



CIGNA MEDICAL COVERAGE POLICY

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Subject Biventricular Pacing/Cardiac Resynchronization Therapy (CRT)

Effective Date 8/15/2011
Next Review Date 8/15/2012
Coverage Policy Number 0174

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Implantable Cardioverter Defibrillator (ICD)
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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 congestive heart failure (CHF) and New York Heart Association (NYHA) classification of heart failure III or IV (See Appendix A) when ALL of the following criteria are met:

- left ventricular ejection fraction (LVEF) \leq 35%
- QRS duration \geq 120 milliseconds (ms)
- sinus rhythm or chronic atrial fibrillation (AF)
- optimal pharmacologic regimen before implantation, which may include the following, unless contraindicated:
 - aldosterone antagonists
 - angiotensin-converting enzyme (ACE) inhibitor
 - angiotensin receptor blocker (ARB)
 - beta blocker
 - digoxin
 - diuretics

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

congestive heart failure (CHF) and New York Heart Association (NYHA) classification of heart failure II (See Appendix A) when ALL of the following criteria are met:

- LVEF \leq 30%
- left bundle branch block with QRS duration \geq 130 ms
- sinus rhythm
- optimal pharmacologic regimen before implantation, which may include the following, unless contraindicated:
 - aldosterone antagonists
 - angiotensin-converting enzyme (ACE) inhibitor
 - angiotensin receptor blocker (ARB)
 - beta blocker
 - digoxin
 - diuretics

CIGNA does not cover the use of a biventricular pacemaker alone or combined with an implantable cardioverter defibrillator for CRT for the treatment of any other 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 moderate 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 most frequently reported complication of CRT is lead dislodgement, which occurs in approximately 9% of patients.

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.

Echocardiography for CRT Therapy

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 (Gorscan, et al., 2008).

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, an left ventricular ejection fraction (LVEF) \leq 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

As a condition of FDA approval, Boston Scientific must conduct two post-approval studies. One study will evaluate complications and long-term mortality benefits of CRT-D in patients with left bundle branch block identified through the National Cardiovascular Data Registry. The other will follow patients from the original MADIT-CRT clinical study every six months for five years to assess long-term mortality benefits of CRT-D versus. ICD (FDA, 2010).

Literature Review CRT in Advanced Heart Failure (NYHA Class III/IV)

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 advanced heart failure (NYHA Class III and IV), with or without ICD indications, left ventricular ejection fraction (LVEF) \leq 35%, QRS duration \geq 120 milliseconds (ms), sinus rhythm or chronic atrial fibrillation (AF), on an 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 2007 National Institute for Health and Clinical Excellence (NICE) (United Kingdom) 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 \leq 35%
- receiving optimal pharmacological therapy

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.

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 \geq 120 ms to $>$ 200 ms. All of the trials restricted enrollment to patients with reduced EFs ranging from \leq 35% to \leq 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).

Literature Review CRT in Mild Heart Failure (NYHA Class I/II)

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 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).

Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT): Tang et al. 2010 conducted a multicenter, double-blind, randomized, controlled study (n=1798), called the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT), to determine whether the addition of CRT to an ICD and optimal medical therapy would reduce mortality and the rate of hospitalization for heart failure, as compared with an ICD and optimal medical therapy alone, among patients with NYHA Class II or III symptoms, left ventricular ejection fraction of 30% or less from ischemic or nonischemic causes, and a wide QRS complex of 120 msec or more, sinus rhythm or permanent atrial fibrillation or flutter with a controlled ventricular rate. Mean follow-up was 40 +/- 20 months. Unlike most previous trials, this trial did not confine enrollment to patients with sinus rhythm, but allowed patients with atrial arrhythmias to participate. However, the number of patients who were not in sinus rhythm was only 12.8% (229/1798). The primary outcome, death from any cause or hospitalization for heart failure, was reduced in the ICD-CRT group compared to the ICD-alone group (33.2% versus 40.3%, p<0.001). There were significant reductions in both individual components of the primary outcome, overall mortality (20.8% versus 26.1%, p=0.003) and hospitalizations (19.5% versus 26.1%, p<0.001). When restricted to patients with NYHA class II heart failure, the improvements in the outcomes of mortality and hospitalizations remained significant. The mortality for class II patients in the ICD-CRT group was 15.5% versus 21.1% in the ICD-alone group (hazard ratio [HR] 0.71, 95% confidence interval [CI]: 0.56-0.91; p<0.006). Hospitalizations for class II patients occurred in 16.2% of patients in the ICD-CRT group compared to 21.1% in the ICD-alone group (HR 0.70, 95% CI: 0.55-0.89, p<0.003). At 30 days after device implantation, adverse events had occurred in 124 subjects in the ICD-CRT group, as compared with 58 in the ICD group (p<0.001). The authors reported that the addition of CRT to the use of an ICD and optimal medical therapy reduced rates of death and hospitalization for heart failure among patients who had NYHA class II or III heart failure with left ventricular systolic dysfunction and a wide QRS complex. These findings support the use of CRT along with an ICD and medical therapy in patients with NYHA class II or III heart failure, left ventricular systolic dysfunction, and a wide QRS complex.

Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT): The largest trial published to date is the ongoing Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial, a single-blind trial that randomized 1820 patients with NYHA class I/II CHF to an ICD alone or an ICD-CRT device (Moss, et al, 2009). The study was designed to determine whether CRT with biventricular pacing would reduce the risk of death or heart-failure events in patients with nonischemic cardiomyopathy, an ejection fraction of $\leq 30\%$, a QRS duration ≥ 130 msec, and NYHA Class I or II symptoms. Patients were randomly assigned in a 3:2 ratio to receive CRT plus an ICD (n=1089) or an ICD alone (n=731). A majority of the patients had ischemic heart disease (55%), 85% of the patients were classified as NYHA Class II, 71% of the patients had a left bundle branch block (LBBB), and 62% of the patients had never been hospitalized for heart failure prior to enrollment. MADIT-CRT patients had a mean LVEF of $24\pm 5\%$ and a mean QRS of 158 ± 20 ms. The majority of patients were medicated on heart failure drugs: 96% of the patients were on an angiotensin converting enzyme (ACE) or angiotensin receptor blockers (ARB); 93% were on a beta blocker; 75% were on a diuretic; 32% were on an aldosterone antagonist; and 67% were on a statin. The primary end point was death from any cause or a nonfatal heart-failure event (whichever came first). For the primary analysis, the hazard ratio of 0.66 indicates that there was a 34% reduction in the risk of death or nonfatal heart failure (whichever came first) among patients in the CRT–ICD group, as compared with those in the ICD-only group. The primary endpoint for all patients was reached by 17.2% of patients in the ICD-CRT group compared to 25.3% of patients in the ICD-alone group (p=0.001). The death rate for all patients was similar between groups. The ICD-CRT group had 13.9% hospitalizations for CHF versus 22.8% for the ICD alone group. There was a total of 173 crossovers (9.5%) and 99 dropouts (5.4%). These dropouts/crossovers were not equally balanced between groups. The ICD-alone group had a dropout/crossover rate of 20% (146/731) compared to a rate of 11.6% (126/1089) for the ICD-CRT group. There was limited enrollment of NYHA Class I patients (~15%). Approximately 40% of the patients were previously hospitalized for heart failure, and 10% of the patients were previously NYHA Class III-IV greater than 3 months prior to enrollment. Serious adverse events were infrequent in the two groups. The authors reported that CRT combined with ICD decreased the risk of heart-failure events in relatively asymptomatic patients with a low ejection fraction and wide QRS complex. The methodological flaws associated with this study preclude the ability to generalize findings and draw strong conclusions regarding the impact on health outcomes.

A sub analysis of the MADIT-CRT trial data of patients with NYHA Class I/II heart failure demonstrated that compared with non-LBBB patients (those with right BBB or nonspecific intraventricular conduction

disturbances), patients with LBBB QRS morphology showed significant clinical benefit from CRT-D therapy, as measured by reduced risk of heart failure event or death and risk of ventricular tachycardia/fibrillation or death. Non-LBBB patients did not benefit clinically despite a significant reduction in left ventricular volumes. These findings formed the basis for recent Food and Drug Administration approval of new broadened indications for CRT in mild or asymptomatic heart failure patients with LBBB. Further research investigating the rationale, mechanisms, and clinical benefit is needed to determine whether CRT therapy should be pursued in non-LBBB patients (Zareba, et al., 2011).

Solomon et al. 2010 reported further on the results of the MADIT-CRT trial using echocardiographic changes to evaluate whether the improvement in outcomes with CRT plus an ICD was associated with favorable alterations in cardiac size and function. Echocardiographic studies were obtained at baseline and 12 months later in 1372 of the MADIT-CRT subjects. Changes in cardiac size and performance between treatment groups were compared and the relationship between these changes was assessed over the first year, as well as subsequent outcomes. Compared with the ICD-only group, the CRT-plus-ICD group had greater improvement in left ventricular end-diastolic volume index (-26.2 versus -7.4 mL/m²), left ventricular end-systolic volume index (-28.7 versus -9.1 mL/m²), left ventricular ejection fraction (11% versus 3%), left atrial volume index (-11.9 versus -4.7 mL/m²), and right ventricular fractional area change (8% versus 5%; p<0.001 for all). Improvement in end-diastolic volume at one year was predictive of subsequent death or heart failure, with adjustment for baseline covariates and treatment group; each 10% decrease in end-diastolic volume was associated with a 40% reduction in risk (p<0.001). The authors of this analysis reported that CRT resulted in significant improvement in cardiac size and performance compared with an ICD-only strategy in those subjects with mildly symptomatic heart failure.

An important determinant of successful cardiac resynchronization therapy for heart failure is the position of the left ventricular (LV) pacing lead. Singh et al. 2011 analyzed the impact of the LV lead position on outcome in patients randomized to cardiac resynchronization-defibrillation in the MADIT-CRT study. The LV lead position was assessed in 799 patients with a follow-up of 29±11 months. The extent of CRT benefit was similar for leads in the anterior, lateral, or posterior position (p=0.652). The apical lead location compared with leads located in the nonapical position (basal or midventricular region) was associated with a significantly increased risk for heart failure/death (p=0.019). The benefit from CRT was similar for LV leads positioned along the anterior, lateral, or posterior wall. LV leads positioned in the apical region were associated with an unfavorable clinical outcome, suggesting that this lead location be avoided in CRT.

Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE): In a multicenter, randomized controlled trial, REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE), Linde et al. (2008) studied whether CRT improves ventricular structure and function in patients with asymptomatic and mildly symptomatic heart failure. A total of 610 patients with NYHA functional class I or II heart failure with a QRS ≥ 120 ms and a LVEF ≤ 40% received a CRT device (±defibrillator) and were randomly assigned to active CRT (CRT-ON; n= 419) or control (CRT-OFF; n=191) for 12 months. The primary end point was the heart failure clinical composite response, which scores patients as improved, unchanged, or worsened. The prospectively powered secondary end point was LV end-systolic volume index. Hospitalization for worsening HF was evaluated in a prospective secondary analysis of health care use. Of the 419 patients assigned to the CRT-on group, 16% worsened compared to 21% of the 191 patients assigned to the CRT-off group, a difference that was not statistically significant (p=0.10). Therefore, the trial results did not meet the primary outcome. There was no significant difference in the number of hospitalizations between the two groups, but the time to first hospitalization was significantly delayed in the CRT-on group (hazard ratio 0.47, p=0.03). Left ventricular end-systolic volume index was evaluated as a measure of left ventricular remodeling. Patients assigned to the CRT-on group experienced a greater improvement in this outcome. These results suggest that while CRT can improve left ventricular remodeling, this improvement did not result in a significant improvement in clinical symptoms at one year.

Multicenter InSync ICD Randomized Clinical Evaluation II (MIRACLE ICD II): The Multicenter InSync ICD Randomized Clinical Evaluation II (MIRACLE ICD II) was a randomized, double-blind, parallel-controlled clinical trial of CRT in NYHA Class II heart failure patients on optimal medical therapy with a left ventricular (LV) ejection fraction ≤ 35%, a QRS ≥ 130 ms, and a class I indication for an ICD. One hundred eighty-six patients were randomized: 101 to the control group (ICD activated, CRT off) and 85 to the CRT group (ICD activated, CRT on). End points included peak VO₂, VE/CO₂, NYHA class, quality of life, 6-minute walk distance, LV volumes and ejection fraction, and composite clinical response. Compared with the control group at six months, no

significant improvement was noted in peak VO₂, yet there were significant improvements in ventricular remodeling indexes, specifically LV diastolic and systolic volumes (p=0.04 and p=0.01, respectively), and LV ejection fraction (p=0.02). CRT patients showed statistically significant improvement in VE/CO₂ (p=0.01), NYHA class (p=0.05), and clinical composite response (p=0.01). No significant differences were noted in six-minute walk distance or quality of life scores. The authors reported that these observations must be confirmed by future randomized controlled trials of mildly symptomatic heart failure patients before the indication for resynchronization therapy is extended to this population (Abraham et al, 2004).

Meta-Analysis and Technology Assessment: Al-Majed et al. 2011 conducted an updated meta-analysis of trials of CRT. The meta-analysis included randomized, controlled trials of CRT compared with usual care and right or left ventricular pacing in adults with heart failure and a LVEF ≤ 40% regardless of their baseline NYHA functional class of heart failure. This study focused on the analysis of trials with Class I/II heart failure patients. Three trials (2616 patients) included patients with NYHA class I or II symptoms exclusively (Moss, et al., 2009; Linde, et al., 2008; Abraham, et al., 2004), and two trials (158 patients) included predominantly patients with NYHA class I or II symptoms (78% and 69% of patients) but did not report outcomes separately for strata of NYHA classes. One trial (798 patients) included predominantly patients with NYHA class II symptoms (80%; the remaining 20% had class III symptoms) and reported outcomes separately for strata of NYHA classes, not permitting the ability to split the data into appropriate NYHA subgroups (Tang, et al., 2010). There was a significant mortality benefit associated with CRT on combined analysis (six trials, 4572 participants; RR 0.83 [95% CI: 0.72—0.96]). This mortality benefit was driven largely by the results of the RAFT trial, which had the most number of events and was given the greatest weight in combined analysis. There was also a significant reduction in heart failure hospitalizations associated with CRT use (4 trials, 4349 participants; RR, 0.71 [CI: 0.57—0.87]). There were no significant benefits reported for quality of life, functional status, or progression to more advanced stages of heart failure. The reported limitation of this meta-analysis was that the subgroup analyses were underpowered and lack data for persons with NYHA Class I symptoms, atrial fibrillation, chronic kidney disease, or right bundle branch block. The authors reported that the data supports the expansion of indications for CRT to less symptomatic patients with heart failure who have LVEF less than 0.35 and QRS duration greater than 120 ms and are in sinus rhythm. However, 85% of less symptomatic patients in these trials had NYHA II symptoms, and high-quality evidence to support this therapy in patients with asymptomatic left ventricular dysfunction or NYHA Class I symptoms is inconclusive.

Summary: Evidence in the published peer-reviewed literature, including randomized controlled trials and a meta-analysis, 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.

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.

Evidence in the published peer-reviewed literature indicates that optimal candidates for biventricular resynchronization therapy include a subgroup of patients with mild heart failure (NYHA Class II), with or without ICD indications, left ventricular ejection fraction (LVEF) ≤ 30%, left bundle branch block with QRS duration ≥ 130 milliseconds (ms), sinus rhythm, on an optimal pharmacologic regimen before implantation. 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.

Literature Review CRT Narrow QRS Interval

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 benefits patient outcomes.

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. (2006) 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 $\leq 35\%$. 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.

Professional Societies/Organizations

The 2009 focused update to the 2005 guideline for the diagnosis and management of chronic heart failure in adults published by the ACC/AHA Task Force on Practice Guidelines, in collaboration with the American College of Chest Physicians and International Society for Heart and Lung Transplantation, addresses CRT and CRT/ICD therapy for the treatment of heart failure (Hunt, et al., 2009). The authors recommend that, "Patients with LVEF of $\leq 35\%$, sinus rhythm, and NYHA functional Class III ambulatory Class IV symptoms despite recommended optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as QRS duration greater than or equal to 0.12 seconds, should receive cardiac resynchronization therapy, with or without an ICD, unless contraindicated." (Class I recommendation. Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful, and/or effective; Level of Evidence A. Data are derived from multiple randomized clinical trials or meta-analysis). The authors recommend that results from ongoing or future clinical trials are needed before recommending CRT for patients with right bundle-branch block, minor conduction abnormality, AF, and pacemaker dependence, as well as inadequate medical therapy.

The American College of Cardiology (ACC)/American Heart Association (AHA) and North American Society for Pacing (NASPE) guideline for device-based therapy for cardiac rhythm abnormalities (Epstein, et al., 2008) addresses recommendations for CRT in patients with severe systolic heart failure. This guideline is an update to the 2002 guideline. The committee reviewed and ranked evidence supporting current recommendations, with the weight of evidence ranked as Level A if the data were derived from multiple randomized clinical trials that involved a large number of individuals, Level B when data were derived either from a limited number of trials that involved a comparatively small number of patients or from well-designed data analyses of nonrandomized studies or observational data registries. Evidence was ranked as Level C when the consensus of experts was the primary source of the recommendation. Recommendations are classified as Class I, Class IIa, Class IIb, and Class III. Class I is defined as conditions for which there is evidence and/or general agreement that a given

procedure or treatment is beneficial, useful and effective; Class II is defined as conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. Class II recommendations are further defined as IIa, for which the weight of evidence/opinion is in favor of usefulness/efficacy, and Class IIb, for which the usefulness/efficacy is less well-established by evidence/opinion. Class III is defined as conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful. This guideline has not been updated since 2008.

Class I

- For patients who have LVEF \leq 35%, a QRS duration \geq 0.12 seconds, and sinus rhythm, CRT with or without an ICD is indicated for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms with optimal recommended medical therapy (Level of evidence A).

Class IIa

- For patients who have LVEF \leq 35%, a QRS duration \geq 0.12 seconds, and AF, CRT with or without an ICD is reasonable for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy (Level of Evidence B).
- For patients with LVEF \leq 35% with NYHA functional Class III or ambulatory Class IV symptoms who are receiving optimal recommended medical therapy and who have frequent dependence on ventricular pacing, CRT is reasonable (Level of evidence C).

Class IIb

- For patients with LVEF \leq 35% with NYHA functional Class I or II symptoms who are receiving optimal recommended medical therapy and who are undergoing implantation of a permanent pacemaker and/or ICD with anticipated frequent ventricular pacing, CRT may be considered (Level of evidence C).

Class III

- CRT is not indicated for asymptomatic patients with reduced LVEF in the absence of other indications for pacing (Level of evidence B).
- CRT is not indicated for patients whose functional status and life expectancy are limited predominantly by chronic noncardiac conditions (Level of evidence C).

The ACC/AHA Task Force on Practice Guidelines and the European Society of Cardiology (ESC) Committee for Practice Guidelines, developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society, updated the practice guideline for the management of patients with AF. In general, the guideline states, "For those with impaired LV function not due to tachycardia, a biventricular pacemaker with or without defibrillator capability should be considered. Upgrading to a biventricular device should be considered for patients with heart failure and an right ventricle (RV) pacing system who have undergone atrioventricular node ablation" (Fuster, et al., 2006). This guideline has not been updated since 2006.

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 \leq 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.

Patient selection criteria for CRT were reported in an AHA Science Advisory by Strickberger et al. (2005). The inclusion criteria for the published trials that have randomized patients to CRT included patients with sinus rhythm, a QRS complex duration > 120–130 ms, heart failure resulting from systolic dysfunction with NYHA Class III or IV symptoms, and optimal medical treatment for heart failure, including beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, and diuretics. Based on the results of the studies and the inclusion criteria, the evidence supports CRT in patients with systolic dysfunction and heart failure resulting from either ischemic or nonischemic cardiomyopathy who have an LVEF ≤ 35%; are in NYHA Class III or IV; are on maximal medical therapy; have a QRS complex duration > 120 ms; and are in sinus rhythm. The authors reported a variety of unresolved issues, including the role of CRT for patients with NYHA Class II symptoms or with AF, identification of responders to CRT, and the role of CRT in other categories of patients.

Summary

The evidence in the peer-reviewed published literature supports the use of cardiac resynchronization therapy (CRT) or biventricular pacing to alleviate some of the symptoms of severe heart failure (i.e., NYHA Class III/IV) in patients who have evidence of ventricular asynchrony, poor cardiac function and failed optimal drug therapy. The clinical studies report improved cardiac function, exercise tolerance, and quality of life in patients with severe heart failure. These studies report a decrease in heart failure-related hospitalizations and a decrease in mortality. Similar findings are reported in clinical studies of CRT plus ICD system (CRT-D) therapy in patients with severe heart failure, ventricular asynchrony, and risk of life-threatening ventricular arrhythmias. Numerous randomized clinical trials provide data to identify appropriate patients for CRT or CRT-D therapy. Optimal candidates for CRT or CRT-D therapy have heart failure with LVEF ≤ 35%, a QRS complex ≥ 120 ms, sinus rhythm or chronic atrial fibrillation (AF) and NYHA functional Class III or IV despite maximal medical therapy for heart failure.

Evidence in the peer-reviewed literature indicates that optimal candidates for CRT or biventricular pacing include a subgroup of patients with mild heart failure (NYHA Class II), with or without ICD indications, left ventricular ejection fraction (LVEF) ≤ 30%, left bundle branch block with QRS duration ≥ 130 milliseconds (ms), sinus rhythm, on an optimal pharmacologic regimen before implantation. 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.

There is insufficient evidence in the published, peer-reviewed, scientific literature demonstrating the safety and efficacy of CRT therapy in other categories of patients. Further randomized controlled studies with larger sample sizes are required in order to validate CRT therapy in other categories of patients.

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
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Coding/Billing Information

Note: This list of codes may not be all-inclusive.

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 or replacement of permanent pacemaker with transvenous electrode(s); ventricular
33208	Insertion or replacement of permanent pacemaker with transvenous electrode(s); atrial and ventricular
33211	Insertion or replacement of temporary transvenous dual chamber pacing electrodes
33213	Insertion or replacement of pacemaker pulse generator; dual chamber
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 transvenous electrode; dual chamber (two electrodes) permanent pacemaker or dual chamber 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 a pocket, removal, insertion and /or replacement of a 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 (including upgrade to dual chamber system)
33226	Repositioning of previously implanted cardiac venous system (left ventricular) electrode (including removal, insertion and/or replacement of a generator)
33240	Insertion of single or dual chamber pacing cardioverter-defibrillator pulse generator
33249	Insertion or repositioning of electrode lead(s) for single or dual chamber pacing cardioverter-defibrillator and insertion of pulse generator

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)
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, nonrate-responsive (implantable)

C2620	Pacemaker, single chamber, nonrate-responsive (implantable)
C2621	Pacemaker, other than single or dual chamber (implantable)

ICD-9-CM Diagnosis Codes	Description
398.91	Rheumatic heart failure (congestive)
402.01	Hypertensive heart disease, malignant, with heart failure
402.11	Hypertensive heart disease, benign, with heart failure
402.91	Hypertensive heart disease, unspecified, with heart failure
404.01	Hypertensive heart and renal disease, malignant, with heart failure
404.03	Hypertensive heart and renal disease, malignant, with heart failure and renal failure
404.11	Hypertensive heart and renal disease, benign, with heart failure
404.13	Hypertensive heart and renal disease, benign, with heart failure and renal failure
404.91	Hypertensive heart and renal disease, unspecified, with heart failure
404.93	Hypertensive heart and renal disease, unspecified, with heart failure and renal failure
425.1	Hypertrophic obstructive cardiomyopathy
425.4	Other primary cardiomyopathies
427.1	Paroxysmal ventricular tachycardia
427.41	Ventricular fibrillation
427.5	Cardiac arrest
428.0-428.9	Heart failure
997.1	Cardiac complications

Experimental/Investigational/Unproven and Not Covered

ICD-9-CM Diagnosis Codes	Description
410.00-410.92	Acute myocardial infarction
412	Old myocardial infarction
414.01	Coronary atherosclerosis of native coronary artery
414.8	Other specified forms of chronic ischemic heart disease
426.0	Atrioventricular block, complete
426.13	Other second degree atrioventricular block
427.31	Atrial fibrillation
427.81	Sinoatrial node dysfunction
427.89	Other specified cardiac dysrhythmias
429.3	Cardiomegaly
780.2	Syncope and collapse
996.04	Mechanical complication due to automatic implantable cardiac defibrillator

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	8/15/2008	0174	Biventricular Pacing/Cardiac

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