2.02.10	Biventricular Pacemakers (Cardiac Resynchronization Therapy) for the Treatment of Heart Failure		
Original Policy Date:	March 29, 2013	**Effective Date:**	March 1, 2024
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Policy Statement

I. Biventricular pacemakers with or without an accompanying implantable cardiac defibrillator (i.e., a combined biventricular pacemaker plus implantable cardiac defibrillator) as a treatment of heart failure may be considered **medically necessary** in **either** of the following criteria:
   A. **New York Heart Association (NYHA) class III or IV** and **all** of the following:
      1. Left ventricular ejection fraction less than or equal to 35% with **either** of the following:
         a. Left bundle branch block
         b. QRS interval greater than or equal to 150 ms
      2. Individuals treated with a guideline-directed medical therapy
      3. Sinus rhythm
   B. **New York Heart Association (NYHA) class II** and **all** of the following:
      1. Left ventricular ejection fraction less than or equal to 30% with **either** of the following:
         a. Left bundle branch block
         b. QRS interval greater than or equal to 150 ms
      2. Individuals treated with a guideline-directed medical therapy
      3. Sinus rhythm

II. Biventricular pacemakers with or without an accompanying implantable cardiac defibrillator, as an alternative to a right ventricular pacemaker (with or without an accompanying implantable cardiac defibrillator) may be considered **medically necessary** when **all** of the following are present:
   A. Left ventricular ejection fraction less than or equal to 50%
   B. New York Heart Association (NYHA) class I, II, III, or IV heart failure
   C. Individuals treated with a guideline-directed medical therapy
   D. The presence of atrioventricular block with requirement for a high percentage of ventricular pacing and **one** or more of the following:
      1. Second-degree AV block or a PR interval of 300 ms or more when paced at 100 beats per minute
      2. Third-degree AV block

III. Biventricular pacemakers, with or without an accompanying implantable cardiac defibrillator are considered **investigational** in **any** of the following situations:
   A. Treatment for individuals with NYHA **class I heart failure** unless all of the following are present:
      1. Left ventricular ejection fraction less than or equal to 50%
      2. Individuals treated with a guideline-directed medical therapy
      3. **Atrioventricular block** with requirement for a high percentage of ventricular pacing) and **1 or more** of the following:
         a. Second-degree AV block or a PR interval of 300 ms or more when paced at 100 beats per minute
         b. Third-degree AV block
   B. Treatment for heart failure in patients with **atrial fibrillation**

IV. The following are considered **investigational**:
   A. Triple-site (triventricular or quadripolar) cardiac resynchronization therapy, using an additional pacing lead
   B. An intrathoracic fluid monitoring as a component of a biventricular pacemaker
   C. Cardiac resynchronization therapy with wireless left ventricular endocardial pacing

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Atrioventricular (AV) block with a requirement for a high percentage of ventricular pacing is considered to be present when there is either:

- Second-degree AV block or a PR interval of 300 ms or more when paced at 100 beats per minute
- Third-degree AV block

Guideline-directed medical therapy for heart failure is outlined in the 2022 American Heart Association, American College of Cardiology, and Heart Failure Society of America guidelines for the management of heart failure (Heidenreich et al [2022]).

Use of a Biventricular Pacemaker with an Implantable Cardioverter Defibrillator

This medical policy only refers to biventricular pacemakers and does not address the medical necessity of an implantable cardioverter defibrillator (ICD). If the biventricular pacemaker has been billed with an ICD, the ICD should be reviewed against the medically necessary criteria for ICDs (See Blue Shield of California Medical Policy: Implantable Cardioverter Defibrillators). Therefore, the use of a biventricular pacemaker with an accompanying ICD should meet the medically necessary criteria of both policies.

New York Heart Association (NYHA) – Classes of Heart Failure

- Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
- Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
- Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20—100 m). Comfortable, only at rest.
- Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Coding

Note that CPT "dual-chamber" codes describe combined right atrial and right ventricular electrode placement. CPT "biventricular" codes describe the additional placement of a left ventricular electrode via the cardiac vein (three leads). A left ventricular pacing lead is placed in the marginal branch of the coronary sinus and into a cardiac vein to allow for biventricular pacing for cardiac resynchronization. CPT notes the following:

> "A single chamber pacemaker system includes a pulse generator and 1 electrode inserted in either the atrium or the ventricle. A dual chamber pacemaker system includes a pulse generator and 1 electrode inserted in the right atrium and 1 electrode inserted in the right ventricle. In certain circumstances, an additional electrode may be required to achieve pacing of the left ventricle (bi-ventricular pacing). In this event, transvenous (cardiac vein) placement of the electrode should be separately reported using the following CPT codes. Epicardial placement of the electrode should be separately reported using 33202-33203."

- **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 (e.g., for upgrade to dual chamber system) (List separately in addition to code for primary procedure)

Use 33225 in conjunction with 33206, 33207, 33208, 33212, 33213, 33214, 33216, 33217, 33221, 33223, 33228, 33229, 33230, 33231, 33233, 33234, 33235, 33240, 33249, 33263, and 33264.

Thus, CPT describes 33225 as an "add-on" code to other pacing or implantable defibrillator procedures.

The following codes are specific to a wireless cardiac stimulator for left ventricular pacing (WiSE-CRT [EBR Systems]):

- **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; both components of pulse generator (battery and transmitter) only
- **0518T**: Removal of pulse generator for wireless cardiac stimulator for left ventricular pacing; battery component only
- **0519T**: Removal and replacement of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; both components (battery and transmitter)
- **0520T**: Removal and replacement of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; battery component only
- **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

Description

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

Related Policies

- Cardiac Hemodynamic Monitoring for the Management of Heart Failure in the Outpatient Setting
- Implantable Cardioverter Defibrillators

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

There are numerous CRT devices, combined implantable cardioverter-defibrillator (ICD) plus CRT devices (CRT-D), and combined CRT plus fluid monitoring devices. Some devices are discussed here. For example, in 2001, the InSync® Biventricular Pacing System (Medtronic), a stand-alone biventricular pacemaker, was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process for the treatment of patients with New York Heart Association (NYHA) class III or IV heart failure, on a stable pharmacologic regimen, who also have a QRS duration of 130 ms or longer and a left ventricular ejection fraction (LVEF) of 35% or less. Devices by Guidant (CONTAK-CD® CRT-D System) and Medtronic (InSync® ICD Model 7272) have been approved by the FDA through the premarket approval process for combined CRT defibrillators for patients at high risk of sudden cardiac death due to ventricular arrhythmias and who have NYHA class III or IV heart failure with a LVEF of 35% or less, QRS interval 130 ms or longer (≥120 ms for the Guidant device), and remain symptomatic despite a stable, optimal heart failure drug therapy. In 2006, Biotronik Inc. received premarket approval from the FDA for its combined CRT-D device with ventricular pacing leads (Tupos LV/ATx CRT-D/Kronos LV-T CRT-D systems[Food and Drug Administration. Summary of Safety an.... b.pdf. Accessed March 8, 2023.]); in 2013, the company received the FDA approval for updated CRT-D devices (Ilesto/Iforia series).[5,]On the basis of the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) study, indications for 3 Guidant CRT-D (Cognis®, Livian®, and Contak Renewal; Boston Scientific) devices were expanded to include patients with heart failure who receive stable optimal pharmacologic therapy for heart failure and who meet any of the following classifications[Food and Drug Administration. Summary of Safety an.... b.pdf. Accessed March 8, 2023.]:

- Moderate-to-severe heart failure (NYHA class III or IV) with an ejection fraction less than 35% and QRS interval greater than 120 ms.
- Left bundle branch block with a QRS interval greater than or equal to 130 ms, ejection fraction less than 30%, and mild (NYHA class II) ischemic or nonischemic heart failure or asymptomatic (NYHA class I) ischemic heart failure.

In April 2014, the FDA further expanded indications for multiple Medtronic CRT devices to include patients with NYHA class I, II, or III heart failure, who have an LVEF of 50% or less on stable, optimal heart failure medical therapy, if indicated, and have atrioventricular block that is expected to require a high percentage of ventricular pacing that cannot be managed with algorithms to minimize right ventricular pacing. The expanded indication was based on data from the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) study, a Medtronic-sponsored randomized controlled trial that evaluated the use of CRT in patients with NYHA class I, II, or III heart failure, LVEF of 50% or less, and atrioventricular block.

Several CRT devices have incorporated a fourth lead, providing quadripolar pacing. The Medtronic Viva™ Quad XT and the Viva Quad S have a fourth lead, and the Medtronic Attain Performa® has a left ventricular lead, which received clearance for marketing from the FDA in August 2014. The

Dynagen™ X4 and Inogen™ X4 devices (Boston Scientific) also incorporate a fourth lead. Other CRT devices with quadripolar leads have been approved for use outside of the U.S. (e.g., St. Jude Quartet™ left ventricular lead).

Multiple devices manufactured by Medtronic combine a CRT with the OptiVol™ monitoring system. For example, in 2005, the InSync Sentry® system was approved by the FDA through the supplemental premarket approval process. This combined biventricular pacemaker plus ICD is also equipped to monitor intrathoracic fluid levels using bioimpedance technology, referred to as OptiVol™ Fluid Status Monitoring. Bioimpedance measures, defined as the electrical resistance of tissue to flow of current, are performed many times a day using a vector from the right ventricular coil on the lead in the right side of the heart to the implanted pacemaker devices; changes in bioimpedance reflect intrathoracic fluid status and are evaluated using a computer algorithm. For example, changes in a patient's daily average of intrathoracic bioimpedance can be monitored; differences in the daily average are compared with a baseline and reported as the OptiVol™ Fluid Index. It has been proposed that these data may be used as an early warning system of cardiac decompensation or may provide feedback that enables a physician to tailor medical therapy. Blue Shield of California Medical Policy: Cardiac Hemodynamic Monitoring for the Management of Heart Failure in the Outpatient Setting addresses the use of external bioimpedance devices as stand-alone devices to assess cardiac output noninvasively.

The WiSE-CRT (EBR Systems) provides CRT with a small wireless electrode that is implanted within the left ventricle and controlled by ultrasound. It has European CE approval and is being studied in a multicenter pivotal trial.

FDA product code: NIK.

Rationale

Background

Heart Failure

An estimated 6.7 million adults in the United States 20 years of age and older had heart failure between 2017 to 2020.[1,] The prevalence continues to increase over time with the aging of the population. Prevalence of disease is higher in women than men 80 years of age and older. Overall prevalence is especially high in Black individuals. A 2008 study demonstrated that Black individuals had the highest risk of developing heart failure, followed by Hispanic, White, and Chinese individuals in the United States.[2,] Higher risk reflected differential prevalence of hypertension, diabetes, and lower socioeconomic status. Black individuals also had the highest proportion of incident heart failure not preceded by myocardial infarction (75%). Additionally, Black individuals have a greater 5-year case fatality rate associated with heart failure compared to White individuals.[3,] It is estimated that 20% to 30% of patients with heart failure have intraventricular conduction disorders resulting in a contraction pattern that is not coordinated and a wide QRS interval on the electrocardiogram. This abnormality appears to be associated with increased morbidity and mortality.

Treatment

Biventricular pacemakers using 3 leads (1 in the right atrium, 1 endocardial in the right ventricle, 1 epicardial for the left ventricle), also known as cardiac resynchronization therapy (CRT), have been investigated as a technique to coordinate the contraction of the ventricles, thus improving patients' hemodynamic status. Originally developed CRT devices typically used 2 ventricular leads for biventricular pacing. Devices and implantation techniques have been developed to allow for multisite pacing, with the goal of improving CRT response. This may be accomplished in 1 of 2 ways: through the use of multiple leads within the coronary sinus (triventricular pacing) or through the use of multipolar left ventricular pacing leads, which can deliver pacing stimuli at multiple sites. Wireless left

ventricular endocardial pacing is also being evaluated for patients who are not candidates for or do not respond to standard epicardial pacing leads.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Cardiac Resynchronization Therapy for Heart Failure

Clinical Context and Therapy Purpose

The purpose of cardiac resynchronization therapy (CRT) in patients who have heart failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with heart failure in the following situations:

- New York Heart Association (NYHA) class III or IV heart failure with a left ventricular ejection fraction (LVEF) of 35% or less who are in sinus rhythm, treated with guideline-directed medical therapy, and have either left bundle branch block (LBBB) or a QRS interval of 150 ms or more.
- NYHA class II heart failure with an LVEF of 30% or less who are in sinus rhythm, treated with guideline-directed medical therapy, and have either LBBB or a QRS interval of 150 ms or more
- NYHA class I heart failure

Interventions

The therapy being considered is CRT with or without defibrillator.

Several types of CRT devices are available, including those that incorporate biventricular pacing into automatic implantable cardioverter-defibrillators (ICDs), stand-alone biventricular pacemakers, and biventricular pacemakers that incorporate fluid monitoring via bioimpedance.

Comparators

The following therapies are currently being used to treat heart failure: medical care and medical care plus defibrillator.

Outcomes

The general outcomes of interest are overall survival (OS), symptoms, functional outcomes, quality of life, hospitalizations, and treatment-related morbidity. Function may be measured by the 6-minute walk test (6MWT). Outcomes for patients with heart failure are assessed between 3 months and 2 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

The use of ICD for select patients with advanced heart failure is supported by a large body of clinical trial evidence. At least 13 systematic reviews have consistently found benefit for CRT versus comparators for all-cause mortality and heart failure-related hospitalizations.[6,-18,] The systematic reviews published after 2010 that include meta-analyses with comparisons of CRT plus ICD (CRT-D) versus ICD alone and/or CRT versus drug therapy are shown in Table 1 and AMSTAR (A MeaSurement Tool to Assess systematic Reviews) quality ratings are shown in Table 2.

Individual RCT characteristics can be found in the following section in Table 3. The majority of patients included in RCTs had NYHA functional class II, III, or IV with an LVEF of less than 35%, prolonged QRS interval (≥120 ms), and were in sinus rhythm. On average, about 75% of participants were men, although the percentages of men ranged from 46% to 100%. Just over half of participants included had ischemic heart disease. The systematic reviews consistently reported a 15% to 20% reduction in mortality with CRT-D versus ICD alone and a 25% reduction in mortality of CRT versus drug therapy. Reviews providing results stratified by NYHA class I or II versus NYHA class III or IV have shown significant effects on mortality in both groups, although few patients in class I were enrolled in RCTs. The individual patient data network meta-analysis by Woods et al (2015) included 12,638 patients and reported a larger reduction in mortality (>40%) for CRT versus drug therapy compared with the other systematic reviews.[16,] The meta-analysis by Sun et al (2016) demonstrated that effects on mortality persist when only pooling trials with more than 1 year of follow-up.[17,]

Table 1. Systematic Reviews of RCTs Assessing the Efficacy of CRT for the Treatment of Heart Failure

Study	Dates	Population	Interventions	Studies (N)	Trials Included	Results
Sun et al (2016)[17,]	Through 2015	NYHA class I/II	• CRT-D • ICD alone	3 RCTs (N=3858) with ≥12-mo follow-up	REVERSE, MADIT-CRT, RAFT	CRT-D vs ICD Heart failure hospitalizations • OR=0.67 (95% CI, 0.50 to 0.89)

Study	Dates	Population	Interventions	Studies (N)	Trials Included	Results
						Mortality • OR=0.78 (95% CI, 0.63 to 0.96)
Woods et al (2015)[16,]	1990-2015	LVEF ≤40%	• CRT or CRT-D • Drug therapy alone or ICD alone	13 RCTs (N=12,638)	CARE-HF, MIRACLE, REVERSE, MUSTIC-SR, RESPOND, VECTOR, COMPANION, CONTAK-CD, MADIT-CRT, RAFT, REThinQ, Piccirillo (2006), Pinter (2009), RHYTHM-ICD, DEFINITE[a], MADIT[a], MADIT II[a], SCD HeFT[a], AMIOVIRT[a], CAT[a]	CRT-D vs drug therapy Mortality • HR=0.58 (95% CrI, 0.50 to 0.68) CRT-D vs ICD Mortality • HR=0.82 (95% CrI, 0.72 to 0.93)

AMIOVIRT: Amiodarone Versus Implantable Cardioverter-Defibrillator Randomized Trial; CARE-HF: Cardiac Resynchronization — Heart Failure; CAT: Cardiomyopathy Trial; CI: confidence interval; COMPANION: Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CONTAK-CD: VENTAK CHF/CONTAK CD/EASYTRAK Biventricular Pacing Study; CrI: credible interval; CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy with implantable cardioverter-defibrillator; DEFINITE: Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; HR: hazard ratio; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; MADIT: Multicenter Automatic Defibrillator Implantation Trial; MADIT-CRT: Multicenter Automatic Implantation Trial-Cardiac Resynchronization; MIRACLE: Multicenter InSync Randomized Clinical Evaluation; MUSTIC-SR: Multisite Stimulation in Cardiomyopathies; NYHA: New York Heart Association; OR: odds ratio; RAFT: Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; RCT: randomized controlled trial; RESPOND: Resynchronization in Patients with Heart Failure and a Normal QRS Duration; REThinQ: Resynchronization Therapy In Narrow QRS; REVERSE: REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction; RHYTHM-ICD: Resynchronisation for HemodYnamic Treatment for Health failure Management ICD; SCD HeFT: Sudden Cardiac Death in Heart Failure Trial; VECTOR: Ventricular Resynchronization Therapy Randomized Trial.
[a] Trials of ICD vs medical therapy; used in the indirect comparisons in the network meta-analysis.

Table 2. AMSTAR Quality of Systematic Reviews of Cardiac Resynchronization Therapy

Study	A Priori Design	Duplicate Selection/ Extraction	Comprehensive Literature Search	Search for Gray Literature	Included/ Excluded Studies Provided	Study Characteristics Provided	Study Scientific Quality Assessed and Documented	Scientific Quality Used in Formulated Conclusions	Appropriate Methods for Synthesis	Publication Bias Assessed	COI Included
Sun (2016)[17,]	Can't answer	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
Woods (2015)[16,]	Can't answer	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes

For a description of AMSTAR items, see https://amstar.ca/docs/AMSTARguideline.pdf.
AMSTAR: A MeaSurement Tool to Assess systematic Reviews; COI: conflict of interest.

Randomized Controlled Trials

At least 30 RCTs evaluating CRT have been published and are included in at least 1 of the meta-analyses listed above.[19,-,30,4,31,-,46,] Table 3 shows the baseline characteristics of the RCTs that have

over 100 patients per group. These RCTs evaluated mostly patients with NYHA class II, III, or IV heart failure. Few patients were enrolled who had NYHA class I heart failure. The 2 largest RCTs (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial [RAFT], Multicenter Automatic Implantation Trial-Cardiac Resynchronization [MADIT-CRT]) are described in greater detail below.

Table 3. RCTs of Cardiac Resynchronization Therapy for the Treatment of Heart Failure

Study	Duration	Treatment Groups	N	Percent NYHA Class				Mean LVEF (SD), %	Mean QRS (SD), ms	Percent ECG Pattern		% AF
				I	*II*	*III*	*IV*			*LBBB*	*RBBB*	
Lozano (2000)[19,]	3 mo	• CRT-D • ICD	• 109 • 113	NA	• 35	• 57	• 8	• 22 (7)	NR	NR	NR	NR
MIRACLE (2002)[23,]	6 mo	• CRT • Inactive	• 228 • 225	NA	NA	• 90 • 91	• 10 • 9	• 22 (6) • 22 (6)	• 167 (21) • 165 (20)	NR	NR	Excluded
CONTAK-CD (2003)[26,]	3 mo	• CRT-D • ICD	• 245 • 245	NA	• 32 • 33	• 60 • 57	• 8 • 10	• 21 (7) • 22 (7)	• 160 (27) • 156 (26)	• 54 • 55	• 14 • 12	Excluded
MIRACLE-ICD (2003)[27,]	6 mo	• CRT-D • ICD	• 187 • 182	NA	NA	• 88 • 89	• 12 • 11	• 24 (7) • 24 (6)	• 165 (22)	NR	• 13 • 13	Excluded
COMPANION (2004)[28,]	15 mo	• CRT • Usual care	• 617 • 308	NA	NA	• 87 • 82	• 13 • 18	• 20[a] • 22[a]	• 160[a] • 158[a]	• 69 • 70	NR	Excluded
CARE-HF (2005)[30,]	29 mo	• CRT • Usual care	• 409 • 404	NA	NA	• 94 • 93	• 6 • 7	• 25[a] • 25[a]	• 160[a] • 160[a]	NR	NR	Excluded
DECREASE-HF (2007)[34,]	6 mo	• Biventricular ICD • LV-ICD	• 205 • 101	NA	NA	• 98 • 97	• 2 • 3	• 23 (7) • 23 (7)	• 167 (16) • 165 (15)	• 94 • 93	• 0 • 1	Excluded
REVERSE (2008)[38,]	12 mo	• CRT on • CRT off	• 419 • 191		• 82 • 83	NA	NA	• 27 (7) • 26 (7)	• 153 (21) • 154 (24)	NR	NR	Excluded
MADIT-CRT (2009)[39,]	2.4 y	• CRT-D • ICD	• 1089 • 731		• 86 • 85	NA	NA	• 24 (5) • 24 (5)	• >150, 64% • >150, 65%	• 70 • 71	• 13 • 13	Excluded
RAFT (2010)[43,]	40 mo	• CRT-D • ICD	• 894 • 904	NA	• 79 • 81	• 21 • 19	NA	• 22 (5) • 22 (5)	• 157 (24) • 158 (24)	• 73 • 71	• 8 • 10	• 13 • 13

AF: atrial fibrillation; CARE-HF: Cardiac Resynchronization — Heart Failure; COMPANION: Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CONTAK-CD: VENTAK CHF/CONTAK CD/EASYTRAK Biventricular Pacing Study; CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy with implantable cardioverter defibrillator; DECREASE-HF: Device Evaluation of CONTAK RENEWAL 2 and EASYTRAK 2: Assessment of Safety and Effectiveness in Heart Failure; ECG: electrocardiogram; ICD: implantable cardioverter-defibrillator; LBBB: left bundle branch block; LV: left ventricle; LVEF: left ventricular ejection fraction; MADIT-CRT: Multicenter Automatic Implantation Trial-Cardiac Resynchronization; MIRACLE: Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD: Multicenter InSync ICD Randomized Clinical Evaluation; MUSTIC-SR: Multisite Stimulation in Cardiomyopathies; NA: not applicable; NR: not reported; NYHA: New York Heart Association; RAFT: Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; RBBB: right bundle branch block; RCT: randomized controlled trial; REVERSE: REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction; SD: standard deviation.

New York Heart Association Class II or III Heart Failure

Resynchronization-Defibrillation for Ambulatory Heart Failure Trial

The RAFT trial randomized 1798 patients with class II or III heart failure and an LVEF of 30% or less to CRT-D or ICD alone, with a mean follow-up 40 months.[43,] Race and ethnicity of participants were not described. Unlike most previous trials, this trial did not confine enrollment to patients with sinus rhythm but also allowed patients with atrial arrhythmias to participate. However, the number of patients who were not in sinus rhythm was only 12.8% (229/1798). On formal quality assessment, this trial met all quality indicators and was given a "good" quality rating.

The primary outcome (death from any cause or hospitalization for heart failure) was reduced in the CRT-D group (33.2%) compared with the ICD alone group (40.3%; p<.001).[43,] There were significant reductions in both individual components of the primary outcome, overall mortality (20.8% vs 26.1%; p=.003) and hospitalizations (19.5% vs 26.1%; p<.001), all respectively. When restricted to patients with NYHA class II heart failure, improvements in the outcomes of mortality and hospitalizations remained significant. The mortality rate for class II patients in the CRT-D group was 15.5% versus 21.1% in the ICD alone group (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.56 to 0.91; p<.006). Hospitalizations for class II patients occurred in 16.2% of patients in the CRT-D group and 21.1% in the ICD alone group (HR, 0.70; 95% CI, 0.55 to 0.89; p<.003).

In a preplanned subgroup analysis of RAFT data focusing on hospitalization rates over the 18-month follow-up period, Gillis et al (2014) reported that fewer patients in the CRT-D group (11.3%) were hospitalized for heart failure than those in the ICD alone group (15.6%; p=.003).[47,] Although the total number of hospitalizations for any cause was lower in the CRT-D group (1448 vs 1553; p=.042), patients randomized to CRT-D had more hospitalizations for device-related indications (246 vs 159; p<.001).

Subgroup analyses from RAFT reported that female sex, a QRS interval of 150 ms or more, an LVEF less than 20%, and QRS morphologic features were predictive of benefit.[43,] Of these factors, the QRS interval was the strongest. Patients with a QRS interval of 150 ms or more had an HR for the primary outcome of approximately 0.50, compared with an HR of approximately 1.0 for patients with a QRS interval less than 150 ms (p=.003 for the difference between the HRs). There was a trend for greater improvement in patients with sinus rhythm compared with patients with atrial arrhythmias, but this difference was not statistically significant.

New York Heart Association Class I or II Heart Failure

Multicenter Automatic Implantation Trial-Cardiac Resynchronization Trial

The largest trial published to date is the single-blind MADIT-CRT trial, which randomized 1820 patients with NYHA class I (n=265) or II (n=1555) heart failure and an LVEF 30% or less to an ICD alone or a CRT-D device.[39,] Of the patients included in the study, 90.5% of patients were White, 7.9% of patients were Black, and 1.6% of patients did not have their race or ethnicity described. The MADIT-CRT trial reported a reduction for the CRT-D group in the primary outcome (ie, death or acute heart failure exacerbation). The primary endpoint was reached by 17.2% of patients in the CRT-D

group compared with 25.3% of patients in the ICD alone group. The first component of the composite outcome (acute heart failure events) occurred in 22.8% of patients in the ICD alone group compared with 13.9% of patients in the CRT-D group (relative risk reduction, 39%; absolute risk reduction, 8.9%; number needed to treat, 11.2). This difference in acute heart failure events accounted entirely for the difference in the primary composite outcome. The death rate was similar between groups. Subgroup analyses found significantly reduced mortality of CRT-D versus ICD for NYHA ischemic and nonischemic class II; however, the effect in NYHA class I patients was not statistically significant. The interaction for class by treatment group was not given but was reported to be not statistically significant.

A follow-up from the MADIT-CRT trial, published by Goldenberg et al (2011), analyzed the reduction in recurrent heart failure events.[48,] This analysis supplemented the original MADIT-CRT outcome of time to first heart failure event, by comparing total heart failure events during an average follow-up of 2.6 years. Over this time period, there was a 38% relative reduction in heart failure events in the CRT group (HR, 0.62; 95% CI, 0.45 to 0.85; p=.003). On subgroup analysis, the benefit was evident in patients with LBBB (HR, 0.50; 95% CI, 0.33 to 0.76; p=.001) but not in patients without LBBB (HR, 0.99; 95% CI, 0.58 to 1.69; p=.96).

Goldenberg et al (2014) analyzed mortality in MADIT-CRT trial subjects with follow-up through 7 years, stratified by the presence or absence of LBBB.[49,] Follow-up was available for a median 5.6 years among all 1691 surviving patients enrolled in the trial, and beyond that for 854 subjects enrolled in posttrial registries. Seventy-three percent and 75% of the ICD-only and CRT-D groups, respectively, had LBBB; 69% of each group had a QRS interval of a least 150 ms. At 7-year follow-up, the cumulative rate of death from any cause among patients with LBBB was 29% in the ICD-only group compared with 18% in the CRT-D group (p=.002; adjusted HR in the CRT-D group, 0.59; 95% CI, 0.43 to 0.80; p<.001). The benefit associated with ICD-CRT was consistent in subgroup analysis among patients with a prolonged QRS interval (≥150 ms) and a shorter QRS interval (<150 ms). In multivariable analysis, there was no significant interaction between QRS interval and OS. Among patients without LBBB, there was no significant difference in the cumulative rate of death from any cause between the ICD-only and CRT-D groups.

Safety of Cardiac Resynchronization Therapy Placement

Hosseini et al (2017) reported on in-hospital complication rates of CRT from 2003 to 2013 using data from the National Inpatient Sample and the Nationwide Inpatient Sample (NIS), the largest all-payer inpatient database of hospital discharge records in the U.S.[50,] The NIS includes approximately 20% of discharges from U.S. hospitals and sampling weights provided by the NIS can be used to produce national estimates from NIS data. A total of 92,480 unweighted records (corresponding to 376,045 weighted records) were analyzed. In patients receiving CRT-D and CRT with a pacemaker (CRT-P), 6.04% and 6.54% had at least 1 complication, respectively. The overall rate of at least 1 complication increased from 5.86% in 2003 to 6.95% in 2013 (p=.01) for CRT-D and from 5.46% to 7.11% (p=.01) in CRT-P. In the CRT-D group, the overall increase in complications was driven by increases in pericardial complications, vascular complications, and postoperative infections. In the CRT-P group, the overall increase in complications was driven by an increase in vascular complications. The most common adverse outcomes were pulmonary complications (1.48%), hemorrhage/hematoma (1.41%), and infection (1.17%). The in-hospital mortality rate was 0.70% for CRT-D and 1.08% for CRT-P.

Factors Influencing Outcomes

For CRT treatment, there is a large variability in the magnitude of response. Some patients do not respond at all, while others have very substantial benefit. As a result, there is interest in defining the clinical features that predict response to better target therapy to those who will benefit most. There is a large body of literature examining predictors of outcomes after CRT placement, and numerous clinical and demographic factors have been identified that predict response. A smaller number of predictors have been proposed as potential selection criteria for CRT placement.

An example of a study examining general predictors of outcome is The Predictors of Response to Cardiac Resynchronization Therapy trial.[51,] This prospective, multicenter trial evaluated the utility of echocardiographic parameters to predict response to CRT. Trial results indicated that the 12 individual echocardiographic parameters varied widely in ability to predict response.[52,] The sensitivity of these individual measures ranged from 6% to 74%, and the specificity ranged from 35% to 91%. The authors concluded it was unlikely that these measures could improve patient selection for CRT. Four additional selection factors are reviewed here: QRS interval/morphology, LBBB, prolonged PR interval, and ventricular dyssynchrony on echocardiography.

QRS Interval/Morphology

It is well accepted that patients with a QRS complex of less than 120 ms who are not selected for dyssynchrony do not benefit from CRT. A more controversial issue is whether patients with a moderately prolonged QRS interval (120 to 150 ms) benefit from CRT, or whether the benefit is confined to subsets of patients such as those with a markedly prolonged QRS interval (>150 to 160 ms) or LBBB.

The Evaluation of Resynchronization Therapy for Heart Failure trial was an RCT designed to compare CRT with no CRT in patients with a QRS complex of less than 120 ms, whether or not ventricular dyssynchrony was present.[53,] This trial was terminated early after 85 patients had been enrolled. Interim analysis revealed futility in achieving benefit on the primary outcomes and a trend toward greater adverse events.

Several meta-analyses of the association between QRS interval and outcomes have been published. Woods et al (2015) performed a network meta-analysis of ICDs to inform a National Institute for Health and Care Excellence guidance.[16,] Thirteen RCTs with 12,638 patients were included. Estimates of CRT effect on mortality were given for 16 subgroups (men vs women; <60 years vs ≥60 years; QRS interval ≥120 ms to <150 ms vs ≥ 150 ms; LBBB vs no LBBB; see Table 4). In women in both age groups, CRT-D statistically significantly reduced mortality compared with medical therapy alone for both QRS intervals (≥120 ms to <150 ms and ≥150 ms) with and without LBBB. Also, in women of both age groups, CRT-P significantly reduced mortality compared with medical therapy alone with QRS intervals of 150 ms or more and LBBB. Mortality was significantly reduced with CRT-D compared with ICD alone for women younger than 60 years with a QRS of 150 ms or more and LBBB, women older than 60 years with QRS intervals ranging from 120 ms to 150 ms and LBBB, and women older than 60 years with QRS intervals of 150 ms or more with or without LBBB. For men in both age groups, CRT-D reduced mortality compared with medical therapy alone in both QRS groups with and without LBBB. However, CRT-P significantly improved survival compared with medical therapy alone only in men older than 60 years with QRS intervals of 150 ms or more and LBBB. Likewise, CRT-D improved survival compared with ICD alone in men older than 60 years with QRS intervals of 150 ms or more and LBBB.

Table 4. Subgroup-Specific Treatment Effects in a Network Meta-Analysis

Sex	Age (years)	QRS	LBBB	CRT-D vs MT		CRT-P vs MT		CRT-D vs ICD	
				HR	*95% CI*	*HR*	*95% CI*	*HR*	*95% CI*
Women	<60	≥120 to <150	N	0.62	0.40 to 0.96	0.86	0.50 to 1.48	0.90	0.58 to 1.39
Women	<60	≥120 to <150	Y	0.55	0.36 to 0.84	0.76	0.46 to 1.25	0.74	0.48 to 1.13
Women	<60	≥150	N	0.55	0.35 to 0.86	0.74	0.42 to 1.28	0.71	0.46 to 1.12
Women	<60	≥150	Y	0.48	0.33 to 0.72	0.65	0.42 to 1.00	0.59	0.40 to 0.87
Women	≥60	≥120 to <150	N	0.60	0.41 to 0.90	0.75	0.46 to 1.21	0.71	0.48 to 1.04
Women	≥60	≥120 to <150	Y	0.53	0.37 to 0.78	0.65	0.42 to 1.02	0.59	0.41 to 0.84
Women	≥60	≥150	N	0.53	0.35 to 0.80	0.64	0.39 to 1.03	0.57	0.38 to 0.84
Women	≥60	≥150	Y	0.47	0.34 to 0.66	0.56	0.40 to 0.79	0.47	0.34 to 0.64
Men	<60	≥120 to <150	N	0.72	0.51 to 1.01	1.07	0.70 to 1.64	1.37	0.98 to 1.92
Men	<60	≥120 to <150	Y	0.63	0.44 to 0.91	0.94	0.61 to 1.43	1.13	0.80 to 1.61
Men	<60	≥150	N	0.63	0.44 to 0.91	0.91	0.58 to 1.42	1.10	0.78 to 1.54

Sex	Age (years)	QRS	LBBB	CRT-D vs MT		CRT-P vs MT		CRT-D vs ICD	
Men	<60	≥150	Y	0.56	0.40 to 0.77	0.80	0.56 to 1.14	0.90	0.67 to 1.23
Men	≥60	≥120 to <150	N	0.70	0.53 to 0.92	0.92	0.64 to 1.32	1.09	0.85 to 1.39
Men	≥60	≥120 to <150	Y	0.62	0.46 to 0.83	0.81	0.57 to 1.16	0.90	0.69 to 1.16
Men	≥60	≥150	N	0.62	0.46 to 0.83	0.79	0.55 to 1.12	0.87	0.67 to 1.12
Men	≥60	≥150	Y	0.54	0.43 to 0.69	0.69	0.55 to 0.87	0.72	0.59 to 0.87

Adapted from Woods et al (2015).[16,]
CI: confidence interval; CRT-D: cardiac resynchronization therapy with implantable cardioverter-defibrillator; CRT-P: cardiac resynchronization therapy with pacemaker; HR: hazard ratio; ICD: implantable cardioverter-defibrillator; LBBB: left bundle branch block; MT: medical therapy; N: no; Y: yes.

Other meta-analyses have come to similar conclusions, reporting benefits for patients with a QRS interval of more than 150 ms, and little to no benefit for patients with shorter QRS intervals.[54,-,60,] In 1 of these studies, the benefit of CRT was confined to patients with LBBB.[57,] There was no benefit demonstrated for patients with right bundle branch block or intraventricular conduction delay. These reviewers suggested that QRS morphology may be as important, or more important, than QRS duration in predicting response to CRT.

Left Bundle Branch Block

Peterson et al (2013) published results of a retrospective cohort study of Medicare beneficiaries who underwent combined CRT-D placement to assess associations between QRS interval and morphology and outcomes.[61,] Among 24,169 patients admitted for CRT-D placement and followed for up to 3 years, rates of 3-year mortality and 1-year all-cause rehospitalization were lowest in patients with LBBB and QRS intervals of 150 ms or more. Patients with no LBBB and QRS intervals from 120 to 149 ms had an adjusted HR of 1.52 (95% CI, 1.38 to 1.67) after controlling for a number of clinical and demographic confounders (vs those with LBBB and markedly prolonged QRS interval).

Prolonged PR Interval

The data are inconsistent on the association between PR interval and outcomes in CRT.

Kutyifa et al (2014) evaluated whether prolonged PR predicts heart failure or death among 537 (30%) of MADIT-CRT trial subjects who did not have an LBBB.[62,] Among the 96 patients with a prolonged PR interval, compared with ICD alone, CRT-D treatment was associated with reduced risk of heart failure or death (HR, 0.27; 95% CI, 0.13 to 0.57; p<.001). In contrast, among the 438 subjects with a normal PR interval, CRT-D treatment was associated with a nonsignificant trend toward increased risk of heart failure or death (HR, 1.45; 95% CI, 0.96 to 2.19; p=.078). In long-term follow-up of MADIT-CRT, the reduction in mortality for CRT-D versus ICD in those with prolonged PR was similar to the short-term results (HR, 0.24; 95% CI, 0.07 to 0.80), but the increase in mortality for CRT-D versus ICD in normal PR was larger than in the short-term results (HR, 2.27; 95% CI, 1.16 to 4.44).[63,]

In an analysis of 26,451 CRT-eligible (ejection fraction ≤35%, QRS interval ≥120 ms) patients from the National Cardiovascular Data Registry, Friedman et al (2016) examined the association between prolonged PR interval (≥230 ms), receipt of CRT-D versus ICD-only, and outcomes.[64,] All Medicare beneficiaries who receive a primary prevention ICD are enrolled in this ICD registry. Patients with a prolonged PR interval were more often male, older, with comorbid ischemic heart disease, atrial arrhythmias, cerebrovascular disease, diabetes, and chronic kidney disease. After adjusting for other risk factors, a prolonged PR was associated with increased risk of heart failure hospitalization or death among CRT-D (HR, 1.2; 95% CI, 1.1 to 1.3; p<.001) compared with normal PR interval. There was no association between PR interval and hospitalization or death among ICD-only recipients (HR, 1.1; 95% CI, 1.0 to 1.2; p=.17). Receipt of CRT-D was associated with lower rates of heart failure hospitalization or death compared with ICD-only among patients who had a PR interval less than 230 (HR, 0.79; 95% CI, 0.73 to 0.85; p<.001) but not with PR interval of 230 or more (HR, 1.01; 95% CI, 0.87 to 1.17; p=.90). Limitations of this analysis included lack of randomization (i.e., residual confounding) and potential inaccuracies in registry data.

Ventricular Dyssynchrony

Observational studies of patients who meet criteria for CRT have shown that measures of dyssynchrony on echocardiography correlate with treatment response, as defined by improvements in left ventricular (LV) end-systolic volume (LVESV), ejection fraction, or clinical criteria.[65,] This finding prompted investigation of whether ventricular dyssynchrony could discriminate between responders and nonresponders to CRT, for patients who would otherwise qualify for CRT and for those who would not (i.e., those with a narrow QRS interval).

The Narrow QRS Ischemic Patients Treated With Cardiac Resynchronization Therapy (NARROW-CRT) RCT compared CRT using dual-chamber ICD among patients who had heart failure (NYHA class II or III) of ischemic origin, ejection fraction of 35% or less, QRS interval less than 120 ms, and marked mechanical dyssynchrony on echocardiogram.[66,] One hundred twenty patients were randomized to CRT (n=60) or ICD (n=60). For the trial's primary outcome (heart failure clinical composite score), compared with those in the ICD group, patients in the CRT group were more likely to have improved clinical composite scores at 1 year postimplantation (41% vs 16%, p=.004). Patients in the CRT group had higher rates of avoiding the combined endpoint of heart failure hospitalization, heart failure death, and spontaneous ventricular fibrillation (p=.028).

The Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) study was intended to evaluate the role of CRT for subjects with heart failure (NYHA class III or IV) with narrow QRS interval (<130 ms) and echocardiographic evidence of ventricular dyssynchrony. All enrolled patients were implanted with a CRT-D, and then randomized to CRT with the device on or off. The study was stopped for futility after enrollment of 809 patients; results from the enrolled patients who had been followed for a mean of 19.4 months were reported by Ruschitzka et al (2013).[67,] Four hundred four patients were randomized to the CRT group and 405 to the control group. The primary efficacy outcome (death from any cause or hospitalization for worsening heart failure) occurred in 116 (28.7%) of 404 patients in the CRT group and 102 (25.2%) of 405 in the control group (HR with CRT, 1.20; 95% CI, 0.92 to 1.57; p=.15). There was a significantly higher death rate in the CRT group: 45 (11.1%) of 404 patients died in the CRT group while 26 (6.4%) of 50 died in the control group (HR, 1.81; 95% CI, 1.11 to 2.93; p=.02).

The Resynchronization Therapy in Normal QRS Trial randomized 172 patients with a narrow QRS interval and evidence of dyssynchrony to a CRT device, turned on or not, who were followed for 6 months.[36,] The CRT-treated patients (46%) were no more likely than non-CRT patients (41%) to show improvement (meet the endpoint of improvement in exercise capacity [Vo_2peak]). A subset of patients with QRS intervals of 120 to 130 ms or more showed improvement (p=.02), whereas those with a QRS interval less than 120 ms did not (p=.45).

Section Summary: Cardiac Resynchronization Therapy for Heart Failure

New York Heart Association Class III or IV Heart Failure

There is a large body of clinical trial evidence that supports the use of CRT in patients with NYHA class III or IV heart failure. Results of RCTs have consistently reported that CRT treatment leads to reduced mortality, improved functional status, and improved quality of life for patients with NYHA class III or IV heart failure.

New York Heart Association Class I or II Heart Failure

For patients with mild heart failure (NYHA class I or II), at least 4 RCTs of CRT have been published. A mortality benefit was reported in 1 trial (RAFT). This trial was free of major bias and reported a fairly large absolute difference in overall mortality (5.3%). None of the other 3 RCTs reported a mortality difference. While 2 of the other 3 trials were underpowered to detect differences in mortality, MADIT-CRT was approximately the same size as RAFT and did not show any improvement in mortality. In a subgroup analysis of the MADIT-CRT trial, a mortality benefit was shown in patients with LBBB. It is possible that the sicker patient population and longer follow-up in RAFT accounted for the mortality difference. Among other outcome measures, hospitalizations for heart failure showed consistent

improvements, but quality of life and functional status did not. Most patients in these trials had class II congestive heart failure. Hence it is not possible to determine separately whether patients with class I heart failure achieved benefit.

Predictors of Response

The presence of dyssynchrony on echocardiography may risk-stratify patients, but it is not a good discriminator of responders from nonresponders. A QRS interval of more than 150 ms or the presence of LBBB appears to discriminate well between responders and nonresponders and represents a potential factor in selecting patients for CRT treatment. Subgroup analyses across multiple RCTs, corroborated by pooling of these subgroups in meta-analyses, have reported that QRS intervals of 150 to 160 ms or more, or the presence of LBBB are accurate in discriminating responders from nonresponders. A subgroup analysis of an RCT and a registry study have provided inconsistent results on the role of prolonged PR interval. Patient-level meta-analyses reported that women might benefit at a shorter QRS interval than men.

Cardiac Resynchronization Therapy for Heart Failure and Atrial Fibrillation

Clinical Context and Therapy Purpose

The purpose of CRT in patients who have heart failure and atrial fibrillation (AF) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with heart failure and AF.

Interventions

The therapy being considered is CRT with or without defibrillator.

Several types of CRT devices are available, including those that incorporate biventricular pacing into automatic ICDs, stand-alone biventricular pacemakers, and biventricular pacemakers that incorporate fluid monitoring via bioimpedance.

Comparators

The following therapies are currently being used to treat patients with heart failure and AF: medical care and medical care plus defibrillator.

Outcomes

The general outcomes of interest are OS, symptoms, functional outcomes, quality of life, hospitalizations, and treatment-related morbidity. Function may be measured by the 6MWT. Outcomes for patients with heart failure are assessed between 3 months and 2 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

There is controversy whether CRT leads to health outcome benefits for patients with AF. Many experts believe that, if CRT is used, it should be combined with ablation of the atrioventricular (AV)

node to avoid transmission of atrial impulses through the node that might result in rapid ventricular rates, thus undermining the efficacy of CRT. Most trials of CRT have excluded patients with permanent AF; however, 3 trials (Ablate And Pace Therapy for Permanent Atrial Fibrillation [APAF], MUltisite STimulation In Cardiomyopathies and Atrial Fibrillation [MUSTIC], Ablate and Pace in Atrial Fibrillation plus Cardiac Resynchronization Therapy [APAF-CRT] morbidity trial) have examined CRT specifically in this population. Other RCTs have reported subgroup analyses in patients with permanent or intermittent AF. Analysis from the National Cardiovascular Data Registry is also available.

Randomized Controlled Trials

The design, results, and limitations of the 4 RCTs examining CRT in patients with AF are summarized in Tables 5 through 8.

Brignole et al (2018) reported results from the morbidity phase of the APAF-CRT trial, which compared AV junction ablation plus CRT (with or without defibrillator) to pharmacological rate control therapy (with or without defibrillator) in 102 patients with permanent AF, narrow QRS (110 ms or less), and at least 1 hospitalization for heart failure within the preceding year.[68,] Race or ethnicity of the participants were not described. The APAF-CRT morbidity trial was stopped early after an interim analysis and enrolled only half of the planned number of patients; therefore, the authors caution that the results of the morbidity trial should be considered exploratory, pending confirmation from the APAF-CRT mortality trial. At a median follow-up of 16 months, the primary composite outcome of death due to heart failure, hospitalization due to heart failure, or worsening heart failure had occurred in 10 patients (20%) in the CRT arm and in 20 patients (38%) in the rate control arm (HR, 0.38; 95% CI, 0.18 to 0.81; p=.013). For the individual outcome measures, no significant difference in all-cause mortality was observed. Worsening heart failure was not significantly different between groups, but hospitalizations for heart failure were reduced with CRT.

Brignole et al (2021) published the results of the APAF-CRT mortality trial.[69,] A total of 133 patients were randomized and included for analysis (AV ablation plus CRT, n=63; pharmacologic therapy, n=70). Race or ethnicity of the participants were not described. The median duration of follow-up was 29 months (range, 1 to 56 months). The primary endpoint of all-cause mortality occurred in 7 patients (11%) in the CRT group and in 20 patients (29%) in the rate control group (HR, 0.26; 95% CI, 0.10 to 0.65; p=.004). The estimated death rates at 2 years were 5% and 21%, respectively, and at 4 years, 14% and 41%. The secondary composite endpoint consisting of all-cause mortality or heart failure hospitalization, whichever came first, was significantly lower in the CRT arm (29%) compared to rate control arm (51%; HR, 0.40; 95% CI, 0.22 to 0.73; p=.002). In the prespecified subgroup analysis of ejection fraction, a benefit in all-cause mortality was seen in patients with ejection fraction greater than 35% (HR, 0.27; 95% CI, 0.08 to 0.84; p=.024), but not in patients with ejection fraction less than or equal to 35% (HR, 0.34; 95% CI, 0.06 to 1.92; p=.22).

The APAF (2011) RCT compared CRT with right ventricular (RV) pacing alone in patients with AF. [70,] A total of 186 patients had AV nodal ablation, implantation of a CRT device, and were then randomized to echo-optimized CRT or RV pacing alone and followed for a median of 20 months. Race or ethnicity of the participants were not described. The primary outcome measure was a composite of death from heart failure, hospitalization for heart failure, or worsening heart failure. This combined endpoint occurred in 11% of the CRT group and 26% of the RV pacing group (HR, 0.37; 95% CI, 0.18 to 0.73; p=.005). For the individual outcome measures, there was no significant reduction in mortality (HR, 1.57; 95% CI, 0.58 to 4.27; p=.37), but there were significant reductions in hospitalizations (HR, 0.20; 95% CI, 0.06 to 0.72; p=.013) and worsening heart failure (HR, 0.27; 95% CI, 0.12 to 0.58; p=.37). There were no differences in outcomes on subgroup analysis, including analysis by ejection fraction, NYHA class, and/or QRS interval.

In the MUSTIC (2002) trial, 59 NYHA class III patients with LV systolic dysfunction, slow and permanent AF of greater than 3 months duration, and a paced QRS interval greater than 200 ms

were randomized in a single-blinded, crossover design to RV versus biventricular pacing with 3 months for each period.[22,] Race or ethnicity of the participants were not described. The primary outcome was the 6MWT; secondary outcomes were maximal oxygen uptake (Vo_2max), quality of life, hospitalizations, patients' preferred study period, and mortality. Only 37 patients completed both crossover periods. In intention-to-treat analyses (which included 43 patients), no significant differences were observed between assigned groups.

Table 5. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
APAF-CRT Mortality Trial (2021)[69,]	Europe	11	Oct 2014-Dec 2020	Patients with severely symptomatic permanent AF, narrow QRS (≤110 ms), and at least 1 hospitalization for heart failure in the past year	AV junction ablation plus CRT (n=63)	Pharmacologic rate control therapy (n=70)
APAF-CRT Morbidity Trial (2018)[68,]	Europe	10	Oct 2014-Jun 2018	Patients with severely symptomatic permanent AF, narrow QRS (≤110 ms), and at least 1 hospitalization for heart failure in the past year	AV junction ablation plus CRT (n=50)	Pharmacologic rate control therapy (n=52)
APAF (2011)[70,]	Italy, Spain, Greece	19	Jul 2005-Dec 2009	Patients with severely symptomatic permanent AF, drug-refractory heart failure, depressed LV function, and wide QRS complexes	AV junction ablation plus CRT (n=97)	AV junction ablation plus RV pacing (n=89)
MUSTIC (2002)[22,]	Europe	15	Mar 1998-Jun 1999	Patients with NYHA class III heart failure, LV systolic dysfunction, slow and permanent AF >3 months, and paced QRS >200 ms	CRT (n=43)	RV pacing (n=43)

AF: atrial fibrillation; APAF: Ablate And Pace Therapy for Permanent Atrial Fibrillation; APAF-CRT: Ablate and Pace in Atrial Fibrillation plus Cardiac Resynchronization Therapy; AV: atrioventricular; CRT: cardiac resynchronization therapy; LV: left ventricular; MUSTIC: MUltisite STimulation In Cardiomyopathies and Atrial Fibrillation; NYHA: New York Heart Association; RCT: randomized controlled trial; RV: right ventricular.

Table 6. Summary of Key RCT Results

Study	Heart Failure-Related Mortality, Heart Failure Hospitalization, or Worsening Heart Failure	All-Cause Mortality	Heart Failure Hospitalization	Worsening Heart Failure	6MWD, m (SD)
APAF-CRT Mortality Trial (2021)[69,]	N=133	N=133	n=38[b]	NR	NR
AV junction ablation plus CRT	18 (29%)[a]	7 (11%)	13[b]	NR	NR
Pharmacologic rate control	36 (51%)[a]	20 (29%)	25[b]	NR	NR
HR (95% CI)	0.40 (0.22 to 0.73)[a]	0.26 (0.10 to 0.65)	NR	NR	NR
p value	.002[a]	.004	NR	NR	NR
APAF-CRT Morbidity Trial (2018)[68,]	N=102	N=102	N=102	N=102	NR

Study	Heart Failure-Related Mortality, Heart Failure Hospitalization, or Worsening Heart Failure	All-Cause Mortality	Heart Failure Hospitalization	Worsening Heart Failure	6MWD, m (SD)
AV junction ablation plus CRT	10 (20%)	2 (4%)	5 (10%)	5 (10%)	NR
Pharmacologic rate control	20 (38%)	6 (12%)	13 (25%)	8 (15%)	NR
HR (95% CI)	0.38 (0.18 to 0.81)	0.30 (0.06 to 1.50)	0.30 (0.11 to 0.84)	0.55 (0.18 to 1.68)	NR
p value	.013	.147	.024	.294	NR
APAF (2011)[70,]	N=186	N=186	N=186	N=186	NR
AV junction ablation plus CRT	11 (11%)	NR	NR	NR	NR
AV junction ablation plus RV pacing	23 (26%)	NR	NR	NR	NR
HR (95% CI)	0.37 (0.18 to 0.73)	1.57 (0.58 to 4.27)	0.20 (0.06 to 0.72)	0.27 (0.12 to 0.58)	NR
p value	.005	.372	.013	.001	NR
MUSTIC (2002)[22,]	NR	N=44	N=44	NR	N=38
CRT	NR	1 (2.3%)	3 (7%)	NR	359 (121)
RV pacing	NR	0	10 (23%)	NR	341 (100)
p value	NR	NR	NR	NR	NS

APAF: Ablate And Pace Therapy for Permanent Atrial Fibrillation; APAF-CRT: Ablate and Pace in Atrial Fibrillation plus Cardiac Resynchronization Therapy; AV: atrioventricular; CI: confidence interval; CRT: cardiac resynchronization therapy; HR: hazard ratio; MUSTIC: MUltisite STimulation In Cardiomyopathies and Atrial Fibrillation; NR: not reported; NS: not significant; RCT: randomized controlled trial; RV: right ventricular; SD: standard deviation; 6MWD: 6-minute walk distance.
[a]Composite outcome of death from any cause or hospitalization for heart failure (whichever came first).
[b]From supplemental information file.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
APAF-CRT Mortality Trial (2021)[69,]	2. Correlation to NYHA classification is unclear		3. Drug classes used for background heart failure therapy differed between groups at baseline 3. Pharmacologic therapy at clinician discretion vs guideline directed medical therapy (U.S.)		
APAF-CRT Morbidity Trial (2018)[68,]	2. Correlation to NYHA classification is unclear		3. Drug classes used for background heart failure therapy differed between groups at baseline		

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
APAF (2011)[70,]	2. Correlation to NYHA classification is unclear				
MUSTIC (2002)[22,]	2. Correlation to NYHA classification is unclear				1. Patients received each intervention for only 3 months (insufficient follow-up for secondary outcomes of hospitalization and mortality)

APAF: Ablate And Pace Therapy for Permanent Atrial Fibrillation; APAF-CRT: Ablate and Pace in Atrial Fibrillation plus Cardiac Resynchronization Therapy; MUSTIC: MUltisite STimulation In Cardiomyopathies and Atrial Fibrillation; NYHA: New York Heart Association.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
APAF-CRT Mortality Trial (2021)[69,]						
APAF-CRT Morbidity Trial (2018)[68,]		1. Open label				
APAF (2011)[70,]		1. Treating physicians not blinded				
MUSTIC (2002)[22,]		1. Single blind (patients were blinded)		1. 27 patients (42%) withdrew before completing the full 6-month crossover phase		3. p values not reported for hospitalizations or mortality

APAF: Ablate And Pace Therapy for Permanent Atrial Fibrillation; APAF-CRT: Ablate and Pace in Atrial Fibrillation plus Cardiac Resynchronization Therapy; MUSTIC: MUltisite STimulation In Cardiomyopathies and Atrial Fibrillation.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

In addition to the RCTs described above, 2 subgroup analyses of RCTs have reported on outcomes in patients with AF. Kalscheur et al (2017) reported on a comparison of outcomes between CRT-P and medical therapy in patients with intermittent AF or atrial flutter (n=293) and those without (n=887) in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial.[71,] Intermittent AF and atrial flutter were determined from medical history and chart review at enrollment. Cox proportional hazard models were used to estimate effects. The interaction between history of intermittent AF and atrial flutter and CRT treatment group was statistically significant for both death and hospitalization outcomes (p<.05). In the CRT-P group, there was a significant reduction in the composite outcome of death or any hospitalization (HR, 0.73; 95% CI, 0.60 to 0.89; p=.002) and in the composite of death or heart failure hospitalization (HR, 0.53; 95% CI, 0.41 to 0.68; p<.001). In contrast, in the intermittent AF and atrial flutter group (n=293), CRT-P did not result in improved outcomes versus medical therapy (death or any hospitalization HR, 1.16; 95% CI, 0.83 to 1.63; p=.38; death or heart failure hospitalization HR, 0.97; 95% CI, 0.64 to 1.46; p=.88).

A post hoc analysis of patients with AF enrolled in RAFT was published by Healey et al (2012).[72,] Randomization in this trial was stratified for the presence of AF, allocating 114 patients with AF to the CRT plus defibrillator group and 115 patients with AF to the defibrillator alone group. There was no difference between groups in the primary outcome of death or hospitalization due to heart failure (HR, 0.96; 95% CI, 0.65 to 1.41; p=.82). There were also no differences in cardiovascular death or functional status. There was a trend for patients in the CRT group to have fewer hospitalizations for heart failure than those in the defibrillator alone group, but the difference was not statistically significant.

Registry Data

Khazanie et al (2016) analyzed data from the National Cardiovascular Data Registry, which linked with Medicare claims and compared beneficiaries who receive CRT-D with those who received ICD alone.[73,] The dataset included 8951 patients with heart failure and AF with a QRS interval of 120 ms or more and an LVEF of 35% or less who had a registry record for CRT-D or ICD placement between 2006 and 2009 who were discharged alive to home. The authors used Cox proportional hazard models and inverse probability-weighted estimates to compare outcomes. Receipt of CRT-D was associated with lower mortality (HR, 0.83; 95% CI, 0.75 to 0.92), all-cause readmission (HR, 0.86; 95% CI, 0.80 to 0.92), and heart failure readmission (HR, 0.68; 95% CI, 0.62 to 0.76) compared with ICD alone.

Section Summary: Cardiac Resynchronization Therapy for Heart Failure and Atrial Fibrillation

Data from 4 RCTs enrolling only patients with AF showed different results, with 3 reporting improvements for patients with AF. One reported an all-cause mortality benefit in an advanced heart failure population, and another reporting no significant improvements. Subgroup analyses of the RAFT and COMPANION trials did not show the benefit of CRT in patients with permanent or intermittent AF. A registry study including almost 9000 Medicare beneficiaries reported significant improvements in mortality and hospitalizations for patients with heart failure and AF treated with CRT-D compared with ICD alone.

Cardiac Resynchronization Therapy for Heart Failure and Atrioventricular Nodal Block

Clinical Context and Therapy Purpose

The purpose of CRT in patients who have heart failure and AV nodal block is to provide a treatment option that is an alternative to or an improvement on existing therapies.
The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with heart failure in the following situations:

- NYHA class I, II, III or IV heart failure with LVEF of 50% or less and the presence of AV block with requirement for a high percentage of ventricular pacing
- Heart failure and AV nodal block

Interventions
The therapy being considered is CRT with or without defibrillator.

Several types of CRT devices are available, including those that incorporate biventricular pacing into automatic ICDs, stand-alone biventricular pacemakers, and biventricular pacemakers that incorporate fluid monitoring via bioimpedance.

Comparators
The following therapies are currently being used to treat patients with heart failure and AV block: medical care and medical care plus defibrillator.

Outcomes
The general outcomes of interest are OS, symptoms, functional outcomes, quality of life, hospitalizations, and treatment-related morbidity. Function may be measured by the 6MWT. Outcomes for patients with heart failure are assessed between 3 months and 2 years.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Patients with heart failure may require pacemakers for symptomatic bradycardia; those patients have a high risk of mortality or require heart transplant due to progressive heart failure, which is thought to be due, in part, to dyssynchronous contraction caused by RV pacing.

Randomized Controlled Trials
In 2014, the U.S. Food and Drug Administration (FDA) expanded the indications for several CRT devices to include patients with NYHA functional class I, II, or III heart failure and an LVEF of 50% or less, and AV block. A high percentage of these patients are expected to require ventricular pacing that cannot be managed with algorithms to minimize RV pacing. The FDA approval was based on results of the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) trial, in which patients with an indication for a pacemaker and NYHA class I, II, or III heart failure were implanted with a combined CRT-P or CRT-D (if indicated) and randomized to standard RV pacing or biventricular pacing.[74,] Race or ethnicity of participants were not described. Patients with permanent atrial arrhythmias and intrinsic AV block or AV block due to AV node ablation could be enrolled if they met other enrollment criteria. At baseline, patients met the requirement for ventricular pacing, either because of documented third-degree AV block or a second-degree AV block or a PR interval of 300 ms or more when paced at 100 beats per minute. Nine-hundred eighteen patients were enrolled, 691 of whom underwent randomization after 30 to 60 days of RV pacing, during which time appropriate pharmacologic therapy was established. Approximately half of all enrolled patients (51.6% of the CRT group, 54.1% of the RV pacing group)

had AF. After accounting for censored data due to missing measures of LVESV index, the primary outcome (first event of death from any cause, an urgent care visit for heart failure requiring intravenous therapy, or an increase in the LVESV index of ≥15%) occurred in 160 (45.8%) of 349 patients in the biventricular pacing group and in 190 (55.6%) of 342 in the RV pacing group. In a hierarchical Bayesian proportional hazards model, the HR for the primary outcome was 0.74 for the comparison between biventricular pacing and RV pacing (95% CI, 0.60 to 0.90; posterior probability of HR being ≤1, 0.9978, which is greater than the prespecified threshold for superiority of biventricular to RV pacing of 0.9775). The prespecified secondary outcomes of an urgent care visit for heart failure, death or hospitalization for heart failure, and hospitalization for heart failure were less likely in the biventricular pacing group; however, the secondary outcome of death alone did not differ significantly between groups. Left ventricular lead-related complications occurred in 6.4% of patients. In another publication from the BLOCK HF study, reported by Curtis et al (2016), patients in the CRT group showed greater improvements in NYHA class at 12 months (19% improved, 61% unchanged, 17% worsened) compared with the RV group (12% improved, 61% unchanged, 23% worsened; posterior probability, 0.99).[75,] At 6 months, Packer clinical composite score was improved, unchanged, or worsened in 53%, 24%, and 24% in the CRT group compared with 39%, 33%, and 28% in the RV arm (posterior probability, ≥0.99), respectively. The Packer clinical composite score classifies patients into 3 categories (improved, worsened, unchanged) using clinical outcomes, heart failure status, and patient symptoms.

Results of the BLOCK HF RCT were compared with results from an earlier trial (the Pacing to Avoid Cardiac Enlargement trial), in which 177 patients with bradycardia and a normal ejection fraction in whom a biventricular pacemaker had been implanted were randomized to biventricular pacing (n=89) or RV apical pacing (n=88).[76,77,] In the trial's main results, at 12 months postenrollment, subjects who underwent standard pacing had lower mean LVEF than those randomized to biventricular pacing (54.8% vs 62.2%; p<.001) and higher mean LVESV (35.7 mL vs 27.6 mL; p<.001). No significant differences were reported for quality of life or functional measures or rates of heart failure hospitalization. In long-term follow-up over a mean duration of 4.8 years among 149 subjects, biventricular pacing continued to be associated with improved LV functioning and less LV remodeling.[78,]Also, during long-term follow-up, heart failure hospitalization occurred more frequently in the RV pacing group (23.9% vs 14.6%; p<.001).

Several other RCTs have also corroborated the results of the BLOCK HF and the Pacing to Avoid Cardiac Enlargement trials.[32,42,79,] These trials reported improvements in physiologic parameters of LV function and improvements in functional status measured by the 6MWT. Some, but not all, of these trials also reported improvements in quality of life for patients treated with CRT.

Section Summary: Cardiac Resynchronization Therapy for Heart Failure and Atrioventricular Block

For patients who have AV nodal block, some degree of LV dysfunction, and who would not necessarily meet conventional criteria for CRT but would require ventricular pacing, a large RCT has demonstrated improvements in heart failure-related hospitalizations and urgent care visits among patients treated with CRT instead of RV pacing alone. For patients who require ventricular pacing but have no LV dysfunction, results of a small RCT have suggested that biventricular pacing is associated with improved measures of cardiac function, but the trial was small and underpowered to detect differences in clinical outcomes.

Triple-Site Cardiac Resynchronization Therapy for Heart Failure

Clinical Context and Therapy Purpose

The purpose of triple-site CRT in patients who have heart failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.
The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with heart failure.

Interventions
The therapy being considered is triple-site CRT.
Triple-site CRT, or triventricular pacing, is a variation of conventional CRT that uses an additional pacing lead. The rationale behind triventricular pacing is that a third pacing lead may improve electromechanical synchrony, and thereby lead to better outcomes.

Comparators
The following therapies are currently being used to treat heart failure: standard CRT.

Outcomes
The general outcomes of interest are OS, symptoms, functional outcomes, quality of life, hospitalizations, and treatment-related morbidity. Function may be measured by the 6MWT. Outcomes for patients with heart failure are assessed between 3 months and 2 years.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
To demonstrate improved outcomes, RCTs are needed that compare outcomes of triple-site CRT with conventional CRT. Six RCTs were identified for this review[80,81,82,83,84,85,85,]and are summarized in Table 9. The largest published trial, by 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.[82,] After a follow-up of 1 year, more patients in the conventional arm (30%) were in NYHA class III or IV heart failure than those in the triple-site CRT group (12.5%; p<.05). Implantation success was similar in the triple-site (94%) and conventional groups (98%; p=not significant), but triple-site implantation was associated with longer surgical time and a higher fluoroscopic exposure. Also, more patients in the triple-site group required additional procedures (33% vs 16%, p<.05).

The other 5 trials were smaller, enrolling between 43 and 95 patients. Follow-up in these studies was generally short, with the longest being 1 year. Outcomes reported varied across studies and were a mix of physiologic measures, functional status, and quality of life. No outcome measures reported were common across all studies. Three of the 5 studies reported significant improvements on at least 1 outcome measure, and the fourth and fifth studies reported no significant differences for the outcomes measured. Adverse events were not well-reported.

Table 9. Randomized Controlled Trials Comparing Triple-Site CRT With Standard CRT

Study	N	Group	Outcomes					
			6MWT, m	*MLHFQ, points*	*NYHA Class*	*Response Rate*	*Ejection Fraction*	*QOL, points*
Rogers et al (2012)[84,]	43[a]	Triple-site CRT	+91	-24	NR	NR	NR	NR
		Standard CRT	+65	-18				
p			.008	<.001				

Study	N	Group	Outcomes					
Lenarczyk et al (2012)[82,]	100	Triple-site CRT	NR	NR	12.5%[b]	NR	NR	NR
		Standard CRT			30%			
p					<.05			
Bencardino et al (2016)[81,]	43	Triple-site CRT	NR	NR	96%[c]	NR	+10%	NR
		Standard CRT			60%		+4%	
p					<.05		<.001	
Anselme et al (2016)[80,]	76	Triple-site CRT	+50	NR	NR	78.8%	NR	-8.4
		Standard CRT	+73			81.6%		-15.0
p			.40			.90		.20
Pappone et al (2015)[83,]	44	Triple-site CRT	NR	NR	NR	76%	+15%	NR
		Standard CRT				57%	+5%	
p						.33	<.001	
Gould et al (2021)[85,]	95	Triple-site CRT	+31.2	NR	NR	NR	+6.4%	NR
		Standard CRT	-29.9				+7.3%	
p			.051				.676	

CRT: cardiac resynchronization therapy; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NR; not reported; NYHA: New York Heart Association; QOL: quality of life; 6MWT: 6-minute walk test.
[a] All patients had triple-site device implanted. Device programmed to triple-site or standard CRT randomly.
[b] Percentage of patients in NYHA class III/IV heart failure.
[c] Percentage of patients who improved at least 1 NYHA class.

Zhang et al (2018) conducted a meta-analysis of RCTs and comparative observational studies (N=251 patients) that evaluated similar outcomes.[86,] The meta-analysis included 1 RCT (Anselme et al [2016][80,]; described above), 2 randomized crossover studies, and 2 nonrandomized comparative studies. Two different pacing modalities were used. One type used 1 lead in the right ventricle and leads in 2 different tributaries in the left ventricle. The other used 2 leads in the right ventricle. Patients in the triple-site pacing group had greater improvement in LVEF (weighted mean difference, 4.04; 95% CI, 2.15 to 5.92; p<.001) and NYHA classes (weighted mean difference, -0.27; 95% CI, -0.42 to -0.11; p=.001). However, there were no significant differences in LV end-diastolic volume or LVESV, 6MWT, or Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Section Summary: Triple-Site Cardiac Resynchronization Therapy for Heart Failure

For the use of CRT with triple-site pacing requiring implantation of an additional lead, 6 small RCTs with limited follow-up and a meta-analysis that included nonrandomized studies were identified. All trials except 1 reported improved outcomes on at least 1 measure of functional status and quality of life with triple-site CRT compared with conventional CRT. However, the outcomes reported differed across studies, with no common outcomes reported by all studies. Triple-site CRT was also associated with higher radiation exposure and a greater number of additional procedures postimplantation. Modest improvements in some outcome measures were found in the meta-analysis. Larger, high-quality RCTs are needed to better define the benefit-risk ratio for triple-site CRT compared with conventional CRT.

Cardiac Resynchronization Therapy Combined With Remote Fluid Monitoring for Heart Failure

Clinical Context and Therapy Purpose

The purpose of CRT combined with remote fluid monitoring in patients who have heart failure is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with heart failure.

Interventions
The therapy being considered is CRT combined with remote fluid monitoring.

Intrathoracic fluid status monitoring has been proposed as a more sensitive way to monitor fluid status, permitting prompt identification of impending heart failure, early intervention, and potentially decreased rates of hospitalization.

Comparators
The following therapies are currently being used to treat heart failure: standard CRT only.

Outcomes
The general outcomes of interest are OS, symptoms, functional outcomes, quality of life, hospitalizations, and treatment-related morbidity. Function may be measured by the 6MWT. Outcomes for patients with heart failure are assessed between 3 months and 2 years.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Randomized Controlled Trials
Three RCTs were identified that compared management of patients with heart failure using remote fluid monitoring to usual monitoring.[87,88,89,] Luthje et al (2015) was an unblinded, single-site RCT sponsored by the manufacturer of the OptiVol device.[88,] Patients in the remote monitoring group had alarms set for a rising fluid index, with most patients having their diuretic increased by 50% in response to an alert. Median follow-up was not reported. Outcomes were reported as 1-year estimates using Cox proportional hazards. Four patients were lost to follow-up. Domenichini et al (2016) was an unblinded, single-site RCT sponsored by the U.K. National Health Service.[87,] Patients in the remote monitoring group had alarms set for a rising fluid index, with most patients having their diuretic increased by 50% in response to an alert. Median follow-up was 375 days (range, 350 to 430 days). One patient was lost to follow-up, and 71 (89%) of 80 patients had complete data on patient-reported outcomes. Bohm et al (2016) was an unblinded, multicenter RCT conducted in Germany and also sponsored by the device manufacturer.[89,] One thousand two patients with NYHA class II or III heart failure and an LVEF of 35% or less were randomized to have their ICD or CRT-D devices automatically transmit fluid index telemedicine alerts or not. Alerts were triggered by intrathoracic fluid index threshold crossing, which was programmed at the investigator's discretion. Patients were followed for a mean of 1.9 years. All patients were included in the intention-to-treat Cox proportional hazard analyses.

None of the 3 RCTs reported improvements for the remote monitoring group on any outcome measures. In the Domenichini et al (2016) study, there were no significant differences reported between groups for hospitalizations rates, functional status, or quality of life.[87,] Luthje et al (2015) reported no differences in mortality or hospitalizations.[88,]Also, Luthje et al (2015) reported an HR for time to the first hospitalization that was not significant at 1.23 (95% CI, 0.62 to 2.44, p=.55). Mean number of emergency department visits did not differ between the remote monitoring group (0.10) and the usual care group (0.10; p=.73), but the mean number of urgent care visits was higher for remote monitoring (0.30) than for usual care (0.10; p=.03). Bohm et al (2016) reported no differences

in the composite outcome of all-cause death and cardiovascular hospitalization (HR, 0.87; 95% CI, 0.72 to 1.04) or mortality (HR, 0.89; 95% CI, 0.62 to 1.28).[89,]

Section Summary: Cardiac Resynchronization Therapy Combined With Remote Fluid Monitoring for Heart Failure

Three RCTs have reported no improvement in outcomes associated with remote fluid monitoring for patients with heart failure.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2012 Input

In response to requests, input was received from 1 physician specialty society and 8 academic medical centers while this policy was under review in 2012. There was consensus with the medically necessary statements. For patients with class I heart failure, there was mixed input as to whether cardiac resynchronization therapy (CRT) should be medically necessary. Regarding the duration of the QRS complex, commentators acknowledged that the literature supported use mainly in patients with a QRS interval greater than 150 ms, but most reviewers disagreed with restricting CRT use to patients in that group because that duration was not currently the accepted standard of care. For patients with atrial fibrillation, the input was mixed on whether biventricular pacing improves outcomes.

Further details from clinical input are included in the Appendix.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology et al

The American College of Cardiology (ACC), American Heart Association, and Heart Rhythm Society (2019) published joint guidelines on the evaluation and management of patients with bradycardia and cardiac conduction delay.[90,] These guidelines included the following recommendations on CRT (see Table 10).

Table 10. Joint Guidelines on Treatment of Patients with Bradycardia and Cardiac Conduction Delay

Recommendation	COR	LOE
"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."	IIa	B-R^{SR}
"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%	IIa	B-R

Recommendation	COR	LOE
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)."		

COR: class of recommendation; CRT: cardiac resynchronization therapy; LOE: level of evidence; LVEF: left ventricular ejection fraction; SR: systematic review.

A focused update to 2008 guidelines[91,] for device-based treatment of cardiac rhythm abnormalities was published jointly by ACC Foundation, American Heart Association, and Heart Rhythm Society in 2012.[92,] The ACC and American Heart Association (2013) subsequently published guidelines for the management of heart failure.[93,] These guidelines made recommendations on CRT for heart failure that are in line with those made by the ACC, American Heart Association, and Heart Rhythm Society related to CRT for heart failure in 2012. The ACC, American Heart Association, and Heart Failure Society of America published guidelines on the management of heart failure (2022) to replace the 2013 guidelines.[94,] The most recent recommendations on CRT for heart failure from the guidelines are included in Table 11.

Table 11. 2022 Joint Guidelines on Device-Based Treatment of Cardiac Rhythm Abnormalities

Recommendation	COR	LOE
CRT is indicated for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration greater than or equal to 150 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT	I	B[a]
CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT	IIa	B[b]
CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class II, III, or ambulatory class IV symptoms on GDMT	IIa	B[a]
CRT is reasonable in patients with high-degree or complete heart block and LVEF of 36% to 50%	IIa	B[a]
CRT can be useful in patients with atrial fibrillation and LVEF less than or equal to 35% on GDMT if a) the patient requires ventricular pacing or otherwise meets CRT criteria and b) AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT	IIa	B[b]
CRT can be useful for patients on GDMT who have LVEF less than or equal to 35% and are undergoing new or replacement device placement with anticipated requirement for significant (>40%) ventricular pacing	IIa	B[b]
CRT may be considered for patients who have LVEF less than or equal to 30%, ischemic etiology of heart failure, sinus rhythm, LBBB with a QRS duration of greater than or equal to 150 ms, and NYHA class I symptoms on GDMT	IIb	B[b]
CRT may be considered for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with QRS duration 120 to 149 ms, and NYHA class III/ambulatory class IV on GDMT	IIb	B[b]
CRT is not recommended in patients with QRS duration less than 120 ms	III[c]	B[a]
CRT is not recommended for patients with NYHA class I or II symptoms and non-LBBB pattern with QRS duration less than 150 ms	III[c]	B[b]
CRT-D is not indicated for patients whose comorbidities and/or frailty limit survival with good functional capacity to less than 1 year	III[c]	C[d]

AV: atrioventricular; COR: class of recommendation; CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy with defibrillation; GDMT: guideline-directed medical therapy; LBBB: left bundle branch block; LOE: level of evidence; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; RCT: randomized controlled trial.

[a]Moderate quality evidence from 1 or more RCTs..

[b]Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies.

[c]No benefit.

[d]Limited data.

Heart Failure Society of America

The Heart Failure Society of America (2010) released comprehensive guidelines on the management of heart failure.[95,] The guidelines were updated in conjunction with the ACC and American Heart Association in 2022[94,]; updated recommendations can be found above, in Table 11.

National Institute for Health and Care Excellence

The NICE (2014) guidance provided recommendations on CRT for heart failure.[96,] The recommendations for patients with left ventricular ejection fraction of 35% or less are listed in Table 12.

Table 12. Guidelines on Management of Cardiac Resynchronization Therapy for Heart Failure

Indication	Recommendation
NYHA class I to IV with QRS interval <120 ms	CRT not recommended
NYHA class IV with QRS interval 120 to 149 ms and without LBBB	CRT-P recommended
NYHA class II to III with QRS interval 120 to 149 ms and with LBBB	CRT-D recommended
NYHA class III to IV with QRS interval 120 to 149 ms and with LBBB	CRT-P recommended
NYHA class I to III with QRS interval ≥150 ms (with or without LBBB)	CRT-D recommended
NYHA class III to IV with QRS interval ≥150 ms (with or without LBBB)	CRT-P recommended

CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy with implantable cardioverter-defibrillator; CRT-P: cardiac resynchronization therapy with pacemaker; LBBB: left bundle branch block; NYHA: New York Heart Association.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 13.

Table 13. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01994252	Resynchronization/Defibrillation for Ambulatory Heart Failure Trial in Patients With Permanent Atrial Fibrillation (RAFT-PermAF)	200	Mar 2023
NCT02962791	Prospective Randomized Trial Comparing TRIPLE Site ventriculAr Stimulation Versus Conventional Pacing in CRT canDidates: TRIPLEAD Trial	166	Oct 2021
NCT04225520	Assessment of Mechanical Dyssynchrony as Selection Criterion for Cardiac Resynchronization Therapy	700	Dec 2029
NCT02454439	Assessment of Cardiac Resynchronization Therapy in Patients With Wide QRS and Non-specific Intraventricular Conduction Delay: a Randomized Trial	200	July 2024
NCT03366545[a]	Observation of Clinical Routine Care for Heart Failure Patients Implanted With BIOTRONIK CRT Devices	3000	June 2025

NCT: national clinical trial.
[a]Denotes industry sponsored or co-sponsored trials

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or cardiology consultation report including:
  - Reason for device
  - Type of device requested
  - Documented New York Heart Association functional class
  - Left ventricular ejection fraction
  - Electrocardiogram including QRS duration and cardiac rhythm
  - Documented pharmacological and medical regimen and response to treatment

Post Service (in addition to the above, please include the following):

- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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; both components of pulse generator (battery and transmitter) only ***(Code revision effective 10/1/2023)***
	0518T	Removal of pulse generator for wireless cardiac stimulator for left ventricular pacing; battery component only ***(Code revision effective 10/1/2023)***
	0519T	Removal and replacement of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; both components (battery and transmitter) ***(Code revision effective 10/1/2023)***
	0520T	Removal and replacement of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; battery component only ***(Code revision effective 10/1/2023)***
	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
	0795T	Transcatheter insertion of permanent dual-chamber leadless pacemaker, including imaging guidance (e.g., fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (e.g., interrogation or programming), when performed; complete system (i.e., right atrial and right ventricular pacemaker components) ***(Code effective 7/1/2023)***
	0796T	Transcatheter insertion of permanent dual-chamber leadless pacemaker, including imaging guidance (e.g., fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (e.g., interrogation or programming),

Type	Code	Description
		when performed; right atrial pacemaker component (when an existing right ventricular single leadless pacemaker exists to create a dual-chamber leadless pacemaker system) ***(Code effective 7/1/2023)***
	0797T	Transcatheter insertion of permanent dual-chamber leadless pacemaker, including imaging guidance (e.g., fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (e.g., interrogation or programming), when performed; right ventricular pacemaker component (when part of a dual-chamber leadless pacemaker system) ***(Code effective 7/1/2023)***
	0798T	Transcatheter removal of permanent dual-chamber leadless pacemaker, including imaging guidance (e.g., fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography), when performed; complete system (i.e., right atrial and right ventricular pacemaker components) ***(Code effective 7/1/2023)***
	0799T	Transcatheter removal of permanent dual-chamber leadless pacemaker, including imaging guidance (e.g., fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography), when performed; right atrial pacemaker component ***(Code effective 7/1/2023)***
	0800T	Transcatheter removal of permanent dual-chamber leadless pacemaker, including imaging guidance (e.g., fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography), when performed; right ventricular pacemaker component (when part of a dual-chamber leadless pacemaker system) ***(Code effective 7/1/2023)***
	0801T	Transcatheter removal and replacement of permanent dual-chamber leadless pacemaker, including imaging guidance (e.g., fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (e.g., interrogation or programming), when performed; dual-chamber system (i.e., right atrial and right ventricular pacemaker components) ***(Code effective 7/1/2023)***
	0802T	Transcatheter removal and replacement of permanent dual-chamber leadless pacemaker, including imaging guidance (e.g., fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (e.g., interrogation or programming), when performed; right atrial pacemaker component ***(Code effective 7/1/2023)***
	0803T	Transcatheter removal and replacement of permanent dual-chamber leadless pacemaker, including imaging guidance (e.g., fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (e.g., interrogation or programming), when performed; right ventricular pacemaker component (when part of a dual-chamber leadless pacemaker system) ***(Code effective 7/1/2023)***
	0804T	Programming device evaluation (in person) with iterative adjustment of implantable device to test the function of device and to select optimal permanent programmed values, with analysis, review, and report, by a physician or other qualified health care professional, leadless pacemaker system in dual cardiac chambers ***(Code effective 7/1/2023)***

Type	Code	Description
	0861T	Removal of pulse generator for wireless cardiac stimulator for left ventricular pacing; both components (battery and transmitter) ***(Code effective 1/1/2024)***
	0862T	Relocation of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; battery component only ***(Code effective 1/1/2024)***
	0863T	Relocation of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; transmitter component only ***(Code effective 1/1/2024)***
	33202	Insertion of epicardial electrode(s); open incision (e.g., thoracotomy, median sternotomy, subxiphoid approach)
	33203	Insertion of epicardial electrode(s); endoscopic approach (e.g., thoracoscopy, pericardioscopy)
	33207	Insertion of new or replacement of permanent pacemaker with transvenous electrode(s); ventricular
	33208	Insertion of new or replacement of permanent pacemaker with transvenous electrode(s); atrial and ventricular
	33211	Insertion or replacement of temporary transvenous dual chamber pacing electrodes (separate procedure)
	33213	Insertion of pacemaker pulse generator only; with existing dual leads
	33214	Upgrade of implanted pacemaker system, conversion of single chamber 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
	33220	Repair of 2 transvenous electrodes for 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 (e.g., 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
	33233	Removal of permanent pacemaker pulse generator only
	33235	Removal of transvenous pacemaker electrode(s); dual lead system

Type	Code	Description
	33237	Removal of permanent epicardial pacemaker and electrodes by thoracotomy; dual lead system
	33238	Removal of permanent transvenous electrode(s) by thoracotomy
	33241	Removal of implantable defibrillator pulse generator only
	33243	Removal of single or dual chamber implantable defibrillator electrode(s); by thoracotomy
	33244	Removal of single or dual chamber implantable defibrillator electrode(s); by transvenous extraction
	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
HCPCS	C1785	Pacemaker, dual chamber, rate-responsive (implantable)
	C2619	Pacemaker, dual chamber, nonrate-responsive (implantable)
	C2621	Pacemaker, other than single or dual chamber (implantable)
	C7537	Insertion of new or replacement of permanent pacemaker with atrial transvenous electrode(s), with insertion of pacing electrode, cardiac venous system, for left ventricular pacing, at time of insertion of implantable defibrillator or pacemaker pulse generator (e.g., for upgrade to dual chamber system)
	C7538	Insertion of new or replacement of permanent pacemaker with ventricular transvenous electrode(s), with insertion of pacing electrode, cardiac venous system, for left ventricular pacing, at time of insertion of implantable defibrillator or pacemaker pulse generator (e.g., for upgrade to dual chamber system)
	C7539	Insertion of new or replacement of permanent pacemaker with atrial and ventricular transvenous electrode(s), with insertion of pacing electrode, cardiac venous system, for left ventricular pacing, at time of insertion of implantable defibrillator or pacemaker pulse generator (e.g., for upgrade to dual chamber system)
	C7540	Removal of permanent pacemaker pulse generator with replacement of pacemaker pulse generator, dual lead system, with insertion of pacing electrode, cardiac venous system, for left ventricular pacing, at time of insertion of implantable defibrillator or pacemaker pulse generator (e.g., for upgrade to dual chamber system)
	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

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
03/29/2013	BCBSA Medical Policy adoption
07/31/2015	Coding update
10/30/2015	Policy revision with position change

Effective Date	Action
07/01/2016	Policy revision without position change
07/01/2017	Policy revision without position change
07/01/2018	Policy revision without position change
02/01/2019	Coding update
07/01/2019	Policy revision without position change
05/01/2020	Administrative update. Policy statement and guidelines updated.
07/01/2020	Annual review. No change to policy statement. Literature review updated.
07/01/2021	Annual review. Policy statement and literature review updated.
07/01/2022	Annual review. Policy statement, guidelines and literature review updated.
07/01/2023	Annual review. Policy statement, guidelines and literature review updated. Coding update.
08/01/2023	Coding update.
12/01/2023	Coding update.
03/01/2024	Coding update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue

Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No Changes)	
BEFORE	**AFTER**
Biventricular Pacemakers (Cardiac Resynchronization Therapy) for the Treatment of Heart Failure 2.02.10 **Policy Statement:** I. Biventricular pacemakers with or without an accompanying implantable cardiac defibrillator (i.e., a combined biventricular pacemaker plus implantable cardiac defibrillator) as a treatment of heart failure may be considered **medically necessary** in **either** of the following criteria: A. **New York Heart Association (NYHA) class III or IV** and **all** of the following: 1. Left ventricular ejection fraction less than or equal to 35% with **either** of the following: a. Left bundle branch block b. QRS interval greater than or equal to 150 ms 2. Individuals treated with a guideline-directed medical therapy 3. Sinus rhythm B. **New York Heart Association (NYHA) class II** and **all** of the following: 1. Left ventricular ejection fraction less than or equal to 30% with **either** of the following: c. Left bundle branch block d. QRS interval greater than or equal to 150 ms 2. Individuals treated with a guideline-directed medical therapy 3. Sinus rhythm II. Biventricular pacemakers with or without an accompanying implantable cardiac defibrillator, as an alternative to a right ventricular pacemaker (with or without an accompanying implantable cardiac defibrillator) may be considered **medically necessary** when **all** of the following are present: A. Left ventricular ejection fraction less than or equal to 50%	**Biventricular Pacemakers (Cardiac Resynchronization Therapy) for the Treatment of Heart Failure 2.02.10** **Policy Statement:** I. Biventricular pacemakers with or without an accompanying implantable cardiac defibrillator (i.e., a combined biventricular pacemaker plus implantable cardiac defibrillator) as a treatment of heart failure may be considered **medically necessary** in **either** of the following criteria: A. **New York Heart Association (NYHA) class III or IV** and **all** of the following: 1. Left ventricular ejection fraction less than or equal to 35% with **either** of the following: a. Left bundle branch block b. QRS interval greater than or equal to 150 ms 2. Individuals treated with a guideline-directed medical therapy 3. Sinus rhythm B. **New York Heart Association (NYHA) class II** and **all** of the following: 1. Left ventricular ejection fraction less than or equal to 30% with **either** of the following: a. Left bundle branch block b. QRS interval greater than or equal to 150 ms 2. Individuals treated with a guideline-directed medical therapy 3. Sinus rhythm II. Biventricular pacemakers with or without an accompanying implantable cardiac defibrillator, as an alternative to a right ventricular pacemaker (with or without an accompanying implantable cardiac defibrillator) may be considered **medically necessary** when **all** of the following are present: A. Left ventricular ejection fraction less than or equal to 50%

POLICY STATEMENT (No Changes)	
BEFORE	**AFTER**
B. New York Heart Association (NYHA) class I, II, III, or IV heart failure C. Individuals treated with a guideline-directed medical therapy D. The presence of atrioventricular block with requirement for a high percentage of ventricular pacing and **one** or more of the following: 1. Second-degree AV block or a PR interval of 300 ms or more when paced at 100 beats per minute 2. Third-degree AV block III. Biventricular pacemakers, with or without an accompanying implantable cardiac defibrillator are considered **investigational** in **any** of the following situations: A. Treatment for individuals with NYHA **class I heart failure** unless all of the following are present: 1. Left ventricular ejection fraction less than or equal to 50% 2. Individuals treated with a guideline-directed medical therapy 3. **Atrioventricular block** with requirement for a high percentage of ventricular pacing) and **1 or more** of the following: a. Second-degree AV block or a PR interval of 300 ms or more when paced at 100 beats per minute b. Third-degree AV block B. Treatment for heart failure in patients with **atrial fibrillation** IV. The following are considered **investigational**: A. Triple-site (triventricular or quadripolar) cardiac resynchronization therapy, using an additional pacing lead B. An intrathoracic fluid monitoring as a component of a biventricular pacemaker C. Cardiac resynchronization therapy with wireless left ventricular endocardial pacing	B. New York Heart Association (NYHA) class I, II, III, or IV heart failure C. Individuals treated with a guideline-directed medical therapy D. The presence of atrioventricular block with requirement for a high percentage of ventricular pacing and **one** or more of the following: 1. Second-degree AV block or a PR interval of 300 ms or more when paced at 100 beats per minute 2. Third-degree AV block III. Biventricular pacemakers, with or without an accompanying implantable cardiac defibrillator are considered **investigational** in **any** of the following situations: A. Treatment for individuals with NYHA **class I heart failure** unless all of the following are present: 1. Left ventricular ejection fraction less than or equal to 50% 2. Individuals treated with a guideline-directed medical therapy 3. **Atrioventricular block** with requirement for a high percentage of ventricular pacing) and **1 or more** of the following: a. Second-degree AV block or a PR interval of 300 ms or more when paced at 100 beats per minute b. Third-degree AV block B. Treatment for heart failure in patients with **atrial fibrillation** IV. The following are considered **investigational**: A. Triple-site (triventricular or quadripolar) cardiac resynchronization therapy, using an additional pacing lead B. An intrathoracic fluid monitoring as a component of a biventricular pacemaker C. Cardiac resynchronization therapy with wireless left ventricular endocardial pacing