



# Medical Coverage Policy

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## Cardiac Resynchronization Therapy (CRT) and Advanced Cardiac Pacing Technologies

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### Overview

This Coverage Policy addresses the use of a biventricular pacemaker (alone or combined with an implantable cardioverter defibrillator [ICD]) for cardiac resynchronization therapy (CRT), triple-site or triventricular pacing CRT, wireless pacing CRT, His bundle pacing, body surface potential mapping, and leadless pacemakers.

### Coverage Policy

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

- **Ischemic cardiomyopathy, left ventricular ejection fraction (LVEF) ≤ 35%, no prior implant, sinus rhythm (SR) for ANY of the following:**

- QRS 120-149 milliseconds (ms), left bundle branch block (LBBB), New York Heart Association (NYHA) Class I, II, III-IV
  - QRS ≥ 150 ms, LBBB, NYHA Class I, II, III-IV
  - QRS 120-149 ms, non-LBBB, NYHA Class III-IV
  - QRS ≥ 150 ms, non-LBBB, NYHA Class II, III-IV
- **Nonischemic cardiomyopathy, LVEF ≤ 30%, no prior implant, SR for ANY of the following:**
    - QRS 120-149 ms, LBBB, NYHA Class II,III-IV
    - QRS ≥ 150 ms, LBBB, NYHA Class I, II, III-IV
    - QRS 120-149 ms, non-LBBB, NYHA Class III-IV
    - QRS ≥ 150 ms, non-LBBB, NYHA Class I, II, III-IV
- **Nonischemic cardiomyopathy, LVEF 31-35%, no prior implant, SR for ANY of the following:**
    - QRS 120-149 ms, LBBB, NYHA Class I, II, III-IV
    - QRS ≥ 150 ms, LBBB, NYHA Class I, II, III-IV
    - QRS 120-149 ms, non-LBBB, NYHA Class III-IV
    - QRS ≥ 150 ms, non-LBBB, NYHA Class I, II, III-IV
- **LVEF > 35% of any etiology, ICD indicated, no prior implant, SR, QRS ≥ 150 ms, LBBB, NYHA Class III-IV**
- **LVEF ≤ 35% of any etiology, NYHA Class IV on intravenous inotropic support, no prior implant for EITHER of the following:**
    - QRS 120-149 ms, LBBB
    - QRS ≥ 150 ms, LBBB or non-LBBB
- **Pre-existing or anticipated right ventricular (RV) pacing with a clinical indication for ICD or pacemaker implantation, intrinsic narrow QRS for EITHER of the following:**
    - RV pacing anticipated ≤ 40%, LVEF ≤ 35%, NYHA Class III-IV
    - RV pacing anticipated > 40%, NYHA Class I,II, III-IV
- **Refractory NYHA Class III/IV heart failure < 3 months post revascularization and/or ≤ 40 days post-myocardial infarction (MI) and ALL of the following:**
    - LVEF ≤ 35%
    - QRS > 120 ms
    - LBBB or non-LBBB
    - no other indication for ventricular pacing

**\*Note: Please reference Cigna Medical Coverage policy “Implantable Cardioverter Defibrillator (ICD)” for conditions of coverage of an ICD device.**

**Replacement of a biventricular pacemaker generator alone or in combination with an implantable cardioverter defibrillator and/or leads is considered medically necessary.**

**The use of a biventricular pacemaker alone or combined with an implantable cardioverter defibrillator for CRT for any other indication is considered experimental, investigational or unproven.**

**Each of the following is considered experimental, investigational or unproven for any indication:**

- triple-site or triventricular pacing CRT

- wireless pacing CRT
- His bundle pacing (HBP)
- body surface potential mapping
- leadless pacemaker

## General Background

### Heart Failure

Congestive heart failure (CHF), or heart failure (HF), is a clinical condition characterized by the heart's inability to generate a cardiac output sufficient to meet the body's circulatory demands. Approximately one-third of patients with heart failure may have intraventricular conduction delays, which can cause the contraction of the heart's ventricles to become uncoordinated. This dyssynchrony is evidenced by a wide QRS interval on electrocardiogram (ECG). Ventricular dyssynchrony can worsen the heart's ability to pump effectively and exacerbate heart failure symptoms. 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.

The New York Heart Association (NYHA) classification of heart failure is a 4-tier system that categorizes patients based on a 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 (Colucci, 2019).

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

### Cardiac Resynchronization Therapy (CRT)

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

An implantable biventricular pacemaker is an advanced version of a standard 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 goals of improving left ventricle (LV) function, reducing presystolic mitral regurgitation, and improving LV diastolic filling time.

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

### **CRT plus Implantable Cardioverter Defibrillator (ICD) System (CRT-D)**

Some individuals with heart failure are also at high risk for life-threatening heart rhythms, including ventricular tachycardia and 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 right and left ventricles beat at the same time in a normal sequence. 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.

CRT-D may be considered for people who fulfill the criteria for implantation of a CRT-pacing (CRT-P) device and who also separately fulfill the criteria for the use of an ICD device. Clinical indications for ICD devices are discussed in further detail in Cigna Medical Coverage policy "Implantable Cardioverter Defibrillator (ICD)".

### **Replacement of Device**

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

### **U.S. Food and Drug Administration (FDA)**

Multiple biventricular pacemakers have been approved by the U.S. Food and Drug Administration (FDA) through the Premarket Approval (PMA) process for biventricular pacing alone (CRT-P) or biventricular pacing and defibrillation (CRT-D). CRT-P and CRT-D devices are FDA Class III devices. Manufacturers of biventricular devices include St. Jude Medical (Sunnyvale, CA), Medtronic (Minneapolis, MN), Guidant Corp. (St. Paul, MN), and ELA Medical, Inc. (Plymouth, MN).

The FDA device approval notifications and manufacturer labels note the following contraindications to CRT-P and CRT-D devices:

- 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 (FDA, 2014).

## Literature Review

**CRT in NYHA Class III and IV:** Evidence in the published peer-reviewed literature, including randomized controlled trials, meta-analyses and systematic reviews, indicates that cardiac resynchronization therapy is effective at improving quality of life, patient functional capacity and heart failure symptoms in a subgroup of patients with heart failure, with or without ICD indications, decreased cardiac function and ventricular dyssynchrony who are on optimal pharmacologic regimen before implantation. The following benchmark large-scale trials included primarily NYHA Class III and IV patients with a wide QRS complex: MULTIsite STimulation In Cardiomyopathies (MUSTIC); Multicenter InSync Randomized Clinical Evaluation (MIRACLE); Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD); Contak CD; Cardiac Resynchronization — Heart Failure (CARE-HF); and Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION). (Deng, et al., 2015; Cleland, et al., 2009; Upadhyay, et al., 2008; Auricchio, et al., 2007; McAlister, et al., 2007a; 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; Higgins, et al., 2003; Abraham, et al., 2002; Leclercq, et al., 2002; Leon, et al., 2002).

**CRT in NYHA Class I and II:** The majority of newer 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). While lower morbidity and reduction or alleviation of symptoms are the goals of CRT in advanced heart failure, preventing heart failure progression is the primary objective for CRT in NYHA Classes I and II. The role of CRT in patients with mild or less severe heart failure is less established. Four key randomized controlled trials have been published in the peer-reviewed literature: Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT), Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE), Multicenter InSync ICD Randomized Clinical Evaluation II (MIRACLE ICD II) and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). These trials enrolled 4,414 patients which included patients with NYHA Class I or II heart failure, at least 25 patients per treatment group, and reported on at least one relevant health outcome with follow-up ranging from six months to 2.4 years (Tang, et al., 2010; Moss, et al., 2009; Linde, et al., 2008, Abraham, et al., 2004).

Evidence in the published peer-reviewed literature, including randomized controlled trials and a meta-analysis (Al-Majed, et al., 2011), indicates that there is a consistent benefit for CRT in reducing hospitalizations for a subgroup of patients with mild heart failure (NYHA Class I or II) and in improving echocardiographic parameters. Data indicates that biventricular resynchronization therapy does not demonstrate benefit on quality of life, functional status, or progression to more advanced stages of heart failure. The evidence on mortality differs among the available studies. Of the two largest studies, MADIT-CRT and RAFT, one reported a mortality difference while the other does not. The RAFT trial had patients with more severe illness, a higher baseline death rate, and a longer follow-up period concluding that CRT is likely to improve mortality for patients with NYHA class II heart failure. A subanalysis of the RAFT study found that women in particular benefitted from CRT-D, and had a significantly reduced incidence of death and heart failure hospitalization as compared to men ( $p < 0.001$ ) (de Waard, et al., 2019). Robust evidence to support biventricular resynchronization therapy in patients with asymptomatic left ventricular dysfunction or NYHA Class I symptoms is inconclusive resulting in the inability to draw strong conclusions regarding the impact on health outcomes (Santangeli, et al., 2011; Al-Majed, et al., 2011, Adabag, et al., 2011; Zareba, et al., 2011, Versteeg, et al., 2011; Pouleur, et al., 2011, Solomon, et al., 2010, Tang, et al., 2010; Moss, et al., 2009; Linde, et al., 2008, Abraham, et al., 2004).

**Literature Review – Patient Selection Criteria:** Biventricular pacing is an established method of CRT, and is most effective for individuals experiencing heart failure with reduced ejection fraction (EF), left bundle branch block (LBBB), and a wide QRS. Pacing is also supported in individuals with a low EF receiving a new or replacement device and who require  $\geq 40\%$  ventricular pacing. However, approximately 30-50% of patients do not improve with biventricular pacing due to anatomical variances, a narrow QRS, non-LBBB presentation, or other factors (Sharma and Vijayaraman, 2021). Since some patients do not respond favorably after undergoing CRT, studies addressing optimal patient selection criteria for CRT are ongoing.

A recent review of indications for CRT reported that there are inconsistencies in guideline recommendations for CRT indications which is due to limited evidence of CRT benefit in these patients. Two areas that have a paucity of evidence in the published peer-reviewed literature include management of patients with atrial fibrillation and the choice of the most appropriate device (i.e., pacemaker CRT vs. defibrillator CRT) (Normand, et al., 2018).

**QRS Duration:** A meta-analysis reported that patients with intrinsic QRS duration  $\geq 150$  ms experienced a significant 42% reduction in the incidence of the primary endpoint of death or hospitalization for HF with the use of CRT (Stavrakis, et al., 2012).

Some patients with narrower 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 the use of CRT in heart failure patients with a narrow QRS complex (i.e.,  $< 120$  ms) benefits patient outcomes.

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

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

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

In a prospective randomized clinical trial, Beshai et al. (2007) enrolled 172 patients who had a standard indication for an ICD. Patients received a CRT-D 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 pre-specified subgroup with a QRS interval of  $\geq 120$  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  $\leq 120$  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.

In a prospective pilot study, Bleeker et al. (2006a) studied the effects of CRT in heart failure patients with narrow QRS complex (<120 ms) and evidence of LV dyssynchrony on tissue Doppler imaging (TDI). The study participants included a total of 33 consecutive patients with narrow QRS complex and 33 consecutive patients with wide QRS complex (control group). Patient inclusion criteria included: LV dyssynchrony  $\geq 65$  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.

**QRS morphology:** In a retrospective study, Dupont et al. (2012) evaluated the relative impact of QRS morphology and duration in echocardiographic responses to CRT and clinical outcomes. Baseline characteristics, clinical and echocardiographic response, and outcomes of all patients who received CRT at a single center were evaluated. Patients were stratified into four groups according to their baseline QRS morphology and QRS duration. A total of 496 patients were included in the study; 216 (43.5%) had LBBB and a QRS  $150 \geq$  ms, 85 (17.1%) had LBBB and QRS < 150 ms, 92 (18.5%) had non-LBBB and a QRS  $\geq 150$  ms, and 103 (20.8%) had non-LBBB and QRS <150 ms. Echocardiographic response (change in ejection fraction) was better in patients with LBBB and QRS  $\geq 150$  than in those with LBBB and QRS < 150 ms, non-LBBB and QRS  $\geq 150$ , and non-LBBB and QRS >150 ms ( $p<0.0001$ ). In a multivariate stepwise model with change in ejection fraction as the dependent variable, the presented classification was the most important independent variable ( $p=0.0003$ ). Long-term survival was better in LBBB patients with QRS  $\geq 150$  ( $p=0.02$ ), but this difference was not significant after adjustment for other baseline characteristics ( $p=0.15$ ) suggesting that comorbid conditions may confound the treatment responses. The authors stated that "due to the lack of sufficiently powered trials in these subgroups, guideline committees have the difficult task of using this and similar studies to refine patient selection for CRT".

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

## Other Cardiac Resynchronization and Pacing Technologies

To further evaluate potential solutions for CRT "nonresponders", studies have explored alternative lead placement strategies, including triple-site (triventricular), His bundle, and wireless pacing.

### Triple-site CRT (Triventricular Pacing)

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

Triventricular pacing has been proposed as an alternative approach to improve the response rate in CRT recipients. It has been suggested that failure of response to biventricular pacing is probably due to a combination of factors including placement of the pacing lead over a zone of slow conduction, the presence of scar within the

left ventricle, variable electrical response of the diseased ventricle to pacing, or suboptimal positioning of the pacing leads with regard to the area of latest contraction (Rogers, et al., 2012).

**Literature Review:** Bordachar et al. (2018) conducted a multicenter parallel randomized prospective trial ( $V^3$  trial) (n=84) to assess the feasibility and safety of adding a second left ventricular (LV) lead to CRT nonresponders and its clinical impact. The trial enrolled patients that were eligible for a CRT system and considered as nonresponders as per clinical composite score (CCS). They were randomized to the  $V^3$  arm (implantation of an additional LV lead; n=43) or control arm (no change; n=41). Implant success rate, incidence of severe adverse events, CCS, and secondary clinical and echocardiographic end points were evaluated at 12 and 24 months. Positioning of a second LV lead was successful at first (40 of 44 - 90.9%) or second (4 of 44 - 9.09%) attempt. The perioperative complication rate (infection, system explant, pneumothorax, and hematoma) was high (procedures or system-related complications for nine patients- 20.4%). After 24 months, 35 systems (79.5%) were working properly.  $V^3$  treatment had no significant influence ( $p=0.27$ ) on the CCS, number of heart failure hospitalizations, time to first heart failure hospitalization, New York Heart Association class, and LV ejection fraction at 12 and 24 months. The authors reported that although addition of a second LV lead in CRT nonresponders is feasible with a high success rate, this approach is associated with a significant rate of severe adverse events and does not provide significant long-term clinical benefits.

Zhang et al. (2017) conducted a meta-analysis of randomized controlled trials (RCTs) and comparative observational studies (n=251) comparing the benefits of triple-site ventricular (Tri-V pacing) versus Bi-V pacing on the left ventricular (LV) remodeling, quality of life, and exercise capacity in patients with heart failure (HF). The meta-analysis included one RCT, two randomized crossover studies, and two nonrandomized comparative studies. Two different pacing modalities were used. One type used one lead in the right ventricle and leads in two different tributaries in the left ventricle. The other used two leads in the right ventricle. Patients in the triple-site pacing group had greater improvement in LVEF ( $p<0.001$ ) and NYHA classes ( $p=0.001$ ) compared with the control group. There were no significant differences in left ventricular geometry, six-minute walk distance, or Minnesota Living With Heart Failure Questionnaire score between the two groups. The subgroup analyses showed there might be a greater improvement in LVEF in the Tri-V pacing group in patients with QRS duration  $\geq 155$  ms ( $p<0.001$ ). The studies were limited by small sample size, short-term follow-up and lack of randomization. No study in this meta-analysis had power to assess the benefits of Tri-V pacing in terms of mortality, mobility, or other clinical outcomes.

Anselme et al. (2016) conducted a pilot multicenter randomized study (n=76) to assess the safety and feasibility of triple-site ventricular stimulation (TRIV) with two right ventricular leads and one left ventricular leads compared to conventional CRT. The primary end-point was the rate of severe adverse events at six months. Secondary end-points included functional improvement parameters, quality-of-life (QOL) score, and changes of echocardiographic indices at six and 12 months in a subset of patients. All implant procedures but one were successful. At six months, there was no statistical difference between proportions of patients with at least one severe adverse event in both groups (34.1% versus 25.7%). There was no difference between functional improvement parameters, 6-minute walking distances, QOL scores, and echographic indices. At 12 months, the proportions of patients with a left ventricular ejection fraction gain of more than 5%, 10%, or 15% were significantly superior with TRIV. This study is limited by the small sample size and short-term follow-up.

Rogers et al. (2012) performed a double-blind randomized controlled trial 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 12-month follow-up period was completed by 37 patients. The triventricular group had greater improvements in the 6-minute walk distance compared to the conventional CRT group (increase of 82 minutes versus 56 minutes,  $p=0.008$ ), and greater improvement on the Minnesota Living with Heart Failure scale (reduction of 24 points versus 18 points,  $p<0.0001$ ). Complications did not differ between groups; however, since all patients had three leads implanted, this was not a valid comparison of complications for biventricular versus triventricular pacing.

In a randomized controlled trial, Lenarczyk et al. (2012) reported on 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 CRT arm were in NYHA class III or IV heart failure compared to the triple-site CRT group (30% versus 12.5%,  $p<0.05$ ). Implantation



success was similar in the triple-site and conventional groups (94% versus 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% versus 16%, p<0.05). Triple-site CRT was associated with higher radiation exposure and a greater number of additional procedures post-implantation.

There is a paucity of adequately powered randomized controlled clinical trials or comparative studies in the peer-reviewed literature assessing the impact of triple-site resynchronization on long-term health outcomes in patients compared to conventional biventricular pacing.

### **CRT with Wireless Left Ventricle Endocardial Pacing**

The WiSE Cardiac Resynchronization Therapy System® (ebrSystems®, Sunnyvale, CA) is a wireless left ventricle (LV) pacing system that works with a conventional pacemaker and/or defibrillator for individuals in whom CRT is indicated. The WiSE CRT System is proposed to be used for patients who have failed conventional CRT or are not candidates for coronary sinus lead placement. The WiSE CRT system eliminates the need for a LV pacing wire in the coronary sinus. An ultrasonic transmitter attached to a battery unit and a tiny wireless receiver, measuring 10 x 2.6 mm acts as a pacing electrode. The transmitter is implanted in a left intercostal space, and the electrode is inserted into the LV via a retrograde aortic approach in a catheter-based procedure. After pacing-sensing mapping of the LV for site selection, the electrode is attached to the endocardial surface with a fixation barb. Sensing of RV pacing output from the conventional pacemaker device triggers ultrasonic energy transmission to the LV electrode from the transmitter, which stimulates synchronous contraction of the LV. The system allows the provider to customize electrode placement to the optimal location for pacing, which varies among patients; this differs significantly from conventional LV pacing leads, which are limited by coronary sinus anatomy (Hayes, 2021).

**U.S. Food and Drug Administration (FDA):** The WiSE CRT System is approved by the FDA Investigational Device Exemption (IDE) approval process. On September 10, 2019, the manufacturer announced that the FDA had granted the WiSE CRT system breakthrough device designation status for the treatment of heart failure. A U.S. regulatory filing for the device has not yet been submitted. The U.S. pivotal Stimulation Of the Left Ventricle Endocardially (SOLVE) CRT study began in January 2018 and is ongoing.

**Literature Review:** There have been a limited number of studies published in the peer-reviewed literature addressing the use of this technology. The studies are primarily nonrandomized, have small patient populations, short term follow up, and lack a formal comparator group (Hayes, 2021; Okabe, et al., 2021; Sidhu, et al., 2021; Sieniewicz, et al., 2020; Sidhu, et al., 2020; Singh, et al., 2019; Reddy, et al., 2017; Gamble, et al., 2018; Auricchio, et al., 2014). There is a lack of published randomized controlled trials evaluating CRT with wireless LV endocardial pacing. Clinical trials are ongoing.

### **His Bundle Pacing (HBP)**

His bundle pacing (HBP) is an alternative approach to RV and biventricular pacing and is performed with the aim of maintaining a physiological pattern of ventricular activation via the native His-Purkinje system. CRT with coronary sinus (CS) lead placement has become established as a first-line treatment for a subset of patients. Despite the development of sophisticated tool sets to facilitate implant and intraprocedural strategies that have evolved to consider mechanical and electrical delay in LV lead targeting, the rate of suboptimal or nonresponse to CRT remains around 30%. Rates of implant failure for CRT range between 5% and 9%, in part due to high rates of CS lead dislodgement (3% to 7% reported across major trials). Alternative strategies to achieve resynchronization have been explored, including permanent HBP. Permanent HBP was initially performed using standard pacing leads by reshaping the stylet or using a deflectable stylet to precisely position the lead at a site near the electrophysiology mapping catheter demonstrating the largest His deflection. This approach was technically challenging and time consuming. Case reports and review articles report that HBP may be an alternative approach in an attempt to achieve cardiac resynchronization in technically challenging cases where the standard endovascular approach via the coronary sinus is not possible (Lewis, et al., 2019; Vijayaraman, 2018).

**U.S. Food and Drug Administration (FDA):** June 28, 2018, the FDA granted Premarket Approval (PMA) to expand the indication for use of the Medtronic SelectSure 3830 lead, to include pacing at the bundle of His.

**Literature Review:** There is a paucity of large randomized controlled clinical trials or comparative studies in the peer-reviewed literature assessing the impact of HBP on long-term health outcomes in patients compared to conventional biventricular pacing with traditional coronary sinus or epicardial LV leads. (Zweerink, et al., 2021; Huang, et al., 2019; Boczar, et al., 2019, 2018; Sharma, et al., 2018, 2017; Vijayaraman, 2018; Bhatt, et al., 2017; Teng, et al., 2016).

Upadhyay et al. (2019a) published an on-treatment analysis of the His-SYNC pilot study randomized controlled trial (n=41), which aimed to assess the feasibility and efficacy of His bundle pacing cardiac resynchronization therapy (His-CRT) compared to biventricular pacing (BiV-CRT). Subjects had a diagnosis of heart failure, were 18 years or older, and met American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Heart Rhythm Society (HRS) class I or II guideline indications for CRT. Excluded from the study were persons with an existing CRT device or pregnant. Most participants (n=35) had LBBB, and 33% had atrial fibrillation. His-CRT was performed utilizing the Medtronic SelectSecure Model 3830 lead. The BiV-CRT group underwent standard lead placements for CRT. Intraprocedural group crossover for patients randomized to His-CRT was required if the paced QRS width did not narrow by at least 20% or to a QRS width of  $\leq 130$  ms, or if placement of the HBP lead could not be performed with sufficient stability or pacing output. Similarly, crossover for patients randomized to the BiV-CRT group occurred when an LV lead could not be placed, or when diaphragmatic stimulation occurred due to phrenic nerve capture. Ultimately, crossover occurred in 48% of patients assigned to the His-CRT group, and 26% of patients in the BiV-CRT arm; a total of 16 subjects received His-CRT. The His-CRT group demonstrated a significant decrease in QRS duration ( $p < 0.001$ ) and significant increase in LVEF ( $p < 0.001$ ) at six months. Limitations of the study include the high rates of intraprocedural crossover, small study population, and short term follow up. Additional well-designed randomized controlled trials with large patient populations and long term follow-up are needed to support the clinical effectiveness of His bundle pacing CRT.

Qian et al. (2019) conducted a systematic review and meta-analysis to evaluate the efficacy of HBP in patients with heart failure and LV dyssynchrony. The successful rate of implantation, QRS duration, pacing threshold, LV function at baseline and follow-up, and mortality rates were extracted and summarized. Eleven studies including 494 patients were included in this analysis. The average age of the patients was 71.9 years and 63.2% of patients were male. Patients with ischemic etiology accounted for 32.8% of the population. Four studies reported 173 patients with atrial fibrillation (AF) and cardiomyopathy undergoing atrioventricular (AV) node ablation. The other seven studies focused on CRT candidates including de novo implantation, CRT nonresponders, patients with pacing-induced cardiomyopathy, and failed LV lead placement. The overall successful rate for implantation was 82.4%. The main indications for HBP were CRT candidates and cardiomyopathy with atrial fibrillation undergoing atrioventricular node ablation. Permanent HBP resulted in narrow QRS duration of  $116.3 \pm 13.9$  ms after implantation. LV functions, including echocardiographic parameters and clinical outcomes, significantly improved at follow-up ( $p < 0.001$ ). However, there was a trend of increased capture and bundle branch block correction thresholds at follow-up compared to baseline ( $p = 0.01$  and  $0.02$ , respectively). During a mean follow-up of 23.7 months, 5.9% of the patients experienced heart failure-related hospitalization and the mortality rate was 9.1%. The authors reported limitations of this meta-analysis include the limited sample size and most of the studies were cohort studies with inherent limitations that reduced the internal validity compared to randomized controlled trials. There was limited data on the effect size of HBP on outcomes as the studies included were observational and did not all have comparative arms. Next, some data, including pacing pulse width and follow-up time, were variable and inconsistent, which may influence the study uniformity. In addition, there was no uniformity in measuring QRS durations with selective and nonselective HBP. The authors concluded that although HBP has shown promising results in small and nonrandomized studies in several clinical situations, long-term safety and pacing threshold are needed.

Ali et al. (2018) concluded in a report on HBP that there is currently limited published data available for His pacing in any clinical setting. Although pacing thresholds for His pacing in bradycardia appear to be stable, there is limited long-term follow-up data available. When His pacing is used to deliver ventricular resynchronization in patients with bundle branch block, the pacing thresholds can be relatively high, though comparable to left ventricular pacing thresholds. This has the potential implications on battery longevity, though pacing is only required via a single lead (compared to biventricular pacing). Success rates for His lead implantation have been as low as 60% without dedicated tools and experience. Success rates have improved with the development of dedicated tools; however, the range of tools currently available are still limited, and these could be further

improved. Adequately powered randomized control trials are required to investigate whether the theoretical advantages of physiological ventricular activation are achieved with His pacing and if the encouraging results in observational studies translate into clinical benefit (Ali, et al., 2018).

Ezzeddine et al. (2018) reported that certain problems unique to HBP are faced with conventional active fixation pacing leads, including a higher pacing threshold owing to the fibrous structure of the His bundle and due to current limitations in lead design and delivery. In addition, higher pacing thresholds can lead to increased battery drain and shorter battery longevity compared with traditional RV pacing. Other limitations of permanent HBP include inability to perform lead implantation in 10%-20% of patients, particularly in patients with dilated and remodeled atria or other structural heart disease, which makes mapping of the His bundle and delivery of the lead difficult. Ventricular undersensing, atrial oversensing on the ventricular channel, and atrial capture can also occur and need to be carefully avoided or excluded at the time of implantation. Long-term randomized safety and efficacy data are needed.

### **Body Surface Potential Mapping**

The inadequate or absent response to cardiac resynchronization therapy (CRT) in some individuals may be due in part to inappropriate patient selection, suboptimal left ventricular lead placement, and/or the location of the selected pacing site in relation to a fibrosis-induced conduction block (Epstein, et al., 2013). It has been proposed that standard electrocardiogram (ECG) analysis to assess dyssynchrony may not accurately reflect the heterogeneity of electrical activation, and that the use of body surface potential mapping may help to predict and optimize CRT response.

Body surface potential mapping (BSPM; also known as body surface activation mapping) utilizes up to 300 ECG electrodes to expand the measured area of electrocardiographic activity beyond what is captured by a standard 12-lead ECG. The electrodes may be incorporated into a wearable vest or belt. The data from the electrodes is used to construct a three-dimensional (3D) representation of the thorax, and the potential distributions are displayed in real time throughout activation and recovery (Miller, et al., 2019; Coeytaux, et al, 2010).

BSPM has been used clinically for a variety of applications, including the following: in the acute diagnosis of myocardial ischemia, locating ectopic foci or accessory cardiac conduction pathways, and identifying persons at risk for arrhythmias. However, the clinical usefulness of this technology in CRT has not been established. There are no published standards for the use of BSPM in CRT. The technology is also more expensive, complicated, and time-consuming than standard ECG, and requires experienced personnel to complete (Pereira, et al., 2020).

**U.S. Food and Drug Administration (FDA):** In September 2008, the PRIME ECG® System with Enhanced Diagnostic Algorithm (HeartScape Technologies, Bangor, County Down, United Kingdom) was granted 510(k) approval by the FDA as a Class II device. The PRIME ECG® system employs a single-use vest (electrode array) consisting of 80 leads. The data from the leads is processed to create a color-graded image on a panel display, and to make a recommendation as to the presence of a normal, abnormal, or acute myocardial infarction condition. It is not specifically FDA-approved for use in CRT.

The CardiInsight® Cardiac Mapping System (Medtronic, 2016, Mounds View, MN) and ECVUE Mapping System (CardioInsight Technologies, 2014 and 2015, Cleveland, OH) were also granted 510(k) approval by the FDA as Class II devices. They include a sensor array (vest) of 252 electrodes, a workstation, and software to create a 3D map of the heart from real-time ECG signals and computed tomography (CT) scan data. The systems were approved for acquisition, analysis, display, and storage of cardiac electrophysiological data and maps for analysis. They are not specifically FDA-approved for use in CRT.

**Literature Review:** The studies published in the peer-reviewed literature addressing the use of BSPM in CRT consist primarily of nonrandomized trials with small patient populations, limited or no follow up, and employ a variety of different electrode arrays (Sedova, et al., 2021; Kittnar, et al., 2018; Gage, et al., 2017; Johnson, et al., 2017; Ploux, et al., 2013; Samesima, et al., 2013; Samesima, et al., 2007). There is a lack of published randomized controlled trials comparing body surface potential mapping and standard methods for patient selection or lead placement optimization in CRT. Clinical trials are ongoing investigating the use of BSPM in CRT.

### **Permanent Leadless Pacemaker**

Traditional single-chamber cardiac pacemakers are implanted through a small incision and fitted into a pocket created under the skin of the upper chest near the collarbone with the pacemaker leads placed via transvenous access to the heart chambers and attached to the generator. The leads transmit information from the heart to the generator, and electrical impulses from the generator to heart muscle. Leadless pacemaker systems utilize a self-contained system which includes both the pulse generator and the electrode within a single unit that is placed into the right ventricle via a transvenous approach.

**U.S. Food and Drug Administration (FDA):** In 2016, the FDA granted premarket approval (PMA) for the Micra™ Transcatheter Pacemaker System (TPS) (Medtronic, Mounds View, MN). This device is indicated for use in patients who have experienced one or more of the following conditions:

- symptomatic paroxysmal or permanent high-grade AV block in the presence of AF
- symptomatic paroxysmal or permanent high-grade AV block in the absence of AF, as an alternative to dual chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy
- symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses), as an alternative to atrial or dual chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy

Rate-responsive pacing is indicated to provide increased heart rate appropriate to increasing levels of activity.

The Micra device is contraindicated for patients who have implanted devices that would interfere with the pacemaker, who are severely obese, or who have an intolerance to materials in the device or the blood thinner heparin. It is also contraindicated for patients with veins that are unable to accommodate the 7.8 millimeter introducer sheath or pacemaker implant.

On November 17, 2021, the FDA issued a letter to healthcare providers reaffirming the risk of major complications should cardiac perforation occur during leadless pacemaker implantation. Cardiac perforation is a rare complication of any pacemaker implantation, and the overall risk of perforation associated with leadless pacemaker implantation appears similar to the risk associated with traditional pacing implants. However, per the statement issued: “the Medtronic Micra leadless pacemaker premarket clinical studies suggested major complications related to cardiac perforation appeared to be more severe for patients who received a leadless pacing system compared to patients who received a transvenous pacemaker. The FDA continues to evaluate outcomes in patients who receive leadless pacing systems. Information from real-world use suggests that cardiac perforations associated with Micra leadless pacemakers are more likely to be associated with serious complications, such as cardiac tamponade or death, than with traditional pacemakers” (FDA, 2021).

The Nanostim™ leadless pacemaker (St. Jude Medical, now Abbott Medical, Sylmar, CA) was investigated as part of a Phase I clinical trial between 2013 and 2016; a total of 1,423 devices were implanted. The trial was halted in 2016 and the device recalled due to battery malfunction and difficulty with device retrieval.

**Literature Review:** In a prospective registry, El-Chami et al. (2018) compared the outcomes of the Micra transcatheter pacing system (TPS) to a historical transvenous pacing cohort implanted with dual-chamber pacemakers. The authors report updated performance of the Micra TPS from a worldwide post approval registry (PAR) and compare it with The Micra Investigational Device Exemption (IDE) study as well as a transvenous historical control. The safety objective of the analysis was system- or procedure-related major complications through 12 months postimplantation. A comparison of the major complication rate with that of the 726 patients from the IDE and with a reference data set of 2667 patients with transvenous pacemakers. The Micra device was successfully implanted in 1801 of 1817 patients (99.1%). The mean follow-up period was 6.8 months. Through 12 months, the major complication rate was 2.7%. The risk of major complications for Micra PAR patients was 63% lower than that for patients with transvenous pacemakers through 12 months postimplantation. The major complication rate trended lower in the PAR than in the IDE study, driven by the lower pericardial effusion rate in the PAR. There were three cases of infection associated with the procedure, but none required device removal and there were no battery or telemetry issues. Pacing thresholds were low and stable through 12 months postimplantation. A reported limitation of this study is lack of a randomized controlled study which would allow a direct comparison and would clearly define the benefits and drawbacks of leadless pacing compared to traditional transvenous pacemakers.

Roberts et al. (2017) reported acute performance of the Micra transcatheter pacemaker from a worldwide Post-Approval Registry. The registry is an ongoing prospective single-arm observational study designed to assess the safety and effectiveness of Micra in the post-approval setting. The safety end point was system or procedure-related major complications at 30 days post implant. Major complication rates were compared with that of the 726 patients from the investigational study (Reynolds, et al., 2016). Electrical performance was also characterized. The device was successfully implanted in 792 of 795 registry patients (99.6%) by 149 implanters at 96 centers in 20 countries. Through 30 days post implant, a total of 13 major complications occurred in 12 patients, for a major complication rate of 1.51% (95%). Major complications included cardiac effusion/perforation (1, 0.13%), device dislodgement (1, 0.13%), and sepsis (1, 0.13%). After adjusting for baseline differences, the rate of major complications in the registry trended lower than the investigational trial. Early pacing capture thresholds were low and stable. The data does not include all patients implanted with Micra TPS worldwide. This report is an interim analysis with limited follow-up, including patients who had not yet been followed for 30 days, and it reflects the geographies of enrolled patients who were primarily from Europe. However, enrollment of patients in the United States is continuing, and patients in the registry will be followed for a minimum of nine years. Few patients had follow-up electrical data available, and thus battery projections are preliminary and based on only 54 patients.

In a multicenter prospective international study, the Micra Transcatheter Pacing Study, Duray et al. (2017) reported on long-term safety of Micra at 12 months and electrical performance through 24 months. Enrolled patients met class I or II guideline recommendations for de novo ventricular pacing. The long-term safety objective was freedom from a system- or procedure-related major complication at 12 months. A predefined historical control group of 2667 patients with transvenous pacemakers was used to compare major complication rates. The long-term safety objective was achieved with a freedom from major complication rate of 96.0% at 12 months. The risk of major complications for patients with Micra (n=726) was 48% lower than that for patients with transvenous systems through 12 months postimplant. Across subgroups of age, sex, and comorbidities, Micra reduced the risk of major complications compared to transvenous systems. Electrical performance was excellent through 24 months, with a projected battery longevity of 12.1 years.

In a prospective observational study (n=30), Martinez-Sande et al. (2017) reported on the safety and efficacy of the Micra leadless pacemaker. Outcome measures were major complication (defined as death, serious deterioration of patient's condition, event resulting in vital risk requiring intervention, or hospitalization  $\geq 48$  hrs). Successful implantation was accomplished in all patients referred for leadless implantation. The mean age was 79.4 years; 20 (66.6%) were men and 28 had permanent atrial fibrillation (93.3%); one had atrial tachycardia and one had sinus rhythm. Concomitant atrioventricular node ablation was performed immediately after implantation in five patients (16.6%), and implantation was performed after transcatheter aortic valve implantation in two. With the exception of one moderate pericardial effusion without tamponade, there were no severe complications. The mean follow up was 5.3 months and four patients had more than one year of follow-up. Sensing and pacing parameters were stable both at implantation and during the short- to mid-term follow-up.

Reynolds et al. (2016) reported on interim analysis of an on-going prospective, nonrandomized, single-study-group, multisite, clinical study to evaluate the safety and efficacy of the Micra Transcatheter Pacemaker System (Medtronic). Transcatheter pacemaker was implanted in 725 patients with guideline-based indications for ventricular pacing, with 719 (99.2%) successfully implanted and followed for six months. The primary safety end point was freedom from system-related or procedure-related major complications. The primary efficacy end point was the percentage of patients with low and stable pacing capture thresholds at six months ( $\leq 2.0$  V at a pulse width of 0.24 msec and an increase of  $\leq 1.5$  V from the time of implantation). The safety and efficacy end points were evaluated against performance goals (based on historical data) of 83% and 80%, respectively. A post hoc analysis was completed in which the rates of major complications was compared with a control cohort of 2667 patients with transvenous pacemakers from six previously published studies. The Kaplan–Meier estimate of the rate of the primary safety end point was 96.0% (95% confidence interval [CI], 93.9 to 97.3;  $p < 0.001$  for the comparison with the safety performance goal of 83%); there were 28 major complications in 25 of 725 patients, and no dislodgements. The rate of the primary efficacy for 297 patients end point was 98.3% (95% CI, 96.1 to 99.5;  $p < 0.001$  for the comparison with the efficacy performance goal of 80%) among 292 of 297 patients with paired 6-month data. Patients with transcatheter pacemakers had fewer major complications than did the control patients (hazard ratio, 0.49; 95% CI, 0.33 to 0.75;  $p = 0.001$ ). The study was limited by the lack of randomization,

the comparator was historical data and this was an interim analysis of less than half the participants at six months.

### **Professional Societies/Organizations**

#### **American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) 2018 Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay:**

The 2018 ACC/AHA/HRS document makes the following recommendations for permanent pacing techniques in persons with atrioventricular block:

- In patients with atrioventricular block who have an indication for permanent pacing with a LVEF between 36% and 50% and are expected to require ventricular pacing more than 40% of the time, it is reasonable to choose pacing methods that maintain physiologic ventricular activation (e.g., cardiac resynchronization therapy [CRT] or His bundle pacing) over right ventricular pacing (Class IIa recommendation)
- In patients with atrioventricular block who have an indication for permanent pacing with a LVEF between 36% and 50% and are expected to require ventricular pacing less than 40% of the time, it is reasonable to choose right ventricular pacing over pacing methods that maintain physiologic ventricular activation (e.g., CRT or His bundle pacing) (Class IIa)

Regarding leadless pacemakers, the guideline further notes “pacing with entirely leadless devices is...an emerging area of interest, but the role of these new devices in real-world practice, and their potential interaction with other cardiac devices, is not yet clear” (Kusumoto, et al., 2019).

#### **American College of Cardiology Foundation (ACCF), Heart Rhythm Society (HRS), American Heart Association (AHA), American Society of Echocardiography (ASE), Heart Failure Society of America (HFSA), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Cardiovascular Computed Tomography (SCCT), and Society for Cardiovascular Magnetic Resonance (SCMR) 2013 Appropriate Use Criteria for Implantable Cardioverter-Defibrillators and Cardiac Resynchronization Therapy:**

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

The indications for ICD and CRT were developed by a multidisciplinary writing team and scored by a separate independent technical panel. The final score reflects the median score of the 17 technical panel members and has been labeled according to the categories of Appropriate (median 7 to 9), May Be Appropriate (median 4 to 6), and Rarely Appropriate (median 1 to 3). The authors state that “The relationship of these criteria to existing guidelines was provided to the technical panel. In addition, extensive links to clinical trials and other literature regarding the role of ICD and CRT in each clinical scenario were provided to technical panel members. This document represents the current understanding of the clinical utility of ICD and CRT implantation in clinical practice as measured by physicians with a variety of backgrounds and areas of expertise. It is the goal that these criteria will help provide a guide to inform medical decisions and help clinicians and stakeholders understand areas of consensus as well as uncertainty, while identifying areas where there are gaps in knowledge that warrant additional investigation” (Russo, et al., 2013).

The authors also state that, “Atrial arrhythmias (including atrial fibrillation, atrial flutter, and atrial tachycardia) are not included in the indication tables. There are fewer data available for CRT in patients with persistent atrial arrhythmias, and the writing group elected to avoid additional scenarios for practical reasons, as the document already includes a large number of scenarios. However, it is assumed that the presence of intermittent or persistent atrial arrhythmias would not preclude CRT implantation, and the benefits of CRT would also apply to patients with persistent atrial arrhythmias, as long as CRT is maintained nearly 100% of the time” (Russo, et al., 2013).

Ambulatory class IV is defined as class IV heart failure with: 1) no active acute coronary syndrome; 2) no inotropes; and 3) on guideline-direct medical therapy (GDMT). A normal LVEF is defined as  $\geq 50\%$ . The authors

stated that, “GDMT for heart failure in the setting of LV systolic dysfunction requires individualization but typically should include the combination of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and beta blocker therapy adjusted to target doses as tolerated, with diuretics adjusted if/as needed to control fluid retention. In selected patients, the addition of aldosterone antagonists and hydralazine plus nitrate combinations should be considered. Patients who are going to receive substantial benefit from medical treatment alone usually show some clinical improvement during the first 3 to 6 months. Medical therapy is also assumed to include adequate rate control for tachyarrhythmias, including atrial fibrillation. Therefore, it is recommended that GDMT be provided for at least 3 months before planned reassessment of LV function to consider device implantation. If LV function improves to the point where primary prevention indications no longer apply, then device implantation is not indicated” (Russo, et al., 2013).

Recommendations are provided based on the following scoring method:

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

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

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

**The following indications were rated as Appropriate Care (median score 7-9):**

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

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

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

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

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

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

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

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

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

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

- QRS 120-149 ms, LBBB (7)
- QRS  $\geq$  150 ms, LBBB (8)
- QRS  $\geq$  150 ms, non-LBBB (7)

**The following indications were rated as May Be Appropriate for Care (median score 4-6):**

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

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

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

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

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

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

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

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

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

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

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

- QRS 120-149 ms, LBBB (6) or non-LBBB (4)
- QRS  $\geq$  150 ms, LBBB (6) or non-LBBB (5)

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

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



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

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

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

- Class I: Benefit >>> Risk; Procedure/Treatment should be performed/administered
- Class IIa: Benefit >> Risk; Additional studies with focused objectives needed. It is reasonable to perform procedure/administer treatment.
- Class IIb: Benefit ≥ Risk; Additional studies with broad objectives needed; additional registry data would be helpful. Procedure/treatment may be considered.
- Class III: No Benefit or Harm
  - Class of Recommendation (COR) III: No Benefit
    - Procedure/Test: not helpful
    - Treatment: no proven benefit
  - COR III: Harm
    - Procedure/Test: excess cost w/o benefit or harmful
    - Treatment: harmful to patients

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

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

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

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

#### Class I

- CRT is indicated for patients who have LVEF ≤ 35%, sinus rhythm, LBBB with a QRS duration ≥ 150 ms, and NYHA class II, III, or ambulatory IV symptoms on guideline directed medical therapy (GDMT) (Level of Evidence: A for NYHA class III/IV; Level of Evidence: B for NYHA class II).

#### Class IIa

- CRT can be useful for patients who have LVEF ≤ 35%, sinus rhythm, LBBB with a QRS duration 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT (Level of Evidence: B).
- CRT can be useful for patients who have LVEF ≤ 35%, sinus rhythm, a non-LBBB pattern with a QRS ≥ 150 ms, and NYHA class III/ambulatory class IV symptoms on GDMT (Level of Evidence: A).

- CRT can be useful in patients with atrial fibrillation and LVEF  $\leq$  35% on GDMT if the patient requires ventricular pacing or otherwise meets CRT criteria and b) AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT (Level of Evidence: B).
- CRT can be useful for patients on GDMT who have LVEF  $\leq$  35% and are undergoing new or replacement device placement with anticipated requirement for significant ( $>$  40%) ventricular pacing (Level of Evidence: C).

#### Class IIb

- CRT may be considered for patients who have LVEF  $\leq$  30%, ischemic etiology of heart failure, sinus rhythm, LBBB with a QRS duration of  $\geq$ 150 ms, and NYHA class I symptoms on GDMT (Level of Evidence: C).
- CRT may be considered for patients who have LVEF  $\leq$  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  $\leq$  35%, sinus rhythm, a non-LBBB pattern with a QRS duration  $\geq$  150 ms, and NYHA class II symptoms on GDMT (Level of Evidence: B).

#### Class III: No Benefit

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

**American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Practice Guideline for the Management of Heart Failure:** In 2013, the ACCF/AHA Guideline for the Management of Heart Failure was updated (Yancy, et al., 2013). The CRT recommendations for device therapy for management of Stage C heart failure (i.e., structural heart disease with prior or current symptoms of heart failure) are in complete alignment with recommendations in the 2012 ACCF/AHA/HRS focused update for device-based therapy of cardiac rhythm abnormalities as noted above (Epstein, et al., 2013). The recommendations have not changed in the 2017 focused updated of the ACCF/AHA/HFSA Guideline for the Management of Heart Failure (Yancy, et al., 2017).

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

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

#### **The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative:**

The Heart Rhythm Society states "don't implant pacemakers for asymptomatic sinus bradycardia in the absence of other indications for pacing" (released February 10, 2014).

#### **Use Outside of the U.S.**

St. Jude Medical has CE Mark clearance in Europe for the Quadra Assura MP™ cardiac resynchronization therapy defibrillator allows heart pacing to occur at several locations on the left side of the heart. Quadra Assura MP is an investigational device in the US.

CE Marking was granted for the WiSE CRT System in October 2015. The company anticipates introducing a second-generation WiSE system in Europe. The transmitter size has been reduced by half, making it smaller than a conventional pacemaker. Second-generation battery life is expected to equal conventional CRT systems.

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

**therapy:** The updated 2021 ESC guidelines on cardiac pacing and CRT include expanded recommendations for CRT, and new sections which include leadless pacing and alternative pacing strategies/sites (Glikson, et al., 2021). Guideline recommendations are classified as Class I, Class IIa, Class IIb, and Class III. The classification system is described as follows:

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

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

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

Recommendations for CRT in patients in sinus rhythm (SR):

- CRT is recommended for symptomatic patients with heart failure (HF) with LVEF  $\leq$  35%, QRS duration  $\geq$  150 ms, and left bundle branch block (LBBB) QRS morphology despite optimal medical treatment (OMT) in order to improve symptoms and reduce morbidity and mortality (Class I, Level A)
- CRT should be considered for symptomatic patients with HF with LVEF  $\leq$  35%, QRS duration 130 – 149 ms, and LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity and mortality (Class IIa, Level B)
- CRT should be considered for symptomatic patients with HF LVEF  $\leq$  35%, QRS duration  $\geq$  150 ms, and non-LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity (Class IIa, Level B)
- CRT may be considered for symptomatic patients with HF with LVEF  $\leq$  35%, QRS duration 130 – 149 ms, and non-LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity (Class IIb, Level B)
- CRT is not indicated in patients with HF and QRS duration  $<$ 130 ms without an indication for RV pacing (Class III, Level A)

Recommendations for CRT in patients with persistent or permanent atrial fibrillation (AF):

- Patients with HF with permanent AF who are candidates for CRT:
  - CRT should be considered for patients with HF and LVEF  $\leq$  35% in NYHA class III or IV despite OMT if they are in AF and have intrinsic QRS  $\geq$  130 ms, provided a strategy to ensure biventricular capture is in place, in order to improve symptoms and reduce morbidity and mortality (Class IIa, Level C)
  - Atrioventricular junction (AVJ) ablation should be added in the case of incomplete biventricular pacing ( $<$ 90 – 95%) due to conducted AF (Class IIa, Level B)
- Patients with symptomatic AF and an uncontrolled heart rate who are candidates for AVJ ablation (irrespective of QRS duration):

- CRT is recommended in patients with HF with reduced ejection fraction (<40%) (Class I, Level B)
- CRT rather than standard right ventricular (RV) pacing should be considered in patients with HF with mildly reduced ejection fraction (40 - 49%) (Class IIa, Level C)
- RV pacing should be considered in patients with HF with preserved ejection fraction (≥ 50%) (Class IIa, Level B)
- CRT may be considered in patients with HF with preserved ejection fraction (≥ 50%) (Class IIb, Level C)

Recommendation for upgrade from RV pacing to CRT:

- Patients who have received a conventional pacemaker or an ICD and who subsequently develop symptomatic HF with LVEF ≤ 35% despite OMT, and who have a significant proportion of RV pacing, should be considered for upgrade to CRT (Class IIa, Level B)

Recommendation for patients with HF and atrioventricular block (AVB):

- CRT rather than RV pacing is recommended for patients with HF with reduced ejection fraction (<40%) regardless of NYHA class who have an indication for ventricular pacing and high-degree AVB in order to reduce morbidity. This includes patients with AF (Class I, Level A)

The document also acknowledges the growing interest in both His bundle pacing and leadless pacemakers, however the authors note that large RCTs and long-term follow up are still lacking (Glikson, et al., 2021).

**Canadian Cardiovascular Society (CCS) Guidelines for the Management of Heart Failure:** The 2017 CCS heart failure (HF) management guidelines include recommendations for CRT (Ezekowitz, et al., 2017). The recommendations were developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) standards, described as follows:

- Quality of evidence and definitions state that when the desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not, guideline panels offer strong recommendations. On the other hand, when the trade-offs are less certain—either because of low quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced—weak recommendations become mandatory.
- Quality of evidence and definitions:
  - High quality: Further research is very unlikely to change our confidence in the estimate of effect.
  - Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
  - Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
  - Very low quality: Any estimate of effect is very uncertain.

The following recommendations for CRT are in the 2017 guidelines:

- Recommend CRT for patients in sinus rhythm with NYHA class II, III, or ambulatory class IV HF despite optimal medical therapy, a LVEF ≤ 35%, and QRS duration ≥ 130 ms with left bundle branch block (LBBB) (Strong Recommendation; High-Quality Evidence)
- CRT may be considered for patients in sinus rhythm with NYHA class II, III, or ambulatory class IV HF despite optimal medical therapy, a LVEF ≤ 35%, and QRS duration ≥ 150 ms with non-LBBB (Weak Recommendation; Low-Quality Evidence)
- CRT may be considered for patients in permanent AF who can expect to achieve close to 100% pacing and are otherwise suitable for this therapy (Weak Recommendation; Low-Quality Evidence)
- CRT might be considered for patients who require chronic right ventricular (RV) pacing in the setting of HF symptoms and reduced LVEF (Weak Recommendation; Moderate-Quality Evidence)
- Recommend CRT not be used for patients with QRS < 130 ms, irrespective of HF symptoms, LVEF, or the presence or absence of mechanical dyssynchrony shown on current imaging techniques (Strong Recommendation; Moderate-Quality Evidence)
- Recommend the addition of ICD therapy be considered for patients referred for CRT who meet primary ICD requirements (Strong Recommendation; High-Quality Evidence)

**National Institute for Health and Care Excellence (NICE):** In 2014, NICE published guidance on the use of implantable cardioverter defibrillators and cardiac resynchronization therapy (CRT-P and CRT-D devices) for arrhythmias and heart failure. The authoring committee made the following recommendations for CRT treatment options in persons with heart failure who have left ventricular dysfunction, and an EF ≤ 35%:

- QRS < 120 milliseconds (ms): CRT not indicated
- QRS 120 – 149 ms
  - Without left bundle branch block (LBBB)
    - NYHA Class I – III: CRT not indicated
    - NYHA Class IV: CRT-P
  - With LBBB
    - NYHA Class I: CRT not indicated
    - NYHA Class II: CRT-D
    - NYHA Class III: CRT-P or CRT-D
    - NYHA Class IV: CRT-P
- QRS ≥ 150 ms
  - With or without LBBB
    - NYHA Class I and II: CRT-D
    - NYHA Class III: CRT-P or CRT-D
    - NYHA Class IV: CRT-P

An August 2018 NICE Interventional procedures guidance on leadless cardiac pacemaker implantation for bradyarrhythmias states that “evidence on the safety of leadless cardiac pacemaker implantation for bradyarrhythmias shows that there are serious but well-recognized complications. The evidence on efficacy is inadequate in quantity and quality. Clinicians wishing to do leadless cardiac pacemaker implantation for bradyarrhythmias in people who cannot have conventional cardiac pacemaker implantation should ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy compared with conventional pacemaker implantation, and provide them with clear written information. Further research in people who could have conventional cardiac pacemaker implantation should report the patient selection criteria and compare leadless pacemakers with conventional pacemakers. Follow-up should be for at least 5 years and outcomes should include adverse events, symptom relief, quality of life and device durability in the long-term”.

**Canadian Agency for Drugs and Technologies in Health (CADTH):** The 2015 Canadian Agency for Drugs and Technologies in Health (CADTH) Emerging Health Technologies on leadless pacemakers for the treatment of cardiac arrhythmias states that further evaluation of leadless pacemakers for long-term pacing performance and complication rates compared with traditional pacemakers is required. If long-term efficacy and safety can be demonstrated, leadless pacemakers may provide an additional treatment option for select patients with cardiac arrhythmias.

## Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD	National	Leadless Pacemakers (20.8.4)	1/18/2017
LCD	First Coast Service Options, Inc.	Biventricular Pacing/Cardiac Resynchronization Therapy (L33271)	1/8/2019

Note: Please review the current Medicare Policy for the most up-to-date information.

## Coding/Billing Information

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

**Considered Medically Necessary when used to report the insertion or replacement of a biventricular pacemaker or when combined with an implantable cardioverter defibrillator and/or leads:**

<b>CPT®*</b> <b>Codes</b>	<b>Description</b>
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)
33208	Insertion of new or replacement of permanent pacemaker with transvenous electrode(s); atrial and ventricular
33211	Insertion or replacement of temporary transvenous dual chamber pacing electrodes (separate procedure)
33213	Insertion of pacemaker pulse generator only; with existing dual leads
33214	Upgrade of implanted pacemaker system, conversion of single chamber 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)
33217	Insertion of 2 transvenous electrodes, permanent pacemaker or implantable defibrillator
33221	Insertion of pacemaker pulse generator only; with existing multiple leads
33222	Relocation of skin pocket for pacemaker
33223	Relocation of skin pocket for implantable defibrillator
33224	Insertion of pacing electrode, cardiac venous system, for left ventricular pacing, with attachment to previously placed pacemaker or implantable 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 implantable defibrillator or pacemaker pulse generator (eg, for upgrade to dual chamber system) (List separately in addition to code for primary procedure)
33226	Repositioning of previously implanted cardiac venous system (left ventricular) electrode (including removal, insertion and/or replacement of existing generator)
33228	Removal of permanent pacemaker pulse generator with replacement of pacemaker pulse generator; dual lead system
33229	Removal of permanent pacemaker pulse generator with replacement of pacemaker pulse generator; multiple lead system
33230	Insertion of implantable defibrillator pulse generator only; with existing dual leads
33231	Insertion of implantable defibrillator pulse generator only; with existing multiple leads
33240	Insertion implantable defibrillator pulse generator only; with existing single lead
33249	Insertion or replacement of permanent implantable defibrillator system, with transvenous lead(s), single or dual chamber
33263	Removal of implantable defibrillator pulse generator with replacement of implantable defibrillator pulse generator; dual lead system
33264	Removal of implantable defibrillator pulse generator with replacement of implantable defibrillator pulse generator; multiple lead system

<b>HCPCS</b> <b>Codes</b>	<b>Description</b>
C1721	Cardioverter-defibrillator, dual chamber (implantable)
C1722	Cardioverter-defibrillator, single chamber (implantable)
C1777	Lead, cardioverter-defibrillator, endocardial single coil (implantable)
C1779	Lead, pacemaker, transvenous VDD single pass
C1785	Pacemaker, dual chamber, rate-responsive (implantable)
C1786	Pacemaker, single chamber, rate-responsive (implantable)
C1882	Cardioverter-defibrillator, other than single or dual chamber (implantable)
C1895	Lead, cardioverter-defibrillator, endocardial dual coil (implantable)
C1896	Lead, cardioverter-defibrillator, other than endocardial single or dual coil (implantable)
C1898	Lead, pacemaker, other than transvenous VDD single pass

<b>HCPCS Codes</b>	<b>Description</b>
C1899	Lead, pacemaker/cardioverter-defibrillator combination (implantable)
C1900	Lead, left ventricular coronary venous system
C2619	Pacemaker, dual chamber, non rate-responsive (implantable)
C2620	Pacemaker, single chamber, non rate-responsive (implantable)
C2621	Pacemaker, other than single or dual chamber (implantable)
G0448	Insertion or replacement of a permanent pacing cardioverter-defibrillator system with transvenous lead(s), single or dual chamber with insertion of pacing electrode, cardiac venous system, for left ventricular pacing

**Considered Experimental/Investigational/Unproven:**

<b>CPT®*</b> <b>Codes</b>	<b>Description</b>
33274	Transcatheter insertion or replacement of permanent leadless pacemaker, right ventricular, including imaging guidance (eg, fluoroscopy, venous ultrasound, ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed
33275	Transcatheter removal of permanent leadless pacemaker, right ventricular, including imaging guidance (eg, fluoroscopy, venous ultrasound, ventriculography, femoral venography), when performed
33999†	Unlisted procedure, cardiac surgery
0515T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; complete system (includes electrode and generator [transmitter and battery])
0516T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; electrode only
0517T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; pulse generator component(s) (battery and/or transmitter) only
0518T	Removal of only pulse generator component(s) (battery and/or transmitter) of wireless cardiac stimulator for left ventricular pacing
0519T	Removal and replacement of wireless cardiac stimulator for left ventricular pacing; pulse generator component(s) (battery and/or transmitter)
0520T	Removal and replacement of wireless cardiac stimulator for left ventricular pacing; pulse generator component(s) (battery and/or transmitter), including placement of a new electrode
0521T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording, and disconnection per patient encounter, wireless cardiac stimulator for left ventricular pacing
0522T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, wireless cardiac stimulator for left ventricular pacing
0695T	Body surface–activation mapping of pacemaker or pacing cardioverter-defibrillator lead(s) to optimize electrical synchrony, cardiac resynchronization therapy device, including connection, recording, disconnection, review, and report; at time of implant or replacement (Code effective 01/01/2022)
0696T	Body surface–activation mapping of pacemaker or pacing cardioverter-defibrillator lead(s) to optimize electrical synchrony, cardiac resynchronization therapy device, including connection, recording, disconnection, review, and report; at time of follow-up interrogation or programming device evaluation (Code effective 01/01/2022)

**†Note: Considered Experimental/Investigational/Unproven when used to report His bundle pacing (HBP) for any indication**

**\*Current Procedural Terminology (CPT®) ©2020 American Medical Association: Chicago, IL.**

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