therapy is influenced by QRS morphology, QRS duration, and etiology of heart failure.[8] Reproduced with permission from the Japanese Circulation Society.

dyssynchrony on echocardiography in all individuals. Among all patients with QRS duration <130 ms, there was a significant reduction in NYHA functional class with CRT, but no change in QoL, 6MWD, or LV size and function.[22] Furthermore, in the Predictors of Response to CRT (PROSPECT) study, among 426 patients with QRS duration ≥130 ms, no echocardiograhic measure of dyssynchrony, among 12 parameters studied, could effectively predict in any clinically useful way composite clinical response or improvement in LV size at 6 months better than baseline QRS prolongation.[23] At this point, there are no convincing data to suggest a benefit of CRT in patients with narrow native QRS complexes (<120 ms), regardless of echocardiographic dyssynchrony. QRS prolongation remains the sole indicator of dyssyncrony used in the guidelines to select patients for CRT.

MORPHOLOGY MATTERS

In patients with LBBB QRS morphology, LV activation between the septum and LV free wall is significantly delayed; it may be corrected with CRT, in which pacing of the septum and the LV free wall may resynchronize mechanical contraction. However, in right bundle-branch block (RBBB) or LV hypertrophy with associated QRS prolongation, the LV endocardium is activated normally via the purkinje system and thus may not benefit from LV pacing.[24] Interestingly, however, a study of activation mapping in patients with HF showed that those with RBBB may have an LV endocardial activation delay similar to those with LBBB, suggesting that in patients with HF, RBBB often represents "concealed LBBB," thus providing a rational for potential benefit from CRT in these patients.[25]

However, several large trials have been more consistent in demonstrating a greater benefit from CRT in patients with LBBB, and a lack of benefit (and even potential for harm) in other patients with non-LBBB QRS prolongation. In the COMPANION trial, patients without LBBB did not have a statistically significant benefit from CRT in terms of reduction of hospitalizations or mortality.[1] In a subanalysis of the Cardiac Resynchronization in Heart Failure (CARE-HF) study, although only 5% of patients had RBBB, by multivariable analysis RBBB was a predictor of increased all-cause mortality and unplanned hospitalization for HF (HR, 2.74; $P < 0.0001$).[26] Similarly, in the 14,946 patient Medicare registry, evaluating real-world long-term outcomes after CRT-D implantation, RBBB was associated with higher short- and long-term mortality, even after adjusting for covariates, compared with patients with baseline LBBB (HR 1.44, at 1 year; HR, 1.37 at 3 years; $P < 0.001$). In this registry, patients with nonspecific intraventricular conduction delay had intermediate outcomes, and QRS duration did not have any significant effect on outcomes in the setting of RBBB.[20] Similarly, in less symptomatic patients in the RAFT trial, a reduction in the primary endpoint of death or HF hospitalization was demonstrated for patients with LBBB, but not patients with RBBB, nonspecific intraventricular conduction delay, or paced rhythm ($P = 0.046$ for interaction).[15] Accordingly, LBBB morphology should be considered, along with QRS duration, as the most important criterion in predicting CRT benefit (Fig. 2). As noted, updated consensus guidelines now indicate a class I indication only for patients with very wide LBBBs and lesser recommendations for patients with non-LBBB morphology (class IIa if QRS duration is ≥150 ms and NYHA III/ambulatory IV symptoms, and class IIb for QRS 120-149 ms and NYHA III/ambulatory IV symptoms or QRS ≥150 ms and NYHA II symptoms [Table 1]).

CRT IN PATIENTS WITH ATRIAL FIBRILLATION

As atrial fibrillation (AF) is common in patients with HF and is associated with increased morbidity and mortality,[27] the question of whether CRT may be effective in

these patients has become increasingly relevant. However, the vast majority of patients included in the large trials of CRT were in sinus rhythm, and in most, patients in AF were excluded.[1,2,12,13,19,28-30] In the setting of permanent AF, CRT does not consistently restore atrioventricular dyssynchrony, and the associated rapid and irregular ventricular rates limit regular biventricular (BiV) pacing delivery. Further complicating the matter, outcomes are difficult to measure in patients with AF, as the effects of CRT may be confounded by changes in heart rate control.

The benefit of CRT in patients with AF may be dependent on the frequency of BiV pacing achieved. In 1 large, prospective, observational registry, the effect of CRT was compared between 162 patients with permanent AF and 511 patients in sinus rhythm (LVEF ≤35%, QRS duration ≥120 msec, NYHA class ≥II). After 2 months of CRT, devices were interrogated and revealed that BiV pacing was achieved 98.5% of the time in patients in sinus rhythm, and only 74.6% of the time in patients in AF. Subsequently, patients with AF who had BiV pacing ≤85% of the time underwent prospective atrioventricular nodal ablation; this study found overall sustained improvements in functional capacity and indices of reverse remodeling for patients in sinus rhythm as well as those in AF at a mean follow-up of 25.2 months; however, the benefit from CRT in the setting of AF was seen entirely among the subgroup that underwent atrioventricular nodal ablation. In these patients with AF and atrioventricular nodal ablation, BiV pacing was achieved 98.4% of the time, and the LVEF, LVESV, and functional capacity scores increased to a similar degree as the patients in sinus rhythm. No benefit was seen from CRT in the patients with AF who were treated medically with negative chronotropic therapy and programmed device features, although BiV pacing was eventually achieved 88.2% of the time. The authors concluded that the magnitude of benefit with CRT, in terms of symptoms and LV function, was similar between patients in sinus rhythm and in permanent AF only in those patients undergoing atrioventricular nodal ablation, likely related to the near 100% BiV pacing time achievable only by ablating the atrioventricular node.[31] These findings, as well as the long-term safety of this approach, will need to be established by randomized trials; however, the findings are reflected in both updated US and ESC guidelines: The 2012 ACC/AHA/HRS guidelines support CRT with a class IIa indication for patients with AF and LVEF ≤35% who otherwise meet CRT criteria and have concomitant atrioventricular nodal ablation or pharmacologic rate control that will allow near 100% ventricular pacing with CRT (Table 1).

ETIOLOGY OF HEART FAILURE

Data suggest that the benefit of CRT is more pronounced in HF patients with nonischemic cardiomyopathy. In ischemic heart disease, the infarcted myocardium may be less amenable to active pacing than in other forms of cardiomyopathy, and these patients may therefore be less responsive to CRT. A post hoc analysis of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial demonstrated greater improvements in LVEDV ($P < 0.001$) and LVEF (6.7% increase vs 3.2%; $P < 0.001$) among nonischemic patients compared with patients who had ischemic cardiomyopathy.[32] In the PROSPECT study among more than 400 patients with conventional indications for CRT, there was a greater rate of improvement in composite clinical response (75% vs 64%; $P = 0.01$) and in LVESV (63% vs 50%; $P = 0.03$) among nonischemic patients.[23] In REVERSE, the reduction in LVESV index was 3 times greater among nonischemic patients relative to those with an ischemic etiology.[12] In the European substudy of REVERSE with a 24 month follow-up, the magnitude of CRT-related reduction in the LVESV index was also more than double among patients with nonischemic cardiomyopathy, although the improvements in clinical status and LV function were similar.[16] In the Medicare population, ischemic cardiomyopathy was a predictor of early and late mortality after CRT-D, and the highest mortality was seen in patients with a combination of RBBB and ischemic cardiomyopathy.[20] In contrast, the effect of CRT did not differ with regard to etiology of disease in Cardiac Resynchronization Therapy for the Treatment of Heart Failure in Patients with Intraventricular Conduction Delay and Malignant Ventricular Tachyarrhythmias (CONTAK CD)[33] or MIRACLE ICD,[30] and there was no difference in the mortality benefit from CRT between patients with ischemic or nonischemic cardiomyopathies seen in the COMPANION,[1] CARE-HF,[2] MADIT-CRT,[13] or RAFT trials.[15] Both the 2012 ACC/AHA/HRS guidelines and the 2010 ESC guidelines make no differentiation between ischemic and nonischemic patients with regard to recommendations for CRT,[7] although the US guidelines do qualify the recommendation for patients with NYHA class I symptoms to those with LVEF <30% and an ischemic etiology of HF, reflecting the population studied in MADIT-CRT (Table 1).[7]

CRT IN PATIENTS WITH OTHER INDICATIONS FOR PACING

Chronic RV pacing is now recognized to have detrimental effects on LV systolic function, and may result in increased risk for HF hospitalizations and mortality,[34] particularly among patients with baseline LV dysfunction.[35] The deleterious effects of RV pacing are likely related to the promotion of LV dyssynchrony, similar to the effects of LBBB in patients with HF. In addition, uptitration of β-blockade in patients with HF may result in increased pacemaker dependency, increasing exposure to

pacing-induced dyssynchrony in patients with standard dual-chamber devices. Thus, CRT has the potential to prevent the adverse effects of pacing in HF patients with indications for pacemakers, regardless of baseline QRS duration. In the Pacing to Avoid Cardiac Enlargement (PACE) study, a randomized trial of 177 patients with normal LV function (mean LVEF 62%), normal QRS duration (mean 107 ms), and standard indications for a pacemaker, RV pacing resulted in a reduction in LVEF by 6.7% and an increase in LVESV by 7.1 mL (26%) after 12 months, whereas no change in these parameters was seen in patients receiving CRT.[35]

In patients with pre-existing LV dysfunction, the potential for improved outcomes with CRT over RV pacing is even greater. In the Homburg Biventricular Pacing Evaluation (HOBIPACE) trial, 30 patients with LV dysfunction (LVEF $\leq$40% and LVEDV $\geq$60 mm) and indications for permanent pacing were randomized to RV or BiV pacing; compared with RV pacing, CRT resulted in improvements in all parameters of LV dimension and function, decreased LA diameter, improved NYHA functional class, and improved exercise capacity, although 19 of 30 patients in this study had LBBB at baseline, and thus many may have already had established indications for CRT.[36] In addition, small prospective trials and retrospective series also have demonstrated improvements in LVEF, LV dimensions, and NYHA class in patients with baseline symptomatic LV dysfunction who were upgraded to CRT after long-term RV pacing, regardless of QRS duration or NYHA functional class.[37,38] In contrast, a recent trial of atrial support pacing in addition to CRT did not improve clinical outcomes over atrial tracking alone.[39] The 2012 ACCF/AHA/HRS guidelines state that CRT is reasonable for patients with LVEF $\leq$35% who are undergoing new or replacement device placement with anticipated requirement for significant (>40%) ventricular pacing.[7] The 2010 ESC guidelines similarly recommend CRT in patients with HF and a class I pacemaker indication despite normal QRS duration in the setting of LVEF $\leq$35% and NYHA class III and IV (IIa) or NYHA class II (IIb) symptoms.[6]

CONCLUSION

CRT, with or without ICD capabilities, has been well established in multiple large trials to improve symptoms, hospitalizations, reverse remodeling, and mortality in well-selected patients with HF when used in addition to OMT. Consensus guidelines have identified the patients most likely to benefit from CRT as those with symptomatic HF, LVEF $\leq$35%, and wide QRS duration. However, the identification of patients most likely to benefit from CRT requires a consideration of factors beyond these standard criteria: QRS morphology with particular consideration in patients with LBBB pattern, extent of QRS prolongation, etiology of cardiomyopathy, rhythm, and whether the patient requires or will eventually need anti-bradycardia pacing. Certainly, other factors beyond patient selection also contribute to variable response, such as optimal device programming and position of the LV lead (targeting the basal-to-mid posterior or lateral wall). Furthermore, it remains possible that more refined cardiac imaging technologies, or sophisticated electrophysiologic measurements of dyssynchrony, may eventually help reduce the proportion of nonresponders to CRT.[8] In addition, the baseline severity of functional impairment may influence the type of benefit to be expected from CRT; for example, NYHA class I patients may derive long-term benefit in cardiac structure and function, but no improvement in survival has been shown, and no benefit in symptoms or hospitalizations can be reasonably expected. In contrast, certain NYHA class IV patients may be too sick to realize long-term mortality benefits from CRT, but improvements in functional capacity, and removal of vasoactive medications may represent vital QoL improvements in this population. Although a complete understanding of the spectrum of patients who benefit from CRT is still lacking, it is clear that there is a role for CRT in improving lives and longevity for a significant proportion of HF patients.

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