Cigna Medical Coverage Policy

Subject **Biventricular Pacing/Cardiac Resynchronization Therapy (CRT)**

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Coverage Policy

Cigna covers the use of a biventricular pacemaker alone or in combination with an implantable cardioverter defibrillator for cardiac resynchronization therapy (CRT) as medically necessary for ANY of the following indications when the individual has been on an optimal pharmacologic regimen before consideration of implantation:

- **Ischemic cardiomyopathy**, **left ventricular ejection fraction (LVEF) ≤ 30%, no prior implant, sinus rhythm (SR) for ANY of the following:**
  - QRS 120-149 milliseconds (ms), left bundle branch block (LBBB), New York Heart Association (NYHA) Class I, II, III-IV
  - QRS ≥ 150 ms, LBBB, NYHA Class I, II, III-IV
  - QRS 120-149 ms, non-LBBB, NYHA Class III-IV
  - QRS ≥ 150 ms, non-LBBB, NYHA Class II, III-IV
- **Ischemic cardiomyopathy**, **LVEF 31-35%, no prior implant, SR for ANY of the following:**
  - QRS 120-149 ms, LBBB, NYHA Class I, II, III-IV
  - QRS ≥ 150 ms, LBBB, NYHA Class II,I, III-IV
  - QRS 120-149 ms, non-LBBB, NYHA Class III-IV
  - QRS ≥ 150 ms, non-LBBB, NYHA Class II, III-IV
- **Nonischemic cardiomyopathy, LVEF ≤ 30%, no prior implant, SR for ANY of the following:**

- QRS 120-149 ms, LBBB, NYHA Class II,III-IV
- QRS ≥ 150 ms, LBBB, NYHA Class I, II, III-IV
- QRS 120-149 ms, non-LBBB, NYHA Class III-IV
- QRS ≥ 150 ms, non-LBBB, NYHA Class I, II, III-IV

- **Nonischemic cardiomyopathy, LVEF 31-35%, no prior implant, SR for ANY of the following:**

  - QRS 120-149 ms, LBBB, NYHA Class I, II, III-IV
  - QRS ≥ 150 ms, LBBB, NYHA Class I, II, III-IV
  - QRS 120-149 ms, non-LBBB, NYHA Class III-IV
  - QRS ≥ 150 ms, non-LBBB, NYHA Class I, II, III-IV

- **LVEF > 35% of any etiology (ICD Indicated), no prior implant, SR, QRS ≥ 150 ms, LBBB, NYHA Class III-IV.**

- **LVEF ≤ 35% of any etiology (NYHA Class IV on Intravenous Inotropic Support), no prior implant for ANY of the following:**

  - QRS 120-149 ms, LBBB
  - QRS ≥ 150 ms, LBBB or non-LBBB.

- **Pre-Existing or anticipated right ventricular (RV) pacing with a clinical indication for ICD or pacemaker implantation, intrinsic narrow QRS, LVEF ≤ 35% when RV pacing anticipated is > 40%, NYHA Class I-II, III-IV.**

- **Pre-Existing or anticipated right ventricular (RV) pacing with a clinical indication for ICD or pacemaker implantation, intrinsic narrow QRS for ANY of the following:**

  - LVEF ≤ 35%, RV pacing anticipated ≤ 40%, NYHA Class III-IV
  - LVEF > 35%, RV pacing anticipated > 40%, NHYA Class I,II, III-IV

- **Refractory Class III/IV heart failure < 3 months post revascularization and/or ≤ 40 days post-myocarcial infarction (MI), no other indication for ventricular pacing, LVEF ≤ 35% for ANY of the following:**

  - QRS 120-149 ms, LBBB or non-LBBB
  - QRS ≥ 150 ms, LBBB
  - QRS ≥ 150 ms, non-LBBB

Cigna does not cover the use of a biventricular pacemaker alone or combined with an implantable cardioverter defibrillator for CRT for any other indication because it is considered experimental, investigational or unproven.

Cigna covers replacement of a biventricular pacemaker generator alone or in combination with an implantable cardioverter defibrillator and/or leads as medically necessary.

Cigna does not cover triple-site or triventricular pacing CRT for any indication because it is considered experimental, investigational or unproven.

General Background

Congestive heart failure (CHF), or heart failure, is a clinical condition characterized by the heart's inability to generate a cardiac output sufficient to meet the body's circulatory demands. Approximately 20–30% of patients with heart failure may have intra-ventricular conduction delays, evidenced by a wide QRS interval on electrocardiogram (EKG), which can worsen left ventricular systolic dysfunction through asynchronous

ventricular contraction. This abnormality appears to be associated with increased morbidity and mortality. The most frequently used index of cardiac function is the left ventricular ejection fraction (LVEF). Normal LVEF ranges from 50–75% at rest. Severe heart failure can reduce LVEF to < 35%. Treatment for heart failure includes: pharmacological therapy, which can include a combination of diuretics, digoxin, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta-blockers and aldosterone antagonists. Some patients may remain symptomatic despite drug therapy. The definitive therapy for end-stage heart failure patients is heart transplantation.

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, accounting for approximately one third of hospitalizations for cardiac rhythm disturbance. AF is prevalent in patients with CHF or valvular heart disease and increases in prevalence with the severity of these conditions. There are a number of AF treatment options. The first line of treatment involves medications, but there are other treatments which may be appropriate (e.g., catheter ablation, an atrioventricular node ablation, cardiac surgical ablation, or cardioversion).

Cardiac Resynchronization Therapy (CRT)
Despite the combination of various therapies for heart failure, some patients remain refractory to full medical treatment. Of the various nonpharmacological approaches, biventricular pacing or CRT has gained interest since its introduction in the early 1990s. CRT is the term applied to reestablishing synchronous contraction between the left ventricular free wall and the ventricular septum in an attempt to improve left ventricular efficiency and, subsequently, to improve functional class. Generally, CRT has been used to describe biventricular pacing, but cardiac resynchronization can be achieved by left ventricular pacing only in some patients. Selected patients with mild to severe heart failure may benefit from CRT or biventricular pacing. CRT, in combination with stable optimal medical therapy, may help the lower chambers of the heart beat together and improve the heart's ability to supply blood and oxygen to the body. CRT is designed to help the right and left ventricle (LV)s beat at the same time in a normal sequence treating ventricular dyssynchrony.

An implantable biventricular pacemaker is an advanced version of a standardized implantable pacemaker. The biventricular pacemaker is implanted in the muscle tissue of the chest, below the collarbone, or in the abdomen. Three leads or wires, one atrial lead and two ventricular leads, are transvenously connected from the pacemaker to both sides of the heart. In a small percentage of cases, it may not be possible to place the left ventricular lead transvenously. In such situations, some centers are opting for an epicardial approach if the transvenous approach is unsuccessful. The pacemaker sends out electrical impulses to the heart through the leads. Placement of a biventricular pacemaker can usually be accomplished in an outpatient setting under sedation or general anesthesia. A short inpatient stay may be required for epicardial left ventricular lead placement. Once the pacemaker is implanted, it is programmed so that both ventricles are stimulated to contract after atrial contraction with the goal of improving left ventricle function, reducing presystolic mitral regurgitation and improving LV diastolic filling time.

The benefits of CRT need to be weighed against the risks of the procedure along with the adverse effects of having a CRT device implanted long term. The reported risks of the procedure are uncommon but some events may be serious such as pericardial effusion with tamponade or coronary dissection. Minor reported adverse events such as lead dislodgement are more common and may involve some degree of morbidity and result in repeat procedures.

CRT plus Implantable Cardioverter Defibrillator (ICD) System (CRT-D)
Some individuals with heart failure are also at high risk for life-threatening heart rhythms, ventricular tachycardia or ventricular fibrillation. Patients with heart failure who are at high risk for ventricular tachycardia and ventricular fibrillation may require a CRT system that includes implantable cardioverter defibrillator (ICD) therapy. The CRT plus ICD system (CRT-D) is designed to help the two lower heart chambers, the right and LVs, beat at the same time in a normal sequence, treating ventricular dyssynchrony. Additionally, should an individual experience an episode of ventricular tachycardia or ventricular fibrillation, the CRT-D system will detect the life-threatening arrhythmia and automatically correct the heart's rhythm.

Contraindications
Contraindications to biventricular pacemakers (CRT) or combination resynchronization-defibrillator devices are:

- Asynchronous pacing is contraindicated in the presence or likelihood of competitive paced and intrinsic rhythms.
- Unipolar pacing is contraindicated in individuals with an ICD because it may cause unwanted delivery or inhibition of defibrillator or ICD therapy.
- CRT-D devices are contraindicated for patients whose ventricular tachyarrhythmias may have transient or reversible causes and for patients with incessant ventricular tachycardia or ventricular fibrillation.
- CRT-D devices are contraindicated for dual chamber atrial pacing in patients with chronic refractory atrial tachyarrhythmias.

CRT-D may be considered for people who fulfill the criteria for implantation of a CRT-pacing (P) device and who also separately fulfill the criteria for the use of an ICD device.

Replacement of Device
When a biventricular pacemaker nears the end of battery life it is replaced; the expected lifespan of biventricular pacemaker pulse generator varies among manufacturers. In addition, leads may become dislodged or fracture and require replacement.

U.S. Food and Drug Administration (FDA)
Multiple biventricular pacemakers have been approved by the U.S. Food and Drug Administration (FDA) through the Premarket Approval (PMA) process for biventricular pacing alone (CRT) or biventricular pacing and defibrillation (CRT-D). Manufacturers of biventricular devices include St. Jude Medical (Sunnyvale, CA), Medtronic (Minneapolis, MN), Guidant Corp. (St. Paul, MN), and ELA Medical, Inc. (Plymouth, MN). FDA labeled indications include providing ventricular antitachycardia pacing and ventricular fibrillation for automated treatment of life-threatening ventricular arrhythmias. The systems are also intended to provide a reduction of the symptoms of moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III or IV) in those patients who remain symptomatic despite stable, optimal heart failure drug therapy, and left ventricular ejection fraction (LVEF) ≤ 35%, and a prolonged QRS duration. St Jude manufactures the Frontier® and Frontier® II biventricular pacing systems which has the additional indication for patients with chronic AF who have undergone atrioventricular node ablation and who have NYHA Class II or III heart failure.

In September 2010, the FDA expanded the indications for three CRT devices (the Cognis® CRT-D, Livian™ CRT-D and Contak Renewal® 3 RF HE CRT-D, Boston Scientific Corp., St. Paul, MN). Boston Scientific Corp. sponsored the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) clinical study to demonstrate the safety and effectiveness of Boston Scientific CRT-Ds in heart failure patients with QRS greater than or equal to 130 milliseconds (ms), ejection fraction less than or equal to 30**%**, and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure.

These CRT-D devices are indicated for individuals with heart failure who receive stable optimal pharmacologic therapy for heart failure and who meet any one of the following classifications:

- moderate to severe heart failure (NYHA Class III-IV) with EF less than or equal to 35% and QRS duration greater than or equal to 120 ms; or

- left bundle branch block (LBBB) with QRS greater than or equal to 130 ms, EF less than or equal to 30%, and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure

Literature Review
Evidence in the published peer-reviewed literature, including randomized controlled trials and meta-analysis and systematic reviews, indicates that biventricular resynchronization therapy is effective at improving quality of life, patient functional capacity and heart failure symptoms among a subgroup of patients with heart failure, with or without ICD indications, decreased cardiac function and ventricular dyssynchrony who are on optimal pharmacologic regimen before implantation (Cleland, et al., 2009; Upadhyay, et al., 2008; Auricchio, et al., 2007; McAlister, et al., 2007; Lindenfeld, et al.,. 2007; Delnoy, et al., 2007; Sutton, et al., 2006; Gasparini, et al., 2006; Cleland, et al., 2005; Molhoek, et al., 2005; Doshi, et al., 2005; Molhoek, et al., 2004; Bristow, et al., 2004; Garrigue, et al., 2003; Abraham, et al., 2002; Leclercq, et al., 2002; Leone, et al., 2002; ECRI, 2002).

The majority of new research in CRT is to evaluate whether the benefits of CRT extend to patients with mild or less severe heart failure (NYHA Class I/II). Four key randomized, controlled trials Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT), Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE), Multicenter InSync ICD Randomized Clinical Evaluation II (MIRACLE ICD II) and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) enrolling 4414 patients which included patients with NYHA Class I or II heart failure enrolling at least 25 patients per treatment group reporting on at least one relevant health outcome with follow-up ranging from six months to 2.4 years have been published in the peer-reviewed literature (Tang, et al., 2010; Moss, et al., 2009; Linde, et al., 2008, Abraham, et al., 2004).

Evidence in the published peer-reviewed literature, including randomized controlled trials and a meta-analysis (Al-Majed, et al., 2011), indicates that there is a consistent benefit for CRT in reducing hospitalizations for a subgroup of patients with mild heart failure (NYHA Class I or II) and in improving echocardiographic parameters. Data indicates that biventricular resynchronization therapy does not demonstrate benefit on quality of life, functional status, or progression to more advanced stages of heart failure. The evidence on mortality differs among the available studies. Of the two largest studies, MADIT-CRT and RAFT, one reported a mortality difference while the other does not. The RAFT trial had patients with more severe illness, a higher baseline death rate, and a longer follow-up period concluding that CRT is likely to improve mortality for patients with NYHA class II heart failure. Robust evidence to support biventricular resynchronization therapy in patients with asymptomatic left ventricular dysfunction or NYHA Class I symptoms is inconclusive resulting in the inability to draw strong conclusions regarding the impact on health outcomes (Santangeli, et al., 2011; Al-Majed, et al., 2011, Adabag, et al., 2011; Zareba, et al., 2011, Versteeg, et al., 2011; Pouleur, et al., 2011, Solomon, et al., 2010, Tang, et al., 2010; Moss, et al., 2009; Linde, et al., 2008, Abraham, et al., 2004).

Literature Review Patient Selection Criteria
It has been reported that approximately 30% of the patients who are selected for therapy, according to the current criteria, do not benefit from CRT (Stavrakis, et al., 2012). A variety of factors have been proposed as contributing to the nonresponder rate associated with CRT, including suboptimal left ventricular lead placement, suboptimal atrioventricular (AV) and ventricle-to-ventricle (V-V) timing, ventricular scar, and heart failure disease progression (Abraham, 2011) . Since some patients do not respond favorably after undergoing CRT, studies addressing optimal patient selection criteria for CRT are ongoing.

QRS Duration: A recent meta-analysis reported that in patients with intrinsic QRS duration ≥ 150 ms, pooled analysis of five randomized controlled trials revealed a significant 42% reduction in the incidence of the primary endpoint of death or hospitalization for HF with the use of CRT compared to control (Stavrakis, et al., 2012).

Some patients with narrow QRS complexes have echocardiographic evidence of left ventricular mechanical dyssynchrony and may also benefit from CRT. Results of published trials are insufficient at this time to demonstrate that use of CRT in heart failure patients with a narrow QRS complex (i.e., < 120 ms) benefits patient outcomes.

The Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial was a randomized, double-blind, 12-center study that was designed to compare the effects of active and inactive cardiac resynchronization therapy in patients with severe left ventricular dysfunction and a QRS duration <120 ms (Thibault, et al., 2013). The trial was interrupted prematurely by the Data Safety and Monitoring Board because of futility and safety concerns after 85 patients were randomized. The authors reported that in patients with a LVEF ≤35%, symptoms of heart failure, and a QRS duration <120 ms, CRT did not improve clinical outcomes or left ventricular remodeling and was associated with potential harm (Thibault, et al., 2013).

In a prospective randomized clinical trial, Beshai et al. (2007) enrolled 172 patients who had a standard indication for an ICD. Patients received the CRT device and were randomly assigned to the CRT group or to a control group (no CRT) for six months. The primary end point was the proportion of patients with an increase in peak oxygen consumption of at least 1.0 ml per kilogram of body weight per minute during cardiopulmonary exercise testing at six months. At six months, the CRT group and the control group did not differ significantly in the proportion of patients with the primary end point (46% and 41%, respectively). In a prespecified subgroup with a QRS interval of ≥ 120 ms, the peak oxygen consumption increased in the CRT group (p=0.02), but it was unchanged in a subgroup with a QRS interval of ≤ 120 ms (p=0.45). There were 24 heart failure events requiring intravenous therapy in 14 patients in the CRT group (16.1%) and 41 events in 19 patients in the control group

(22.3%), but the difference was not significant. The authors reported that CRT did not improve peak oxygen consumption in patients with moderate-to-severe heart failure, providing evidence that patients with heart failure and narrow QRS intervals may not benefit from CRT.

Patients with narrow QRS complex are currently not eligible for CRT, and the potential effects of CRT are not well-studied. In a prospective pilot study, Bleeker et al. (2006a) studied the effects of CRT in heart failure patients with narrow QRS complex (<120 ms) and evidence of LV dyssynchrony on tissue Doppler imaging (TDI). The study participants included a total of 33 consecutive patients with narrow QRS complex and 33 consecutive patients with wide QRS complex (control group). Patient inclusion criteria included: LV dyssynchrony ≥ 65 ms on TDI, NYHA functional Class III/IV heart failure, and LVEF ≤ 35%. Baseline characteristics, particularly LV dyssynchrony, were comparable between patients with narrow and wide QRS complex (p=NS). No significant relationship was observed between baseline QRS duration and LV dyssynchrony (p=NS). The improvement in clinical symptoms and LV reverse remodeling was comparable between patients with narrow and wide QRS complex (mean NYHA functional class reduction 0.9 versus 1.1 (p=NS) and mean LV end-systolic volume reduction 39 versus 44 ml (p=NS). The authors reported that, "CRT appears to be beneficial in patients with narrow QRS complex and severe LV dyssynchrony on TDI, with similar improvement in symptoms and comparable LV reverse remodeling. These effects need confirmation in studies with larger populations." The authors noted that color-coded TDI measures the velocity of the myocardium, which may not always equal active myocardial contraction. Large, comparative studies are needed to define which technique is most accurate in the assessment of LV dyssynchrony.

QRS Duration Meta-Analysis: Stavrakis et al. (2012) conducted a meta-analysis of randomized clinical trials to evaluate the impact of QRS duration on the efficacy of CRT. Only trials that reported subgroup data according to QRS duration were included. Five trials (Tang, et al., 2010; Moss, et al., 2009; Linde, et al., 2008; Cleland, et al., 2005; Bristow, et al., 2004) involving 6501 patients (4437 with QRS ≥ 150 ms and 2064 with QRS < 150 ms) were included. Three trials, enrolling patients with mild to moderate HF, compared CRT-implantable cardioverter defibrillator with CRT, whereas CRT versus medical therapy was compared in the other two trials, which included patients with advanced HF. In patients with intrinsic QRS duration ≥ 150 ms, pooled analysis of the five trials revealed a significant 42% reduction in the incidence of the of the primary endpoint of death or hospitalization for HF with the use of CRT compared to control (HR = 0.58, 95% CI: 0.50-0.68; p<0.00001), but not in patients with QRS < 150 ms (HR = 0.95, 95% CI: 0.83-1.10; p=0.51). These results were consistent across all degrees of HF severity. In patients with intrinsic QRS duration <150 ms, pooled analysis of the five trials showed no significant benefit from CRT (with or without ICD) compared to control (HR = 0.95, 95% CI: 0.83–1.10; p=0.51). The lack of benefit was consistent between the two subgroups based on the severity of heart failure. There was no heterogeneity between the trials.

Sipahi et al. (2011) conducted a meta-analysis of published randomized controlled trials that evaluated whether patients with modest prolongations of the QRS complex benefited from CRT. This study identified five trials enrolling a total of 5813 patients that reported on outcomes stratified by QRS duration. There was some variability in the definition of QRS categories, but the authors were able to categorize studies into those with moderately prolonged QRS, generally 120-149 msec, and severely prolonged QRS, generally ≥150 msec. For patients with a moderately prolonged QRS, there was no significant benefit for CRT in reducing composite outcomes of adverse cardiac events (Risk ratio [RR]: 0.95, 95% CI: 0.82 to 1.10, p=0.49). In contrast, for patients with a severely prolonged QRS, there was a 40% relative reduction in the composite outcomes (RR: 0.60, 95% CI: 0.53 to 0.67, p<0.001). Multiple limitations to these findings were reported including use of summary versus individual data in the meta-analysis; use of heterogeneous enrollment criteria by the five included trials with variable composite outcome measures; unknown morphology of the QRS complex in participants with a QRS duration less than 150 msec. and unknown percentages of study participants with RBBB (right bundle branch block). The authors reported that further analysis of individual subject-specific data from all relevant clinical trials can further refine the QRS cutoffs for different types of conduction abnormalities.

QRS Morphology: In a retrospective study, Dupont et al. (2012) evaluated the relative impact of QRS morphology and duration in echocardiographic responses to CRT and clinical outcomes. Baseline characteristics, clinical and echocardiographic response, and outcomes of all patients who received CRT at a single center were evaluated. Patients were stratified into four groups according to their baseline QRS morphology and QRS duration. A total of 496 patients were included in the study; 216 (43.5%) had LBBB and a QRS 150 ≥ ms, 85 (17.1%) had LBBB and QRS < 150 ms, 92 (18.5%) had non-LBBB and a QRS ≥150 ms, and 103 (20.8%) had non-LBBB and QRS <150 ms. Echocardiographic response (change in ejection fraction) was

better in patients with LBBB and QRS ≥150 than in those with LBBB and QRS < 150 ms, non-LBBB and QRS ≥150, and non-LBBB and QRS >150 ms (p<0.0001). In a multivariate stepwise model with change in ejection fraction as the dependent variable, the presented classification was the most important independent variable (p=0.0003). Long-term survival was better in LBBB patients with QRS ≥150 (p=0.02), but this difference was not significant after adjustment for other baseline characteristics (p=0.15) suggesting that comorbid conditions may confound the treatment responses. The authors stated that "due to the lack of sufficiently powered trials in these subgroups, guideline committees have the difficult task of using this and similar studies to refine patient selection for CRT".

In a meta-analysis, Sipah et al. (2012) evaluated the effect of CRT on clinical events (including death and heart failure hospitalizations) with regards to bundle branch block morphologies. Four randomized controlled trials totaling 5356 patients met the inclusion criteria. The authors reported that in patients with a LBBB, CRT was very effective in reducing adverse events with a relative risk reduction of 36% (p=0.00001). However, no benefit was observed in patients with other types of conduction abnormalities and a QRS duration > 120 milliseconds.

Echocardiography: Echocardiographic and Doppler imaging techniques have emerged to play a potential role in the care of the patient with CRT. Since some patients do not respond favorably after undergoing CRT, it has been suggested that one reason for nonresponse to CRT is that the ECG widened QRS is a suboptimal marker for dyssynchrony. The echocardiographic quantification of dyssynchrony may potentially play a role in improving patient selection for CRT (Diab, et al., 2011, Gorscan, et al., 2008).

Triple-site CRT (Triventricular Pacing)

Triple-site cardiac resynchronization or triventricular pacing involves the addition of an additional ventricular pacing lead. The right ventricular and atrial leads are implanted as in conventional CRT. The third ventricular lead is joined in parallel with a Y-connector and connected to the left ventricular port of the CRT system.

Triventricular pacing has been proposed as an alternative approach to improve the response rate in CRT recipients. It has been suggested that failure of response to biventricular pacing is probably due to a combination of factors including placement of the pacing lead over a zone of slow conduction, the presence of scar within the left ventricle, variable electrical response of the diseased ventricle to pacing, or suboptimal positioning of the pacing leads with regard to the area of latest contraction (Rogers, et al., 2012).

There is a paucity of randomized controlled clinical trials or comparative studies in the peer-reviewed literature assessing the impact of triple-site resynchronization on long-term health outcomes in patients compared to conventional biventricular pacing (Rogers, et al., 2012; Lenarczyk, et al., 2012).

Technology Assessments

The Agency for HealthCare Research and Quality (AHRQ) published a technology assessment in 2004 to examine the success rate and safety of biventricular pacemaker implantation and the efficacy of CRT in patients with heart failure. Nine trials were reviewed with a total of 3216 patients randomized to receive CRT. The mean age was 64; 74% were male; 75% had NYHA Class III symptoms; and 10% had NYHA Class IV symptoms. The QRS duration ranged from ≥ 120 ms to > 200 ms. All of the trials restricted enrollment to patients with reduced EFs ranging from ≤ 35% to ≤ 40%. The authors reported that CRT improves functional and hemodynamic markers and reduces all-cause mortality by 25% and heart failure hospitalizations by 32% in patients with NYHA Class III or IV CHF, despite optimal medical management, reduced EFs, and prolonged QRS duration (McAlister, et al., 2004).

Professional Societies/Organizations

Professional society recommendations have been published or updated in an effort to guide appropriate care/indications to scenarios for which clinical trial evidence and/or clinical experience was available that support device implantation for CRT.

American College of Cardiology Foundation (ACCF), Heart Rhythm Society (HRS), American Heart Association (AHA), American Society of Echocardiography (ASE), Heart Failure Society of America (HFSA), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Cardiovascular Computed Tomography (SCCT), and Society for Cardiovascular Magnetic Resonance (SCMR) 2013

Appropriate Use Criteria for Implantable Cardioverter-Defibrillators and Cardiac Resynchronization Therapy

The 2013 ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR document addresses the appropriate use of implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) for selected patient populations (Russo, et al., 2013). The authors state that the appropriate use criteria should be used in conjunction with the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities and the 2012 focused update (Epstein, et al., 2008; Tracy, et al., 2012).

The final score reflects the median score of the 17 technical panel members and has been labeled according to the categories of Appropriate (median 7 to 9), May Be Appropriate (median 4 to 6), and Rarely Appropriate (median 1 to 3). The authors state that "The relationship of these criteria to existing guidelines was provided to the technical panel. In addition, extensive links to clinical trials and other literature regarding the role of ICD and CRT in each clinical scenario were provided to technical panel members. This document represents the current understanding of the clinical utility of ICD and CRT implantation in clinical practice as measured by physicians with a variety of backgrounds and areas of expertise. It is the goal that these criteria will help provide a guide to inform medical decisions and help clinicians and stakeholders understand areas of consensus as well as uncertainty, while identifying areas where there are gaps in knowledge that warrant additional investigation".

The authors stated that, "Atrial arrhythmias (including atrial fibrillation, atrial flutter, and atrial tachycardia) are not included in the indication tables. There are fewer data available for CRT in patients with persistent atrial arrhythmias, and the writing group elected to avoid additional scenarios for practical reasons, as the document already includes a large number of scenarios. However, it is assumed that the presence of intermittent or persistent atrial arrhythmias would not preclude CRT implantation, and the benefits of CRT would also apply to patients with persistent atrial arrhythmias, as long as CRT is maintained nearly 100% of the time".

Ambulatory class IV is defined as class IV heart failure with: 1) no active acute coronary syndrome; 2) no inotropes; and 3) on guideline-direct medical therapy (GDMT). A normal LVEF is defined as ≥ 50%. The authors state that, "GDMT for heart failure in the setting of LV systolic dysfunction requires individualization but typically should include the combination of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and betablocker therapy adjusted to target doses as tolerated, with diuretics adjusted if/as needed to control fluid retention. In selected patients, the addition of aldosterone antagonists and hydralazine plus nitrate combinations should be considered. Patients who are going to receive substantial benefit from medical treatment alone usually show some clinical improvement during the first 3 to 6 months. Medical therapy is also assumed to include adequate rate control for tachyarrhythmias, including atrial fibrillation. Therefore, it is recommended that GDMT be provided for at least 3 months before planned reassessment of LV function to consider device implantation. If LV function improves to the point where primary prevention indications no longer apply, then device implantation is not indicated.

Recommendations are provided based on the following scoring method:

- Median score 7-9: Appropriate care: An appropriate option for management of patients in this population due to benefits generally outweighing risks; effective option for individual care plans, although not always necessary, depending on physician judgment and patient-specific preferences (i.e., procedure is generally acceptable and is generally reasonable for the indication).
- Median score 4-6: May be appropriate for care: At times an appropriate option for management of patients in this population due to variable evidence or agreement regarding the benefit/risk ratio, potential benefit based on practice experience in the absence of evidence, and/or variability in the population; effectiveness for individual care must be determined by a patient's physician in consultation with the patient based on additional clinical variables and judgment along with patient preferences (i.e., procedure may be acceptable and may be reasonable for the indication).
- Median score 1-3: Rarely appropriate care: Rarely an appropriate option for management of patients in this population due to the lack of a clear benefit/risk advantage; rarely an effective option for individual care plans; exceptions should have documentation of the clinical reasons for proceeding with this care option (i.e., procedure is not generally acceptable and is not generally reasonable for the indication).

Generally, criteria that have been deemed Appropriate or May Be Appropriate in these scenarios often meet Class I, IIa, or IIb criteria in guideline documents, are supported by a critical mass of existing data, or were deemed by the technical panel to meet sufficient clinical judgment to be reasonable and appropriate.

Indications rated as Appropriate or May be Appropriate are detailed below; indications rated as Rarely Appropriate (Median score 1-3) are outlined in the appropriate use criteria document described above.

The following indications were rated as appropriate care (median score 7-9):

Ischemic cardiomyopathy, left ventricular ejection fraction (LVEF) ≤ 30%, no prior implant, sinus rhythm (SR) for ANY of the following:

- QRS 120-149 milliseconds (ms), left bundle branch block (LBBB), New York Heart Association (NYHA) Class II (7), III-IV (8)
- QRS ≥ 150 ms, LBBB, NYHA Class I (7) II (8), III-IV (9)
- QRS ≥ 150 ms, non-LBBB, NYHA Class III-IV (7)

Ischemic cardiomyopathy, LVEF 31-35%, no prior implant, SR for ANY of the following:

- QRS 120-149 ms, LBBB, NYHA Class II (7), III-IV (8)
- QRS ≥ 150 ms, LBBB, NYHA Class II (8), III-IV (9)
- QRS ≥ 150 ms, non-LBBB, NYHA Class III-IV (7)

Nonischemic cardiomyopathy, LVEF ≤ 30%, no prior implant, SR for ANY of the following:

- QRS 120-149 ms, LBBB, NYHA Class II (7), III-IV (8)
- QRS ≥ 150 ms, LBBB, NYHA Class II (9), III-IV (9)
- QRS ≥ 150 ms, non-LBBB, NYHA Class III-IV (8)

Nonischemic cardiomyopathy, LVEF 31-35%, no prior implant, SR for ANY of the following:

- QRS 120-149 ms, LBBB, NYHA Class II (7), III-IV (8)
- QRS ≥ 150 ms, LBBB, NYHA Class II (8), III-IV (9)
- QRS ≥ 150 ms, non-LBBB, NYHA Class III-IV (7)

Pre-Existing or anticipated right ventricular (RV) pacing with a clinical indication for ICD or pacemaker implantation, intrinsic narrow QRS, LVEF ≤ 35% when RV pacing anticipated is > 40%, NYHA Class I-II (7), III-IV (8).

Refractory Class III/IV heart failure < 3 months post revascularization and/or ≤ 40 days post-myocarcial infarction (MI), no other indication for ventricular pacing, LVEF ≤ 35% for ANY of the following:

- QRS 120-149 ms, LBBB (7)
- QRS ≥ 150 ms, LBBB (8)
- QRS ≥ 150 ms, non-LBBB (7)

The following indications were rated as may be appropriate for care (median score 4-6):

Ischemic cardiomyopathy, LVEF ≤ 30%, no prior implant, SR for ANY of the following:

- QRS 120-149 ms, LBBB, NYHA Class I (5)
- QRS 120-149 ms, non-LBBB, NYHA Class III-amb. IV (6)
- QRS ≥ 150 ms, non-LBBB, NYHA Class I (4), II (6)

Ischemic cardiomyopathy, LVEF 31-35%, no prior implant, SR for ANY of the following:

- QRS 120-149 ms, LBBB, NYHA Class I (5)

- QRS ≥ 150 ms, LBBB, NYHA Class I (6)
- QRS 120-149 ms, non-LBBB, NYHA Class III-IV (6)
- QRS ≥ 150 ms, non-LBBB, NYHA Class I (4), Class II (6)

Nonischemic cardiomyopathy, LVEF ≤ 30%, no prior implant, SR for ANY of the following:

- QRS 120-149 ms, LBBB, NYHA Class I (4)
- QRS ≥ 150 ms, LBBB, NYHA Class I (6)
- QRS 120-149 ms, non-LBBB, NYHA Class III-IV (6)
- QRS ≥ 150 ms, non-LBBB, NYHA Class I (5), II (6)

Nonischemic cardiomyopathy, LVEF 31-35%, no prior implant, SR for ANY of the following:

- QRS 120-149 ms, LBBB, NYHA Class I (5)
- QRS ≥ 150 ms, LBBB, NYHA Class I (6)
- QRS 120-149 ms, non-LBBB, NYHA Class III-IV (6)
- QRS ≥ 150 ms, non-LBBB, NYHA Class I (5), II (6)

LVEF > 35% of any etiology (ICD Indicated), no prior implant, SR:

- QRS 120-149 ms, LBBB, NYHA Class III-IV (4)
- QRS ≥ 150 ms, LBBB, NYHA Class I-II (4), III-IV (5)
- QRS ≥ 150 ms, non-LBBB, NYHA Class III-IV (4)

LVEF ≤ 35% of any etiology (NYHA Class IV on Intravenous Inotropic Support), no prior implant:

- QRS 120-149 ms, LBBB (6) or non-LBBB (4)
- QRS ≥ 150 ms, LBBB (6) or non-LBBB (5)

Pre-Existing or anticipated RV pacing with a clinical indication for ICD or pacemaker implantation-intrinsic narrow QRS:

- LVEF ≤ 35%, RV pacing anticipated ≤ 40%, NYHA Class I-II (4), III-amb. IV (5)
- LVEF > 35%, RV pacing anticipated ≤ 40%, NHYA Class III-IV (4)
- LVEF > 35%, RV pacing anticipated > 40%, NHYA Class I-II (5), III-IV (6)

Refractory Class III/IV heart failure < 3 months post revascularization and/or ≤ 40 days post-MI, no other indication for ventricular pacing:

- LVEF ≤ 35%, QRS 120-149 ms, non-LBBB (5)
- LVEF 36-50%, QRS ≥ 150, LBBB (4)

American College of Cardiology Foundation (ACCF), American Heart Association (AHA) and Heart Rhythm Society (HRS) Guideline for Device-Based Therapy for Cardiac Rhythm Abnormalities
The 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities addresses recommendations for CRT (Epstein, et al., 2013; Tracy, et al., 2012). Guideline recommendations are classified as Class I, Class IIa, Class IIb, and Class III. The classification system is described as follows:

- Class I: Benefit >>>Risk; Procedure/Treatment should be perfomed/administered
- Class IIa: Benefit >> Risk; Additional studies with focused objectives needed. It is reasonable to perform procedure/administer treatment
- Class IIb: Benefit ≥ Risk; Additional studies with broad objectives needed; additional registry data would be helpful. Procedure/treatment may be considered.
- Class III: No Benefit or No Harm
  - Class of Recommendation (COR) III: No Benefit

- Procedure/Test: not helpful
- Treatment: no proven benefit

➢ COR III: Harm
- Procedure/Test: excess cost w/o benefit or harmful
- Treatment: harmful to patients

The weight of evidence supporting each recommendation is classified as follows:

- Level A: Multiple populations evaluated. Data derived from multiple randomized clinical trials or meta-analyses.
- Level B: Limited populations evaluated. Data derived from a single randomized trial or nonrandomized studies.
- Level C: Very limited populations evaluated. Only consensus opinion of experts, case studies, or standard of care.

The updated guideline proposes several changes in recommendations for CRT, compared with the 2008 document. The most significant changes are limitation of the Class I indication to patients with QRS duration ≥150 ms; limitation of the Class I indication to patients with left bundle-branch block (LBBB) pattern; expansion of Class I indication to New York Heart Association (NYHA) class II (and with LBBB with QRS duration ≥150 ms); and the addition of a Class IIb recommendation for patients who have LVEF ≤30%, ischemic etiology of heart failure (HF), sinus rhythm, LBBB with a QRS duration ≥150 ms, and NYHA class I symptoms.

The following recommendations for CRT placement are included in the 2012 guideline:

Class I

- CRT is indicated for patients who have LVEF ≤ 35%, sinus rhythm, LBBB with a QRS duration ≥ 150 ms, and NYHA class II (Moss, et al., 2009, Tang, et al., 2010) III, or ambulatory IV (Abraham, et al., 2002; Bristow, et al., 2004; Cleland, et al., 2005; Hunt, et al., 2009) symptoms on guideline directed medical therapy (GDMT) (Level of Evidence: A for NYHA class III/IV; Level of Evidence: B for NYHA class II).

Class IIa

- CRT can be useful for patients who have LVEF ≤ 35%, sinus rhythm, LBBB with a QRS duration 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT (Abraham, et al., 2002; Bristow, et al., 2004; Cleland, et al., 2005; Moss, et al., 2009; Tang, et al., 2010; Linde, et al., 2008) (Level of Evidence: B).
- CRT can be useful for patients who have LVEF ≤ 35%, sinus rhythm, a non-LBBB pattern with a QRS ≥ 150 ms, and NYHA class III/ambulatory class IV symptoms on GDMT (Abraham, et al., 2002; Bristow, et al., 2004; Cleland, et al., 2005; Tang, et al., 2010) (Level of Evidence: A).
- CRT can be useful in patients with atrial fibrillation and LVEF ≤ 35% on GDMT if the patient requires ventricular pacing or otherwise meets CRT criteria and b) AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT (Brignole, et al., 2005; Brignole, et al., 2011; Doshi, et al., 2005; Wilton, et al., 2011; Upadhyay, et al., 2008) (Level of Evidence: B).
- CRT can be useful for patients on GDMT who have LVEF ≤ 35% and are undergoing new or replacement device placement with anticipated requirement for significant (> 40%) ventricular pacing (Doshi, et al., 2005; Wilkoff, et al., 2002; Adelstein, et al., 2011; Vatankulu, et al., 2009) (Level of Evidence: C).

Class IIb

- CRT may be considered for patients who have LVEF ≤ 30%, ischemic etiology of heart failure, sinus rhythm, LBBB with a QRS duration of ≥150 ms, and NYHA class I symptoms on GDMT (Moss, et al., 2009; Tang, et al., 2010) (Level of Evidence: C).
- CRT may be considered for patients who have LVEF ≤ 35%, sinus rhythm, a non-LBBB pattern with QRS duration 120 to 149 ms, and NYH class III/ambulatory class IV on GDMT (Tang, et al., 2010; Rickard, et al., 2011) (Level of Evidence: B).

- CRT may be considered for patients who have LVEF ≤ 35%, sinus rhythm, a non-LBBB pattern with a QRS duration ≥ 150 ms, and NYHA class II symptoms on GDMT (Moss, et al., 2009; Tang, et al., 2010) (Level of Evidence: B).

Class III: No Benefit

- CRT is not recommended for patients with NYHA class I or II symptoms and non-LBBB pattern with QRS duration less than 150 ms (Moss, et al., 2009; Tang, et al., 2010; Rickard, et al., 2011) (Level of Evidence: B).
- CRT is not indicated for patients whose comorbidities and/or frailty limit survival with good functional capacity to less than 1 year (Moss, et al., 2009) (Level of Evidence: C).

American College of Cardiology Foundation (ACCF)/ American Heart Association (AHA) Practice Guideline for the Management of Heart Failure
In 2013, the ACCF/AHA Guideline for the Management of Heart Failure was updated (Yancy, et al., 2013). The CRT recommendations for device therapy for management of Stage C heart failure (i.e., structural heart disease with prior or current symptoms of heart failure) are in complete alignment with recommendations in the 2012 ACCF/AHA/HRS focused update for device-based therapy of cardiac rhythm abnormalities as noted above (Tracy, et al., 2012).

Heart Failure Society Indications for Cardiac Resynchronization Therapy
The updated 2011 Heart Failure Society Indications for Cardiac Resynchronization Therapy states that, "After evaluating the totality of evidence and based on the general consistency across clinical trials, the HFSA Guideline Committee determined that CRT is recommended for patients in sinus rhythm with a widened QRS interval (≥ 150 ms) that is not due to right bundle branch block who have severe LV systolic dysfunction (LVEF ≤ 35%) and persistent mild-to-moderate heart failure (NYHA functional class II-III) despite optimal medical therapy. CRT may be considered for ambulatory NYHA functional class IV patients with QRS interval ≥150 ms and severe LV systolic dysfunction (LVEF ≤ 35%). CRT may be considered for patients with a QRS interval of ≥120 to < 150 ms and severe LV systolic dysfunction (LVEF ≤ 35%) who have persistent mild to severe heart failure (NYHA functional class II to ambulatory class IV) despite optimal medical therapy ":

The HFSA uses 4 levels of strength in its guideline recommendations. These include ''is recommended,'' indicating that the therapy should be part of routine care and exceptions minimized; ''should be considered,'' indicating that the majority of patients should receive the intervention; ''may be considered,'' indicating that patient individualization is needed in the application of therapy; and ''is not recommended,'' indicating that the therapy should not be used (Stevenson, et al., 2012).

American College of Cardiology; American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death
The ACC/AHA/ESC 2006 guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death addresses ventricular arrhythmias associated with cardiomyopathies. Class IIa recommendations with a level of evidence B are given for heart failure. The authors recommend, "ICD therapy combined with biventricular pacing can be effective for primary prevention to reduce total mortality by a reduction in sudden cardiac death (SCD) in patients with NYHA functional Class III or IV, are receiving optimal medical therapy, in sinus rhythm with a QRS complex of at least 120 ms, and who have reasonable expectation of survival with a good functional status for more than one year." Additionally, the authors recommend, "Biventricular pacing in the absence of ICD therapy is reasonable for the prevention of SCD in patients with NYHA functional Class III or IV heart failure, a LVEF ≤ 35%, and a QRS complex equal to or wider than 160 ms (or at least 120 ms in the presence of other evidence of ventricular dyssynchrony) who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than one year" (Zipes, et al., 2006). This guideline has not been updated since 2006.

Use Outside of the US
Canadian Cardiovascular Society (CCS)
The 2013 CCS guidelines on the use of cardiac resynchronization therapy: implementation was developed to address the practical use of cardiac resynchronization therapy (CRT), beyond clinical trial inclusion/exclusion

criteria, in a real world population. The nine recommendations in the document are based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment method and expert consensus.

Quality of evidence and definitions state that when the desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not, guideline panels offer strong recommendations. On the other hand, when the trade-offs are less certain—either because of low quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced—weak recommendations become mandatory.

Quality of evidence and definitions:

- High quality: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: Any estimate of effect is very uncertain.

The following recommendations are in the 2013 guideline:

- Recommend that the prescription of CRT and the choice of platform (CRT-P versus CRT-D) should take into account clinical factors that would affect the overall goals of care (Strong Recommendation, Moderate-Quality Evidence).

- Suggest that CRT might be considered for patients with new-onset high-degree AV block requiring chronic RV pacing, signs and/or symptoms of heart failure, and LVEF ≤45% (Conditional Recommendation, Moderate-Quality Evidence).

- Recommend that all patients with heart failure who are planned to receive a cardiac implantable electronic device system revision should be considered for their eligibility for upgrade to CRT (Strong Recommendation, Low-Quality Evidence).

- Suggest that placement of an LV lead at the time of open heart surgery, for the purpose of facilitating future CRT, might be considered in patients for whom CRT is recommended and the need for device therapy is unlikely to be changed by the surgical procedure (Conditional Recommendation, Low-Quality Evidence).

- Recommend that in patients taking warfarin for whom perioperative anticoagulation is deemed necessary, continued warfarin is recommended over the use of heparin-based bridging (Strong Recommendation, Moderate-Quality Evidence).

- Recommend that CRT implantation be performed only in facilities that have strict infection prevention control standards (Strong Recommendation, Low-Quality Evidence).

- Recommend that appropriate fluoroscopic equipment, radiation shielding, and radiation reduction imaging methods be used to minimize radiation exposure to the operator, patient, and other staff (Strong Recommendation, Low-Quality Evidence).

- Recommend that alterations in clinical parameters after versus before CRT be assessed within 6 to 12 months after CRT implantation to guide ongoing heart failure management (Strong Recommendation, Low-Quality Evidence).

- Suggest that CRT implantation occur within 6-8 weeks from the decision to implant to avoid preventable adverse events, such as heart failure hospitalizations and death (Conditional Recommendation, Low-Quality Evidence).

European Society of Cardiology (ESC) Guidelines on cardiac pacing and cardiac resynchronization therapy

The following recommendations for CRT placement are included in the 2013 guideline. Guideline recommendations are classified as Class I, Class IIa, Class IIb, and Class III. The classification system is described as follows (Brignole, et al., 2013):

- Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
- Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
- Class IIa: Weight of evidence/opinion is in favour of usefulness/efficacy.
- Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
- Class III: Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

The weight of evidence supporting each recommendation is classified as follows:

- Level A: Data derived from multiple randomized clinical trials or meta-analysis.
- Level B: Data derived from a single randomized clinical trial or large non-randomized clinical trials.
- Level C: Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Indications for CRT in patients in SR:

- LBBB with QRS duration >150 ms. CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment (Class I, Level A).
- LBBB with QRS duration 120–150 ms. CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment (Class I, Level B).
- Non-LBBB with QRS duration >150 ms. CRT should be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment (Class IIa, Level B).
- Non-LBBB with QRS duration 120–150 ms. CRT may be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment (Class IIb, Level B).
- CRT in patients with chronic HF with QRS duration <120 ms is not recommended (Class III, Level B).

Indications for CRT in patients with permanent atrial fibrillation:

- Patients with HF, wide QRS and reduced LVEF:
  - CRT should be considered in chronic HF patients, intrinsic QRS ≥120 ms and LVEF ≤35% who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment, provided that a BiV pacing as close to 100% as possible can be achieved (Class IIa, Level B).
  - AV junction ablation should be added in case of incomplete BiV pacing (Class IIa, Level B).
- Patients with uncontrolled heart rate who are candidates for AV junction ablation. CRT should be considered in patients with reduced LVEF who are candidates for AV junction ablation for rate control (Class IIa, Level B).

European Society of Cardiology (ESC) Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure

The 2012 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure have the following recommendations for CRT (McMurray, et al., 2012).

Recommendations for the use of CRT where the evidence is strong—patients in sinus rhythm with NYHA functional class III and ambulatory class IV heart failure and a persistently reduced ejection fraction, despite optimal pharmacological therapy:

- CRT-P/CRT-D is recommended in patients in sinus rhythm with a QRS duration of ≥120 ms, LBBB QRS morphology, and an EF ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death (Class I, Level A).
- CRT-P/CRT-D should be considered in patients in sinus rhythm with a QRS duration of ≥150 ms, irrespective of QRS morphology, and an EF ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death (Class IIa, Level A).

Recommendations for the use of CRT where the evidence is strong—patients in sinus rhythm with NYHA functional class II heart failure and a persistently reduced ejection fraction, despite optimal pharmacological therapy:

- CRT, preferably CRT-D is recommended in patients in sinus rhythm with a QRS duration of ≥130 ms, LBBB QRS morphology, and an EF ≤30%, who are expected to survive for >1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death (Class I, Level A).
- CRT, preferably CRT-D should be considered in patients in sinus rhythm with a QRS duration of ≥150 ms, irrespective of QRS morphology, and an EF ≤30%, who are expected to survive for >1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death (Class IIa, Level A).

Recommendations for the use of CRT where the evidence is uncertain—patients with symptomatic HF (NYHA functional class II–IV) and a persistently reduced EF despite optimal pharmacological therapy and in AF or with a conventional pacing indication:

- Patients in permanent AF: CRT-P/CRT-D may be considered in patients in NYHA functional class III or ambulatory class IV with a QRS duration ≥120 ms and an EF ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of HF worsening if:
    - The patient requires pacing because of an intrinsically slow ventricular rate (Class IIb, Level C).
    - The patient is pacemaker dependent as a result of AV nodal ablation (Class IIa, Level B).
    - The patient's ventricular rate is ≤60 b.p.m. at rest and ≤90 b.p.m. on exercise (Class IIb, Level C).
- Patients with an indication for conventional pacing and no other indication for CRT: In patients who are expected to survive with good functional status for >1 year:
    - CRT should be considered in those in NYHA functional class III or IV with an EF ≤35%, irrespective of QRS duration, to reduce the risk of worsening of HF (Class IIa, Level C).
    - CRT may be considered in those in NYHA functional class II with an EF ≤35%, irrespective of QRS duration, toreduce the risk of worsening of HF (Class IIb, Level C).

European Society of Cardiology (ESC) Guidelines on Device Therapy in Heart Failure
The 2010 focused update of ESC guidelines on device therapy in heart failure (Dickstein, et al., 2010) have the following recommendations for cardiac resynchronization therapy:

Recommendation in patients with heart failure in NYHA class III/IV:

- CRT-P/CRT-D is recommended to reduce morbidity and mortality for: NYHA class III/IV, LVEF ≤35%, QRS ≥120 ms, SR, optimal medical therapy, class IV patients should be ambulatory (Class I, Level A).

Recommendation in patients with heart failure in New York Heart Association function class II:

- CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression for: NYHA function class II, LVEF ≤35%, QRS ≥150 ms, SR, optimal medical therapy (Class I, Level A).

Recommendations in patients with heart failure and permanent atrial fibrillation:

- CRT-P/CRT-D should be considered to reduce morbidity for:
  - NYHA class III/IV, LVEF ≤ 35%, QRS ≥ 130 ms, pacemaker dependency induced by AV nodal ablation (Class IIa, Level B).
  - NYHA class III/IV, LVEF ≤ 35%, QRS ≥ 130 ms, slow ventricular rate and frequent pacing (i.e., ≥ 95% pacemaker dependence. (Class IIa, Level C).

Recommendations in patients with heart failure and a concomitant class I pacemaker indication:

- CRT-P/CRT-D is recommended to reduce morbidity for:
  - NYHA class III/IV, LVEF ≤35%, QRS ≥120 ms (Class I, Level B).
  - NYHA class III/IV, LVEF ≤35%, QRS <120 ms (Class IIa, Level C).
  - NYHA class II, LVEF ≤35%, QRS <120 ms (Class IIb, Level C).

National Institute for Health and Clinical Excellence (NICE) (United Kingdom)
The 2007 NICE technology appraisal guidance document titled "Cardiac Resynchronisation Therapy for the Treatment of Heart Failure" recommends CRT as a treatment option for people with heart failure who meet the following criteria:

- currently or have recently experienced NYHA Class III–IV symptoms
- in sinus rhythm either with a QRS duration of 150 ms or longer estimated by standard electrocardiogram or with a QRS duration of 120–149 ms estimated by electrocardiogram and mechanical dyssynchrony that is confirmed by echocardiography.
- LVEF ≤ 35%
- receiving optimal pharmacological therapy

Summary
Professional society recommendations have been published and/or updated in an effort to guide appropriate care/indications for a subset of patients for which evidence in the peer-reviewed literature and/or specialist clinical experience are available that support device implantation for cardiac resynchronization therapy (CRT) or biventricular pacing. Additionally, recently published professional society guidelines have outlined indications for which CRT or biventricular pacing is not indicated due to insufficient evidence in the published, peer-reviewed, scientific literature. Since some patients do not respond favorably after undergoing CRT, studies addressing optimal patient selection criteria for CRT are ongoing.

Triventricular pacing has been proposed as an alternative approach to improve the response rate in CRT recipients. There is a paucity of randomized controlled clinical trials or comparative studies in the peer-reviewed literature assessing the impact of triple-site resynchronization on long-term health outcomes in patients compared to conventional biventricular pacing.

Appendix A

The New York Heart Association (NYHA) classification of heart failure is a 4-tier system that categorizes patients based on subjective impression of the degree of functional compromise. The chart below defines the four NYHA functional classes. Advanced heart failure is categorized as NYHA Class III and Class IV.

Class I:	patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain; symptoms only occur on severe exertion

Class II:	patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain
Class III:	patients with cardiac disease resulting in marked limitation of physical activity; they are comfortable at rest; less than ordinary activity (e.g., mild exertion) causes fatigue, palpitation, dyspnea or anginal pain
Class IV:	patients with cardiac disease resulting in inability to carry on any physical activity without discomfort; symptoms of cardiac insufficiency or anginal syndrome is present at rest; if any physical activity is undertaken, discomfort is increased

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Covered when medically necessary:

CPT®* Codes	**Description**
33202	Insertion of epicardial electrode(s); open incision (eg, thoracotomy, median sternotomy, subxiphoid approach)
33203	Insertion of epicardial electrode(s); endoscopic approach (eg, thoracoscopy, pericardioscopy)
33207	Insertion of new or replacement of permanent pacemaker with transvenous electrode(s); ventricular
33208	Insertion of new or replacement of permanent pacemaker with transvenous electrode(s); atrial and ventricular
33211	Insertion or replacement of temporary transvenous dual chamber pacing electrodes (separate procedure)
33213	Insertion of pacemaker pulse generator only; with existing dual leads
33214	Upgrade of implanted pacemaker system, conversion of single chamber to dual chamber system (includes removal of previously placed generator, testing of existing lead, insertion of new lead, insertion of new pulse generator)
33217	Insertion of 2 transvenous electrodes, permanent pacemaker or cardioverter-defibrillator
33218	Repair of single transvenous electrode, permanent pacemaker or pacing cardioverter-defibrillator
33224	Insertion of pacing electrode, cardiac venous system, for left ventricular pacing, with attachment to previously placed pacemaker or pacing cardioverter-defibrillator pulse generator (including revision of pocket, removal, insertion, and/or replacement of existing generator)
33225	Insertion of pacing electrode, cardiac venous system, for left ventricular pacing, at time of insertion of pacing cardioverter-defibrillator or pacemaker pulse generator (for upgrade to dual chamber system) (List separately in addition to code for primary procedure)
33226	Repositioning of previously implanted cardiac venous system (left ventricular) electrode (including removal, insertion and/or replacement of existing generator)
33230	Insertion of pacing cardioverter-defibrillator pulse generator only; with existing dual leads
33231	Insertion of pacing cardioverter-defibrillator pulse generator only; with existing multiple leads
33240	Insertion of pacing cardioverter-defibrillator pulse generator only; with existing

	single lead
33249	Insertion or replacement of permanent pacing cardioverter-defibrillator system with transvenous lead(s), single or dual chamber

HCPCS Codes	Description
C1721	Cardioverter-defibrillator, dual chamber (implantable)
C1722	Cardioverter-defibrillator, single chamber (implantable)
C1777	Lead, cardioverter-defibrillator, endocardial single coil (implantable)
C1779	Lead, pacemaker, transvenous VDD single pass
C1785	Pacemaker, dual chamber, rate-responsive (implantable)
C1786	Pacemaker, single chamber, rate-responsive (implantable)
C1882	Cardioverter-defibrillator, other than single or dual chamber (implantable)
C1895	Lead, cardioverter-defibrillator, endocardial dual coil (implantable)
C1896	Lead, cardioverter-defibrillator, other than endocardial single or dual coil (implantable)
C1898	Lead, pacemaker, other than transvenous VDD single pass
C1899	Lead, pacemaker/cardioverter-defibrillator combination (implantable)
C1900	Lead, left ventricular coronary venous system
C2619	Pacemaker, dual chamber, non rate-responsive (implantable)
C2620	Pacemaker, single chamber, non rate-responsive (implantable)
C2621	Pacemaker, other than single or dual chamber (implantable)
G0448	Insertion or replacement of a permanent pacing cardioverter-defibrillator system with transvenous lead(s), single or dual chamber with insertion of pacing electrode, cardiac venous system, for left ventricular pacing

***Current Procedural Terminology (CPT®) ©2013 American Medical Association: Chicago, IL.**

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