



Name of Policy:

**Bi-Ventricular Pacemakers (Cardiac Resynchronization Therapy)
for the Treatment of Heart Failure**

Policy #: 055
Category: Surgery

Latest Review Date: April 2014
Policy Grade: A

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

- 1. In accordance with generally accepted standards of medical practice; and*
- 2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
- 3. Not primarily for the convenience of the patient, physician or other health care provider; and*
- 4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Cardiac resynchronization therapy (CRT), which consists of synchronized pacing of the left and right ventricles, is intended to treat patients with heart failure and dyssynchronous ventricular contractions. Treatment involves placement of a device that paces both ventricles and which coordinates ventricular pacing to maximize cardiac pumping function and left ventricular ejection fraction (LVEF).

It is estimated that 20%-30% of patients with heart failure (HF) have intraventricular conduction disorders resulting in a disorganized contraction pattern and a wide QRS interval on the electrocardiogram (ECG). This abnormality appears to be associated with increased morbidity and mortality. Biventricular pacemakers using three leads (one in the right atrium and one in each ventricle) have been investigated as a technique to coordinate the contraction of the ventricles, thus improving patients' hemodynamic status. Two strategies are being explored: incorporating biventricular pacing into automatic implantable cardiac defibrillators and the development of stand-alone biventricular pacemakers. While initial studies focused on use of biventricular pacemakers for patients with New York Heart Association (NYHA) class III and IV heart failure, more recent studies are evaluating use of biventricular pacemakers (cardiac resynchronization therapy [CRT]) in patients with NYHA Class I and II heart failure.

A biventricular pacing system consists of a pulse generator that is implanted in the subcutaneous tissue of the chest. The generator is connected to the heart by three leads that deliver electrical impulses. One lead is placed in the right atrium and the other two are placed overlying the R and L ventricles in a cardiac vein. When impulses are generated, the right and left ventricles will be stimulated simultaneously resulting in synchronization of the ventricles. By coordinating the contractions of the ventricles, the hemodynamic status of the patient improves.

Currently, there is a stand-alone biventricular pacemaker approved by the U.S. Food and Drug Administration (FDA), the InSync[®] Biventricular Pacing System by Medtronic for the treatment of patients with New York Heart Association (NYHA) Class III or IV heart failure, on a stable pharmacologic regimen, who also have a QRS duration of ≥ 130 msec and a left ventricular ejection fraction of $\leq 35\%$. In addition, frequently these patients have other ventricular disorders, which have led to the incorporation of a biventricular pacemaker into an automatic implantable cardiac defibrillator. In 2002, two companies, Guidant (CONTAK CD[®] CRT-D System) and Medtronic (InSync[®] ICD Model 7272), received FDA approval for combined cardiac resynchronization therapy defibrillators for patients at high risk of sudden cardiac death due to ventricular arrhythmias and who have NYHA Class III or IV heart failure with left ventricular ejection fraction of $< 35\%$, QRS duration ≥ 130 ms (≥ 120 ms for Guidant) and remain symptomatic despite a stable, heart failure drug therapy.

In September 2010, the FDA expanded the indications for CRT to include patients with Class I and II heart failure. In addition to NYHA Class I/II heart failure, indications for CRT in mild heart failure include a left ventricular (LV) ejection fraction of less than 30% and a QRS duration of 130 msec or greater.

In 2005, the InSync Sentry system received FDA approval through the supplemental premarket approval (PMA) process. This combined biventricular pacemaker/AICD is also equipped to monitor intrathoracic fluid levels using bioimpedance technology, referred to as OptiVol Fluid

Status monitoring. Bioimpedance measures, defined as the electrical resistance of tissue to flow of current, are performed many times per day using a vector from the right ventricular coil on the lead in the right side of the heart to the implanted pacemaker devices; changes in bioimpedance reflect intrathoracic fluid status and are evaluated based on a computer algorithm. For example, changes in a patient's daily average of intrathoracic bioimpedance can be monitored; differences in the daily average compared to a baseline are reported as the OptiVol Fluid Index. It has been proposed that these data may be used as an early warning system of cardiac decompensation, or provide additional feedback enabling a physician to further tailor medical therapy.

Policy:

Effective for dates of service on or after July 6, 2014:

Biventricular Pacemakers, with or without an accompanying implantable cardiac defibrillator (i.e., a combined biventricular pacemaker/ICD) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of heart failure (HF) when all of the following criteria are met:

New York Heart Association (NYHA) Class III or IV.

- Left ventricular ejection fraction $\leq 35\%$.
- Sinus rhythm
- QRS duration of ≥ 120 msec-130 msec.*
- Patients treated with a stable pharmacological medical regimen prior to implant, such as an angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin receptor blocker) and a beta blocker (or angiotensin receptor blocker), digoxin and/or diuretics.

New York Heart Association (NYHA) Class II

- Left ventricular ejection fraction $\leq 30\%$
- Sinus rhythm
- QRS duration of ≥ 120 -130* msec, and
- Patients treated with a stable pharmacological medical regimen prior to implant, such as an angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin receptor blocker) and a beta blocker (or angiotensin receptor blocker), digoxin and/or diuretics

*The FDA-labeled indications for QRS duration vary by device. For some devices, FDA approval is based on QRS duration of ≥ 130 (e.g., InSync® device) while for others, it is based on QRS duration ≥ 120 msec (e.g., CONTAK CD® CRT-D System). These differences in QRS duration arise from differences in the eligibility criteria in the trials on which the FDA approval is based.

A combined biventricular pacemaker and implantable cardiac defibrillator(ICD) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for patients who meet criteria for BOTH a biventricular pacemaker and an ICD. Please see policy # 168 (Cardiac Defibrillators) for criteria for the ICD.

Biventricular pacemakers, with or without an accompanying implantable cardiac defibrillator do not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational** for the following indications:

- Treatment for patients with NYHA class I heart failure
- Unstable angina, myocardial infarction, prior coronary artery revascularization or angioplasty within the past 3 months

Intrathoracic fluid monitoring sensor as a component of a biventricular pacemaker does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Triple-site (triventricular) CRT, using an additional pacing lead does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Effective for dates of service prior to July 6, 2013:

Biventricular Pacemakers, with or without an accompanying implantable cardiac defibrillator (i.e., a combined biventricular pacemaker/ICD) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of heart failure (HF) when all of the following criteria are met:

New York Heart Association (NYHA) Class III or IV.

- Left ventricular ejection fraction $\leq 35\%$.
- QRS duration of ≥ 120 msec-130 msec.*
- Patients who remain symptomatic despite stable pharmacological medical regimen prior to implant, including an ACE inhibitor (or an angiotensin receptor blocker) and a beta-blocker if tolerated, digoxin and diuretics

New York Heart Association (NYHA) Class II

- Left ventricular ejection fraction $\leq 35\%$
- Sinus rhythm
- QRS duration of ≥ 120 -130* msec, and
- Patients treated with a stable pharmacological medical regimen prior to implant, such as an angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin receptor blocker) and a beta blocker (or angiotensin receptor blocker), digoxin and/or diuretics

*The FDA-labeled indications for QRS duration vary by device. For some devices, FDA approval is based on QRS duration of ≥ 130 (e.g., InSync® device) while for others, it is based on QRS duration ≥ 120 msec (e.g., CONTAK CD® CRT-D System). These differences in QRS duration arise from differences in the eligibility criteria in the trials on which the FDA approval is based.

A combined biventricular pacemaker and implantable cardiac defibrillator(ICD) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for patients who meet

criteria for **BOTH** a biventricular pacemaker and an ICD. **Please see policy # 168 (Cardiac Defibrillators) for criteria for the ICD.**

Biventricular pacemakers, with or without an accompanying implantable cardiac defibrillator do not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational** for the following indications:

- Treatment for patients with NYHA class I heart failure
- Unstable angina, myocardial infarction, prior coronary artery revascularization or angioplasty within the past 3 months

Intrathoracic fluid monitoring sensor as a component of a biventricular pacemaker does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Biventricular pacemakers and combined biventricular pacemakers/cardiac defibrillators

Does CRT improve outcomes for patients with heart failure?

Efficacy of CRT (cardiac resynchronization therapy) in advanced heart failure (New York Heart Association [NYHA] Class III/IV)

Use of biventricular pacemakers with or without accompanying implantable cardiac defibrillator (ICD) for selected patients with advanced heart failure is supported by a large body of clinical trial evidence. For patients with the following characteristics, this treatment receives a class I recommendation in the 2005 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the diagnosis and management of patients with heart failure, supported by the "A" level of evidence:

- Left-ventricular ejection fraction $\leq 35\%$
- Sinus rhythm
- New York Heart Association (NYHA) functional class III or IV despite optimal medical therapy
- Cardiac dyssynchrony as defined as a QRS >120 msec
- No contraindications for biventricular pacing

The current ACC/AHA guideline is accompanied by a review of the evidence, which states that more than 4,000 patients have been evaluated in randomized, clinical trials (RCTs) and that these

trials establish benefit for CRT in this patient population in improving functional status and exercise capacity.

A 2009 TEC Assessment of cardiac resynchronization therapy (CRT) in mild heart failure summarized five of the larger trials of CRT for advanced heart failure, showing that CRT improves quality of life (QoL) and functional status for patients with Class III and Class IV heart failure. Four of the five trials reported improvements in functional status for the CRT group. Similarly, four of the trials reported QoL measures, with all four showing significant improvements for the CRT group. Hospitalizations were reduced in two of the four trials, with an additional two trials reporting no difference in hospitalizations. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, which had the highest enrollment and the longest follow-up, reported a significant improvement in mortality. The other trials reported lower mortality for the CRT group, which did not reach statistical significance.

A systematic review of nine RCTs of CRT in Class III/IV heart failure was published in 2004. This quantitative analysis revealed the following conclusions: 1) improvement of 3.5% in left ventricular ejection fraction (LVEF); 2) improved QoL, with weighted mean difference on the Minnesota Living with Heart Failure Questionnaire of 7.6 points (0–100 scale); 3) improved functional capacity and a reduction in all-cause mortality of 21%. This analysis also found some evidence that cardiac morphology may be improved, suggesting that CRT may prevent, delay, or even reverse the changes in morphology resulting from chronic heart failure (reverse remodeling).

Efficacy of CRT in mild heart failure (NYHA Class I/II)

Evaluation of CRT in mild heart failure was originally based on a 2009 TEC Assessment. There is less evidence on treatment of mild heart failure compared to that for advanced heart failure, but clinical trial evidence is available. At least four RCTs enrolling over 3,000 patients, with follow-up ranging from six months to 2.4 years, have been published to date. A summary of the major RCTs in mild heart failure is provided.

MADIT-CRT trial

The largest trial published to date was the Multicenter Automatic Implantation Trial – Cardiac Resynchronization (MADIT-CRT) trial, a single-blind trial that randomized 1,820 patients with NYHA Class I/II heart failure to an ICD alone or an ICD-CRT device. The MADIT-CRT trial reported a reduction for the ICD-CRT group on the primary outcome, i.e., death or acute heart failure exacerbation. The primary endpoint was reached by 17.2% of patients in the ICD-CRT group compared to 25.3% of patients in the ICD-alone group. The first component of the composite outcome, acute heart failure events, occurred in 22.8% of patients in the ICD-alone group compared with 13.9% of patients in the ICD-CRT group (relative risk reduction [RRR]: 39%; absolute risk reduction [ARR]: 8.9%; number needed to treat [NNT]: 11.2). This difference in acute heart failure events accounted entirely for the difference on the primary composite outcome. The death rate was similar between groups.

A follow-up publication from the MADIT-CRT trial was published in 2011 and analyzed the reduction in recurrent heart failure events. This analysis supplemented the original MADIT-CRT outcome of time to first heart failure event, by comparing total heart failure events during an average follow-up of 2.6 years. Over this time period, there was a 38% relative reduction in heart

failure events in the CRT group (hazard ratio [HR] 0.62; 95% confidence interval [CI]: 0.45-0.85; p=0.003). On subgroup analysis, the benefit was evident in patients with left bundle branch block (HR: 0.50; 95% CI: 0.33-0.76; p=0.001) but not in patients without left bundle branch block (HR: 0.99; 95% CI: 0.58-1.69; p=0.96).

RAFT trial

A second, large RCT was the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial or (RAFT) trial, which randomized 1,798 patients with Class II/III heart failure to ICD-CRT or ICD alone, with a mean follow-up 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% (229/1,798). The RAFT trial was included in a 2011 TEC Assessment. On formal quality assessment as part of the TEC Assessment, this trial met all quality indicators and was given a “good” quality rating.

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% vs. 40.3%, respectively; p<0.001). There were significant reductions in both individual components of the primary outcome, overall mortality (20.8% vs. 26.1%; p=0.003) and hospitalizations (19.5% vs. 26.1%, all respectively; 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 (HR: 0.71; 95% 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).

Subgroup analyses from the RAFT trial reported that female gender, QRS duration equal to or greater than 150 msec, LVEF less than 20%, and QRS morphologic features were predictive of benefit. Of these factors, the QRS duration was the strongest factor. Patients with a QRS duration equal to or greater than ≥ 150 msec had a relative risk (RR) for the primary outcome of approximately 0.50, compared with a RR of approximately 1.0 for patients with a QRS duration less than 150 msec (p=0.003 for difference between RRs). There was a trend for greater improvement in patients with sinus rhythm compared to patients with atrial arrhythmias, but this difference did not reach statistical significance.

REVERSE trial

The Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial enrolled a total of 610 patients, all of whom received a CRT device. Patients were randomized to CRT-ON or CRT-OFF for a period of 12 months in double-blind fashion. The primary outcome was a composite measure that classified patients as improved, unchanged, or worse. There were no significant differences reported on this primary outcome. There was a decrease in hospitalizations for heart failure in the CRT-ON group (4.1%, 17/419) compared with the CRT-OFF group (7.9%, 15/191). Changes in functional status, as measured by the six-minute walk, were similar between groups. Quality of life, as measured by the Minnesota Living with Heart Failure Questionnaire, was also similar between groups.

Long-term follow-up from the REVERSE trial subjects who were initially randomized to CRT-ON were published by Linde et al in 2013. At a mean follow up time of 54.8 months, 53 patients died, with death due to heart failure in 21 (40%), sudden cardiac death in 10 (19%), and for noncardiac causes in 22 (42%). Annualized and five-year rates of the composite outcome of death or first heart failure hospitalization were 6.4% and 28.1%, respectively.

MIRACLE ICD trial

The Multicenter InSync ICD Randomized Clinical Evaluation MIRACLE ICD study was the smallest of the three studies, enrolling 186 patients with Class II heart failure and an indication for an ICD in an unblinded fashion. Patients were randomized to ICD/CRT-ON versus ICD/CRT-OFF and followed for six months. There was no difference in the primary outcome of peak oxygen uptake between groups. There were also no differences reported between groups on the secondary outcomes of functional status, as measured by the six-minute walk, QoL, as measured by the Minnesota Living with Heart Failure Questionnaire, and NYHA heart failure class.

Systematic Reviews of CRT for heart failure

Numerous systematic reviews and meta-analyses have been published on CRT for heart failure. The majority compare CRT to medical management and report that outcomes are improved for patients with advanced heart failure and for patients with mild heart failure. For example, a meta-analysis of 25 trials of CRT was published in February 2011 by Al-Majed et al. This study focused on the analysis of trials with Class I/II heart failure patients, identifying six trials treating 4,572 patients. There was a significant mortality benefit associated with CRT on combined analysis (six trials, 4,572 participants; RR 0.83 [95% CI: 0.72 to 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 (four trials, 4,349 participants; RR, 0.71 [CI: 0.57 to 0.87]). There were no significant benefits reported for quality of life, functional status, or progression to more advanced stages of heart failure.

A systematic review and meta-analysis by Chen et al published in 2013, evaluated studies that compared CRT plus implantable cardioverter-defibrillator (CRT-D) to ICD therapy alone. The authors included eight RCTs including 5674 patients comparing the efficacy of CRT-D with ICD therapy that met their inclusion criteria. Follow-up in these studies ranged from three to twelve months. In pooled analysis, CRT-D was associated with lower mortality compared with ICD therapy alone (pooled OR=0.80; 95% CI, 0.67 to 0.95); and was also associated with a lower hospitalization rate (OR=0.70; 95% CI, 0.6 to 0.81). On subgroup analysis of studies that reported mortality at three- to six-month follow-up, there was a trend toward mortality improvement with CRT-D, but this difference was not statistically significant (pooled OR=0.73; 95% CI, 0.46-1.18). Longer-term follow up outcomes of greater than one year were not reported in the included trials.

Adverse Effects of CRT placement

Complications in the main RCTs were not uniformly reported; however, each trial contained some information on short- and long-term complications. Short-term complication rates ranged from 4–22%, with lead dislodgement and hematoma at the access site most common. Long-term

complications were reported by two of the trials, with rates of 16% and 35%. The majority of these long-term complications were lead dislodgement.

A systematic review and meta-analysis was published in 2011 that focused on complications from CRT treatment. This review included seven trials of CRT treatment that reported on in-hospital mortality and complications related to device placement. In all seven CRT trials, the device was placed percutaneously without a thoracotomy. In-hospital mortality occurred at a rate of 0.3%, and 30-day mortality was 0.7%. The most common complications were related to placement of the left ventricular (LV) lead. Lead dislodgement occurred in 5.9% of patients. Other LV lead placement complications included coronary vein dissection in 1.3% and coronary vein perforation in 1.3%. Pneumothorax occurred in 0.9% of patients, and hematoma at the insertion site occurred in 2.4% of patients.

Conclusions

There is a large body of clinical trial evidence that supports the use of CRT in patients with NYHA Class III/IV heart failure. These trials establish that CRT treatment leads to reduced mortality, improved functional status, and improved QoL.

For patients with milder heart failure, at least four RCTs of CRT have been published in the literature. A mortality benefit was reported by one of the four trials, the RAFT trial. This trial was free of major bias and reported a fairly large absolute difference in overall mortality of 5.3%. None of the other three RCTs reported a mortality difference. While two of the other three trials were underpowered to detect differences in mortality, the MADIT-CRT was approximately the same size as the RAFT trial and did not show any improvement in mortality. It is possible that the sicker patient population and longer follow-up in RAFT accounted for the mortality difference. Among other outcome measures, hospitalizations for heart failure showed consistent improvements, but quality of life and functional status did not.

Use of CRT in patients with atrial fibrillation

There is controversy about whether CRT leads to health outcome benefits for patients with atrial fibrillation. Many experts feel that if CRT is to be used, it needs to be combined with ablation of the atrioventricular node, in order to avoid transmission of atrial impulses through the node that might result in rapid ventricular rates, thus undermining the efficacy of CRT.

An RCT was published in 2011 that compared CRT to right ventricular pacing alone in patients with atrial fibrillation. A total of 186 patients had atrioventricular nodal ablation and implantation of a CRT device. Patients were then randomized to echo-optimized CRT or right ventricular pacing alone and followed for a median of 20 months. The primary outcome measure was a composite of death from heart failure, hospitalization for heart failure, or worsening heart failure. This combined endpoint occurred in 11% of the CRT group compared with 26% of the RV pacing group (HR: 0.37; 95% CI: 0.18-0.73; p=0.005). For the individual outcome measures, there was not a significant reduction in mortality (HR: 1.57; 95% CI: 0.58-4.27; p=0.37), but there were significant reductions in hospitalizations (HR: 0.20; 95% CI: 0.06-0.72; p=0.013) and worsening heart failure (HR: 0.27; 95% CI: 0.12-0.58; p=0.003). There were no differences in outcomes on subgroup analysis, including analysis by ejection fraction, NYHA Class, and/or QRS duration.

A systematic review published in 2011 compared outcomes of CRT in patients with and without AF. This analysis included 23 observational studies enrolling 7,495 patients, of whom 1,912 had AF. Outcomes in patients with AF were less favorable on all measures. This included overall mortality (Relative risk [RR]: 1.5; 95% CI: 1.08 to 2.09; $p=0.015$), nonresponse to CRT (RR: 1.32; 95% CI: 1.12 to 1.55; $p=0.001$), change in the Minnesota Living with Heart Failure QoL score (mean difference: -4.1; 95% CI: -1.7 to -6.6; $p=0.001$), and change in the six-minute walk distance (mean difference: -14.1meters, 95% CI: -28.2 to 0.0; $p=0.05$). Five studies compared outcomes of patients with AF who had AV nodal ablation to patients who did not have ablation. Pooled analysis from these studies indicated that AV nodal ablation was associated with a lower rate of non-response (RR: 0.40; 95% CI: 0.28 to 0.58; $p<0.001$).

A second systematic review that evaluated the role of AV node ablation in patients with atrial fibrillation (AF) treated with CRT was published in 2012. This review included non-randomized studies that reported outcomes of CRT and medical therapy. Six studies were included, enrolling a total of 768 patients, 339 of whom underwent atrioventricular (AV) node ablation and 429 who did not. AV nodal ablation was associated with improvements in the outcomes of all-cause mortality (RR: 0.42; 95% CI: 0.26 to 0.68), cardiovascular mortality (RR: 0.44; 95% CI: 0.24 to 0.81), and change in NYHA Class (mean difference: -0.34; 95% CI: -0.56 to -0.13; $p=0.002$).

Since publication of the systematic reviews evaluating CRT in patients with and without AF, in a smaller retrospective cohort study, Eisen et al compared outcomes for patients who underwent CRT with and without AF. The authors evaluated outcomes for 175 patients who underwent CRT implantation from 2004 to 2008 at a single institution, of whom 66 patients (37.7%) had documented AF. There were no differences between patients with and without AF in short-term (30-day) complications post-CRT implantation (6.1% vs 4.6%, $p=0.7$) or in one-year mortality (13.6% vs 11.9%, $p=0.2$).

Conclusions

There is insufficient evidence to determine whether CRT improves outcomes for patients with AF and heart failure. One systematic review of observational studies suggests that patients with AF do not achieve the same degree of benefit as do patients with sinus rhythm. However, this comparison does not determine whether patients with AF have a greater benefit from CRT compared to medical therapy. For patients with AF who are undergoing CRT, one RCT and a systematic review of non-randomized studies conclude that when CRT is used in patients with AF, AV nodal ablation is associated with improved outcomes compared to no AV nodal ablation.

Are there additional criteria that can be used to more appropriately select patients for CRT therapy?

For patients who meet indications for CRT treatment, there is a large variability in the magnitude of response. Some patients do not respond at all, while others have very substantial benefit. As a result, there is interest in better defining the clinical features that predict response in order to better target therapy toward those who will benefit most. There is a large body of literature examining predictors of outcome after CRT placement, and numerous clinical and demographic factors have been identified that predict response. A smaller number of predictors have been proposed as potential selection factors for CRT placement. Two of these potential selection factors will be reviewed here, ventricular dyssynchrony on echocardiography and a QRS duration of more than 150 to 160 ms.

An example of a study examining general predictors of outcome is The Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) study was a prospective, multicenter study that evaluated the ability of echocardiographic parameters to predict response to CRT. Results of this trial indicated that the 12 individual echocardiographic parameters varied widely in their ability to predict response. The sensitivity of these individual measures ranged from 6-74% and the specificity ranged from 35-91%. The authors concluded that it was unlikely that these echocardiographic measures could improve patient selection for CRT.

Ventricular dyssynchrony

Observational studies of patients who meet criteria for treatment have shown that measures of dyssynchrony on echocardiography are correlated with treatment response, as defined by improvements in left ventricular end systolic volume, ejection fraction, or clinical criteria. This finding led to several clinical trials that assessed whether ventricular dyssynchrony could discriminate between responders and nonresponders to CRT, for both patients who would otherwise qualify for CRT and for those who would not (i.e., those with a narrow QRS).

A small randomized controlled trial (RCT) that compared outcomes of CRT in patients with ventricular dyssynchrony versus those without was published in 2011. A total of 73 patients with Class II/IV were evaluated, 44 of whom were found to have dyssynchrony on echocardiography. These 44 patients were randomized to a combined CRT-defibrillator or a defibrillator alone. Outcomes measures were peak O₂ consumption (VO₂max), NYHA Class, and echocardiographic parameters. At six months of follow-up, more patients in the CRT group had an increase of at least 1 mL/kg/min in VO₂max (62% vs. 50% p=0.04). There were significant within-group improvements in NYHA Class and echocardiographic measures, but the between-group comparisons with the no-CRT group did not reach statistical significance.

The NARROW-CRT trial was an RCT designed to compare CRT with dual chamber ICD among patients with heart failure (NYHA Class II-III) of ischemic origin, ejection fraction of 35% or less, QRS less than 120 ms, and marked mechanical dyssynchrony on echocardiogram. One hundred-twenty patients were randomized to CRT (n=60) or ICD (n=60). For the study's primary outcome of the heart failure clinical composite score, compared with those in the ICD group, patients in the CRT were more likely to have an improvement in their clinical composite score at one year postimplantation (41% vs 16%, p=0.004). Patients in the CRT group had higher rates of avoiding the combined end point of heart failure hospitalization, heart failure death, and spontaneous ventricular fibrillation (p=0.028).

The EchoCRT study (NCT00683696) was intended to evaluate the role of CRT for subjects with heart failure (NYHA Class III or IV) with narrow QRS (<130 ms) and echocardiographic evidence of ventricular dyssynchrony. All enrolled patients were implanted with an ICD with CRT, and patients were randomized to either CRT-ON or CRT-OFF. The study was stopped for futility at the recommendation of the data safety and monitoring board after enrollment of 809 patients; results from the enrolled patients who had been followed for a mean of 19.4 months were published by Ruschitzka et al. Four hundred four patients were randomized to the CRT group and 405 to the control group. The primary efficacy outcome, death from any cause or hospitalization for worsening heart failure, occurred in 116 of 404 patients (28.7%) in the CRT group, compared with 102 of 405 (25.2%) in the control group (HR with CRT=1.20; 95% CI,

0.92 to 1.57; p= 0.15). There was a significantly higher rate of deaths in the CRT group, with 45 of 404 (11.1%) patients dying in the CRT group, compared with 26 of 50 (6.4%) in the control group (HR=1.81; 95% CI, 1.11 to 2.93; p=0.02).

The Resynchronization Therapy in Normal QRS Trial [RethinQ study]) randomized 172 patients with a narrow QRS and evidence of dyssynchrony to receive a CRT device, turned on or not, and followed up for six months. CRT-treated patients were not more likely to have improvement than non-CRT patients (46% vs 41%, respectively, met the end point of improvement in exercise capacity [Vo_{2peak}]). A subset of patients with QRS duration 120 to 130 ms or more showed improvement (p=0.02), whereas patients with QRS less than 120 ms did not (p=0.45).

QRS duration

It is well accepted that patients with a QRS complex of less than 120 ms who are not selected for dyssynchrony do not benefit from CRT. The LESSER-EARTH trial was an RCT designed to compare CRT versus no CRT in patients with a QRS complex of less than 120 ms, whether ventricular dyssynchrony was present or absent. This trial was terminated early after 85 patients had been enrolled. Interim analysis revealed futility in achieving benefit on the primary outcomes, and a trend toward greater adverse events.

A more controversial issue is whether patients with moderately prolonged QRS duration (120-150 ms) benefit from CRT, or whether the benefit is confined to patients with a markedly prolonged QRS (>150-160 ms). Several meta-analyses of the association of QRS duration with outcomes have been published. The first of these was published in 2011 and evaluated whether patients with modest prolongations of the QRS complex benefited from CRT. This study identified five trials enrolling 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 to 149 ms, and severely prolonged QRS, generally 150 ms or more. For patients with a moderately prolonged QRS, there was no significant benefit for CRT in reducing composite outcomes of adverse cardiac events (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). There were no differences in outcomes on sensitivity analysis according to NYHA class and ICD status.

Other meta-analyses have come to similar conclusions, reporting benefit in patients with a QRS of more than 150, and little to no benefit in patients with shorter QRS duration. In one of these studies, the benefit of CRT was confined to patients with left bundle-branch block (LBBB). There was no benefit demonstrated for patients with right bundle-branch block or intraventricular conduction delay. These authors suggest that QRS morphology may be as important, or more important, than QRS duration in prediction response to CRT.

In 2013, Peterson et al published results of a retrospective cohort study of Medicare beneficiaries who underwent combined CRT/ICD implantation to assess associations between QRS duration and morphology and outcomes. Among 24,169 patients admitted for CRT/ICD implantation and followed for up to three years, rates of three-year mortality and one-year all-cause rehospitalization were lowest in patients with LBBB and QRS duration 150 ms or more. Patients with no LBBB and QRS duration from 120 to 149 ms had an adjusted hazard ratio after

controlling for a number of clinical and demographic confounders (compared with those with LBBB and markedly prolonged QRS) of 1.52 (95% CI, 1.38 to 1.67).

Conclusions

The optimal selection of patients for CRT treatment remains an active area of investigation. The presence of dyssynchrony on echocardiography may risk-stratify patients, but it is not a good discriminator of responders versus nonresponders. RCT evidence is mixed, but overall, suggests that patients with dyssynchrony without a prolonged QRS duration do not have reduced rates of death or hospitalization with a CRT-D compared with an ICD alone. In contrast, a QRS duration of more than 150 ms, or the presence of LBBB, appears to discriminate well between responders and nonresponders and represents a potential factor on which patients may be selected for CRT treatment. Subgroup analyses of RCTs across multiple studies, corroborated by quantitative pooling of these subgroup analyses in meta-analyses, have reported that a QRS duration of 150 to 160 ms or more is accurate in discriminating responders from nonresponders.

Triple-Site CRT (Triventricular Pacing)

Triple-site CRT, or triventricular pacing, is a variation of conventional CRT that uses an additional pacing lead. The rationale behind triventricular pacing is that a third pacing lead may improve electromechanical synchrony, thereby leading to better outcomes. Two RCTs have been published that compared triple-site CRT with conventional CRT. Rogers et al performed a double-blind RCT in 43 patients referred for CRT. All patients had three leads implanted, but patients in the conventional CRT arm had their device programmed to biventricular pacing. The triventricular group had greater improvements in the six-minute walk distance compared with the conventional CRT group (increase of 91 m vs 65 m, $p=0.008$), and greater improvement on the Minnesota Living with Heart Failure scale (reduction of 24 points vs 18 points, $p<0.001$). Complications did not differ between groups; however, because all patients had three leads implanted, this was not a valid comparison of complications for biventricular versus triventricular pacing.

A second RCT was published by Lenarczyk et al in 2012. This was a report of the first 100 patients randomized to triple-site or conventional CRT in the Triple-Site versus Standard Cardiac Resynchronization Therapy Randomized Trial (TRUST CRT). After a follow-up of one year, more patients in the conventional arm were in NYHA Class III or IV heart failure compared with the triple-site CRT group (30% vs 12.5%, $p<0.05$). Implantation success was similar in the triple-site and conventional groups (94% vs 98%, respectively, $p=NS$), but the triple-site implantation was associated with longer time for implantation and a higher fluoroscopic exposure. In addition, more patients in the triple-site group required additional procedures (33% vs 16%, $p<0.05$).

In 2013, Ogano et al published outcomes from a cohort of 58 patients with NYHA Class III to IV heart failure, LVEF 0.35 or less, and a QRS interval of 120 ms or more who received combined CRT/ICD with either dual-site or triventricular pacing. The choice of dual-site or triventricular pacing was made at the time of CRT/ICD implantation on the basis of hemodynamic response (left ventricular delta P/delta t_{max}); those with a better response to triventricular pacing were assigned to the triventricular group. Follow-up was available for a mean 481 days. Clinical symptoms and echocardiographic parameters improved for all subjects from enrollment to six-month follow-up. Ventricular arrhythmia was less common in the triventricular pacing group.

occurring in two of 22 patients compared with 14 of 36 patients in the dual-site pacing group (p=0.044). While this study suggests that triple-site pacing may be associated with fewer ventricular arrhythmias, it is subject to bias due to the method of selecting patients for triple-site pacing.

Section Summary

Two small RCTs with limited follow-up report improved functional status and QOL with triple-site CRT compared with conventional CRT. However, triple-site CRT was also associated with higher radiation exposure and a greater number of additional procedures postimplantation. Further studies are needed to better define the benefit/risk ratio for triple-site CRT compared with conventional CRT.

Combined automatic implantable cardiac defibrillators/biventricular pacemakers/intrathoracic fluid monitors

Adding intrathoracic fluid status monitoring has been proposed as a more sensitive monitoring technique of the fluid status leading to prompt identification of impending heart failure, permitting early intervention and, it is hoped, a decreased rate of hospitalization. There is a lack of evidence from RCTs on the efficacy of fluid monitoring compared to usual care. The available evidence consists of uncontrolled studies that evaluate the correlation of fluid status information with cardiac events.

A prospective cohort of 558 patients from 34 centers identified the number of “threshold crossing events” and the percent of days with such events as predictors of hospitalization for severe heart failure using multivariate regression. Over a mean of 326 days, 953 threshold crossing events in 351 patients resulted in 63 hospitalizations among 49 patients. Each subsequent event was associated with a 36% increased risk of hospitalization; however, the extent to which the presence of threshold crossing events influenced the decision to hospitalize is not known.

A similar retrospective study, that evaluated “threshold crossings” as a predictor of arrhythmogenic events, was published in 2011. This analysis included 282 patients with NYHA Class III or IV heart failure followed for a mean of 10 months. Patients were categorized into those that had “threshold crossings” (n=145, 51%) and those that did not (n=137, 49%). Tachyarrhythmic events were more common in patients with threshold crossings than in patients without (3,241 vs. 1,484 events; p<0.0001).

The Medtronic Impedance Diagnostics in Heart Failure (MID-HeFT) study was a retrospective study designed to investigate the feasibility of predicting heart failure hospitalization based on intrathoracic bioimpedance and to validate impedance measurements as a surrogate measure of pulmonary congestion based on pulmonary capillary wedge pressure. The device that was used was a modified pacemaker and thus was not incorporated into a biventricular pacemaker/ICD. A total of nine abstracts are derived from this study. One abstract included 33 patients. Among the 10 patients with 26 hospitalizations for heart failure during an 18-month follow-up, thoracic bioimpedance gradually decreased prior to the hospitalization, in many instances before the onset of clinical symptoms.

The Fluid Accumulation Status Trial (FAST) was a prospective trial investigating the use of the algorithm used to analyze the collected bioimpedance data.

The Sensitivity of the InSync Sentry for Prediction of Heart Failure (SENSE-HF) study was designed to prospectively evaluate the sensitivity of the OptiVol fluid trends feature in predicting heart failure hospitalizations with signs and/or symptoms of pulmonary congestion and then to define OptiVol clinical guidelines for patient management. The SENSE-HF study was completed in March 2009. Baseline characteristics of the PARTNERS-HF study have been published; study outcomes have not been published in the peer-reviewed literature. Conraads et al reported results in 2011. The study enrolled 501 patients who underwent CRT placement with the OptiVol fluid monitoring system. During the first six months postimplantation, the patient and physician were blinded to the fluid monitoring results; following that, the physician had access to the fluid monitoring results and the patient received alerts with a “heart failure” status. In the final phase, the physician could optimize heart failure treatment based on OptiVol results. During the first phase, “threshold crossings” in OptiVol results lead to a positive predictive value for subsequent heart failure hospitalizations of 4.7%. In the second phase, 233 patients received an OptiVol alert and for 210, their heart failure status was evaluated within 30 days. Heart failure status had worsened for 80 patients (positive predictive value, 38.1%). The authors concluded that the intrathoracic impedance measurements’ sensitivity improved over time but that further literature is needed to determine the role of thoracic impedance monitoring in clinical care.

The Combined Heart Failure Diagnostics Identify Patients at Higher Risk of Subsequent Heart Failure Hospitalization (PARTNERS-HF) is a prospective; nonrandomized postmarketing study conducted in up to 100 U.S. centers that was completed in March 2008 with the goal ~~of the trial~~ ~~is to~~ characterizing the relationship between a variety of diagnostic data derived from the implanted biventricular/ICD devices.

Conclusions

The evidence is not sufficient to determine whether intrathoracic fluid monitoring improves outcomes for patients who receive a CRT device. The available evidence indicates that intrathoracic monitoring may be a more sensitive measure for predicting heart failure exacerbations compared to weight monitoring. However, there is no published data that report improved outcomes associated with fluid monitoring. Although numerous trials have been undertaken, as of April 2012, there were no RCT publications in the peer-reviewed literature that report on outcomes and/or the utility of intrathoracic fluid monitoring in the management of patients with heart failure.

Summary

Evidence from clinical trials and systematic reviews supports the benefit of CRT treatment for patients with NYHA Class III/IV heart failure. For this group, there are improvements in mortality, functional status and quality of life. As a result, CRT treatment may be considered medically necessary for patients with NYHA class III/IV heart failure who have an ejection fraction <35%, sinus rhythm, a QRS duration of at least 120 msec, and who are treated with an optimal pharmacologic regimen.

For patients with milder heart failure, RCT evidence from at least one large, high-quality trial reports a mortality benefit for patients with Class II heart failure, but other RCTs do not report a

mortality benefit. Several studies report a decrease in hospitalizations for Class II patients, but no studies provide evidence of treatment benefit on functional status or QOL outcomes. Despite the lower level of evidence available for mild compared to advanced heart failure, it can be concluded that the benefit of CRT outweighs the risk for these patients. Therefore, CRT treatment may be considered medically necessary for Class II heart failure patients who meet other clinical criteria for treatment. The evidence on Class I heart failure is not sufficient to permit conclusions, as only a small number of Class I patients have been included in some of the trials, and no benefit has been demonstrated for this specific subgroup. As a result, CRT is considered investigational for Class I heart failure.

Treatment of patients with atrial fibrillation and heart failure is controversial. Available evidence establishes that patients with heart failure probably do not derive the same magnitude of benefit as do patients with sinus rhythm and that CRT with AV nodal ablation is probably superior to CRT without AV nodal ablation in patients with heart failure. However, the evidence is insufficient to determine whether CRT treatment is superior to no treatment for this patient group. In addition, clinical input in 2012 was mixed as to whether patients with atrial fibrillation should be treated with CRT. Therefore, CRT remains investigational for patients with atrial fibrillation.

The optimal selection of patients for CRT treatment remains uncertain. Accumulating evidence indicates that benefit is concentrated in patients with a QRS duration of greater than 150 msec. This factor offers a potential method to better select patients for CRT and potentially avoid treatment in patients who will not benefit. Clinical input in 2012 demonstrated support for continued use of QRS threshold of 120 msec, rather than restricting treatment to patients with QRS greater than 150 msec. Other factors for selecting patients, such as ventricular dyssynchrony on echocardiography, have not been shown to be good discriminators of responders versus non-responders.

Practice Guidelines and Position Statements

A focused update to 2008 guidelines for device-based treatment of cardiac rhythm abnormalities were published jointly by ACC/AHA/HRS in 2012. These guidelines included the following recommendations on CRT for heart failure:

Class I recommendations:

- CRT is indicated for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration greater than or equal to 150 ms, and NYHA Class II, III, or ambulatory IV symptoms on GDMT. (Level of Evidence: A for NYHA Class III/IV; Level of Evidence: B for NYHA Class II)

Class IIa recommendations:

- CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration 120 to 149 ms, and NYHA Class II, III, or ambulatory IV symptoms on GDMT. (Level of Evidence: B)
- CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA Class III/ambulatory Class IV symptoms on GDMT. (Level of Evidence: A)
- CRT can be useful in patients with atrial fibrillation and LVEF less than or equal to 35% on GDMT if a) 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. (Level of Evidence: B)

- CRT can be useful for patients on GDMT who have LVEF less than or equal to 35% and are undergoing new or replacement device placement with anticipated requirement for significant (>40%) ventricular pacing. (Level of Evidence: C)

Class IIb recommendations:

- CRT may be considered for patients who have LVEF less than or equal to 30%, ischemic etiology of heart failure, sinus rhythm, LBBB with a QRS duration of greater than or equal to 150 ms, and NYHA class I symptoms on GDMT. (Level of Evidence: C)
- CRT may be considered for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with QRS duration 120 to 149 ms, and NYHA Class III/ambulatory Class IV on GDMT. (Level of Evidence: B)
- CRT may be considered for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA Class II symptoms on GDMT. (Level of Evidence: B)

Class III recommendations (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. (Level of Evidence: B)
- CRT is not indicated for patients whose comorbidities and/or frailty limit survival with good functional capacity to less than one year. (Level of Evidence: C)

The European Society of Cardiology and the European Heart Rhythm Association released guidelines on cardiac pacing and cardiac resynchronization therapy in 2013. These guidelines included the following recommendations on CRT for heart failure with sinus rhythm:

Class I recommendations:

- LBBB with QRS duration greater than 150 ms. CRT is recommended in chronic heart failure patients and LVEF less than or equal to 35% who remain in NYHA functional Class II, III, and ambulatory IV despite adequate medical treatment. (Level of Evidence: A).
- LBBB with QRS duration from 120 to 150 ms. CRT is recommended in chronic heart failure patients and LVE less than or equal to 35% who remain in NYHA functional Class II, III, and ambulatory IV despite adequate medical treatment. (Level of Evidence: B).

Class IIa recommendations:

- Non-LBBB with QRS duration greater than 150 ms. CRT should be considered in chronic heart failure patients and LVEF less than or equal to 35% who remain in NYHA functional Class II, III, and ambulatory IV despite adequate medical treatment. (Level of Evidence: B).

Class IIb recommendations:

- Non-LBBB with QRS duration 120-150 ms. CRT may be considered in chronic heart failure patients and LVEF less than or equal to 35% who remain in NYHA functional Class II, III, and ambulatory IV despite adequate medical treatment. (Level of Evidence: B).

Class III recommendations:

- CRT in patients with chronic heart failure with SQR duration less than 120 ms is not recommended (Level of Evidence: B).

The Heart Failure Society of America released comprehensive guidelines on the management of heart failure in 2010. The guidelines include the following recommendations related to the use of CRT:

- Biventricular pacing therapy is recommended for patients in sinus rhythm with a widened QRS interval (>120 ms) and severe LV systolic dysfunction (LVEF $<35\%$) who have persistent, moderate to severe HF (NYHA III) despite optimal medical therapy. (Level of Evidence: A).
- Biventricular pacing therapy may be considered for patients with atrial fibrillation with a widened QRS interval (>120 ms) and severe LV systolic dysfunction LVEF $<35\%$ who have persistent, moderate to severe HF (NYHA III) despite optimal medical therapy. (Level of Evidence: B).
- Selected ambulatory NYHA IV patients in sinus rhythm with QRS >120 ms and LV systolic dysfunction may be considered for biventricular pacing therapy. (Level of Evidence: B).
- Biventricular pacing therapy may be considered in patients with reduced LVEF and QRS >150 ms who have NYHA I or II HF symptoms. (Level of Evidence: B).
- In patients with reduced LVEF who require chronic pacing and in whom frequent ventricular pacing is expected, biventricular pacing may be considered. (Level of Evidence: C).

Key Words:

InSync[®], Biventricular Pacemaker, biventricular pacing, congestive heart failure (CHF), pacemaker, cardiac resynchronization, and cardiac resynchronization therapy

Approved by Governing Bodies:

There are numerous CRT devices, combined CRT-ICD devices (CRT-D), and combined CRT and fluid monitoring devices. Some of the devices are discussed here. A stand-alone biventricular pacemaker (InSync[®] Biventricular Pacing System, Medtronic) has received approval by U.S. Food and Drug Administration (FDA) for the treatment of patients with New York Heart Association (NYHA) Class III or IV heart failure, on a stable pharmacologic regimen, who also have a QRS duration of 130 ms or longer and a left ventricular ejection fraction (LVEF) of 35% or less. Biventricular pacemakers have also been combined with automatic ICDs.

Both Guidant (CONTAK CD[®] CRT-D System) and Medtronic (InSync[®] ICD Model 7272) have received FDA approval for combined cardiac resynchronization therapy defibrillators for patients at high risk of sudden cardiac death due to ventricular arrhythmias and who have NYHA Class III or IV heart failure with LVEF of 35% or less, QRS duration 130 ms or longer (>120 ms for the Guidant device), and remain symptomatic despite a stable, optimal heart failure drug therapy.

In 2006, Biotronik Inc. received FDA approval for its combined ICD/CRT device with ventricular pacing leads (Tupos LV/ATx CRT-D/Kronos LV-T CRT-D systems); in 2013, the company received FDA approval for updated ICD/CRT devices (Ilesto/Iforia series).

In September 2010, FDA expanded the indications for CRT to include patients with Class I and II heart failure. In addition to NYHA Class I/II heart failure, indications for CRT in mild heart failure include a LVEF of less than 30% and a QRS duration of 130 ms or more.

Multiple devices manufactured by Medtronic combine a CRT with the OptiVol™ monitoring system. For example, in 2005, the InSync Sentry® system received FDA approval through the supplemental premarket approval (PMA) process. This combined biventricular pacemaker/ICD is also equipped to monitor intrathoracic fluid levels using bioimpedance technology, referred to as OptiVol™ Fluid Status Monitoring. Bioimpedance measures, defined as the electrical resistance of tissue to flow of current, are performed many times per day using a vector from the right ventricular coil on the lead in the right side of the heart to the implanted pacemaker devices; changes in bioimpedance reflect intrathoracic fluid status and are evaluated based on a computer algorithm. For example, changes in a patient's daily average of intrathoracic bioimpedance can be monitored; differences in the daily average compared with a baseline are reported as the OptiVol Fluid Index. It has been proposed that these data may be used as an early warning system of cardiac decompensation or to provide additional feedback enabling a physician to further tailor medical therapy.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply

BellSouth/AT&T contracts: No special provisions

FEP contracts: FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity

Current Coding:

CPT codes:

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 system to dual chamber system (includes removal of previously placed pulse generator, testing of existing lead, insertion of new lead, insertion of new pulse generator)
33220	Repair of two transvenous electrodes for a 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 (including upgrade to dual chamber system and pocket revision) (List separately in addition to code for primary procedure)
33228	<u>Removal of permanent pacemaker pulse generator with replacement of pacemaker pulse generator; dual lead system</u>
33229	<u>Removal of permanent pacemaker pulse generator with replacement of pacemaker pulse generator; multiple lead system</u>

HCPCS Codes:

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
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Policy History:

Medical Review Committee, May 2002

Medical Policy Group, June 2002

Available for comment July 2-August 15, 2002

Medical Policy Group, June 2004 (1)

Medical Policy Administration Committee, June 2004

Available for comment July 12-August 25, 2004

Medical Policy Group, August 2006 (1)

Medical Policy Group, August 2009 (1)

Medical Policy Administration Committee August 2009

Available for comment July 17-August 31, 2009

Medical Policy Group, October 2009 (1)

Medical Policy Administration Committee, October 2009

Available for comment October 20-December 3, 2009

Medical Policy Group, April 2011 (1)

Medical Policy Administration Committee, May 2011

Available for comment May 11 – June 27, 2011

Medical Policy Group, November 2011(1): 2012 Coding Update: Updated verbiage to match 2012 CPT changes

Medical Policy Group, December 2011 (3): 2012 Coding Update-Added Code G0448

Medical Policy Group, April 2012 (1): Update to Description, Key Points and References related to MPP update; “Cardiac resynchronization therapy” added to policy title; no changes to policy statement

Medical Policy Panel, August 2012

Medical Policy Group, April 2013 (1): Update to Policy statement to add ‘sinus rhythm’ to and remove ‘who remain symptomatic despite’ from NYHA Class III or IV criteria and change LVEF to $\leq 30\%$ to NYHA Class II criteria; update to Key Points

Medical Policy Panel, April 2013

Medical Policy Group, April 2013 (4): Update to Policy statement to add triventricular pacing as investigational; update to Key Points and References

Available for comment May 22 through July 5, 2013

Medical Policy Panel, April 2014

Medical Policy Group, April 2014 (4): Updated Approved Governing Bodies, Practice Position and Guidelines, Key Points and References. Also added CPT codes 33228 and 33229. There are no changes to the policy statement at this time.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.