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| **Policy Number** | **MED202.054** |
| **Policy Effective Date** | **11/15/2024** |

# Biventricular Pacemakers (Cardiac Resynchronization Therapy) for the Treatment of Heart Failure

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## Disclaimer

**Carefully check state regulations and/or the member contract.**
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

## Coverage

Biventricular pacemakers with or without an accompanying implantable cardiac defibrillator (ICD) (i.e., a combined biventricular pacemaker plus ICD) **may be considered medically necessary** as a treatment of heart failure (HF) in individuals who meet ALL of the following criteria:

For New York Heart Association (NYHA) class III or IV:

- Left ventricular ejection fraction (LVEF) ≤35%,
- Sinus rhythm,
- Individuals treated with guideline-directed medical therapy for heart failure with reduced ejection fraction including 4 medication classes: 1) renin angiotensin system inhibition with angiotensin receptor-neprilysin inhibitors (ARNi), angiotensin-converting enzyme inhibitors (ACRi), or angiotensin (II) receptor blockers (ARB) alone; 2) beta blockers; 3) mineralocorticoid receptor antagonists (MRAs); and 4) sodium-glucose cotransporter 2 inhibitor (SGLT2i), AND

- Either left bundle branch block OR QRS interval ≥150 milliseconds (ms).

For NYHA class II:
- Left ventricular ejection fraction (LVEF) ≤30%,
- Sinus rhythm,
- Individuals treated with guideline-directed medical therapy for heart failure with reduced ejection fraction including 4 medication classes: 1) renin angiotensin system inhibition with angiotensin receptor-neprilysin inhibitors (ARNi), angiotensin-converting enzyme inhibitors (ACRi), or angiotensin (II) receptor blockers (ARB) alone; 2) beta blockers; 3) mineralocorticoid receptor antagonists (MRAs); and 4) sodium-glucose cotransporter 2 inhibitor (SGLT2i), AND
- Either left bundle branch block OR QRS interval ≥150 ms.

For individuals who do not meet the criteria outlined above, but have an indication for a ventricular pacemaker, biventricular pacemakers with or without an accompanying ICD (i.e., a combined biventricular pacemaker plus ICD) **may be considered medically necessary** as an alternative to a right ventricular pacemaker in individuals who meet all of the following criteria:
- NYHA functional class I, II, or III, or IV heart failure,
- Left ventricular ejection fraction (LVEF) ≤50%,
- Individuals treated with guideline-directed medical therapy for heart failure with mildly reduced ejection fraction therapy (if indicated), and
- The presence of atrioventricular (AV) block with requirement for a high percentage of ventricular pacing.

**NOTE:** Atrioventricular block with a requirement for a high percentage of ventricular pacing is considered to be present when there is either:
- Third-degree AV block; or
- Second-degree AV block or a PR interval of ≥300 ms when paced at 100 beats per minute.

Biventricular pacemakers, with or without an accompanying ICD (i.e., a combined biventricular pacemaker plus ICD), **are considered experimental, investigational and/or unproven** as a treatment for individuals with New York Heart Association class I heart failure who do not meet the above criteria.

Biventricular pacemakers, with or without an accompanying ICD (i.e., a combined biventricular pacemaker plus ICD), **are considered experimental, investigational and/or unproven** as a treatment for heart failure in individuals with atrial fibrillation who do not meet the above criteria.

Triple-site (triventricular) cardiac resynchronization therapy, using an additional pacing lead, **is considered experimental, investigational and/or unproven.**

An intrathoracic fluid monitoring sensor **is considered experimental, investigational and/or unproven** as a component of a biventricular pacemaker**.**

Cardiac resynchronization therapy with wireless left ventricular endocardial pacing **is considered experimental, investigational and/or unproven.**

## Policy Guidelines

MED202.058 addresses the use of external bioimpedance devices as stand-alone devices to assess cardiac output noninvasively.

## 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).

**Heart Failure**

An estimated 6.7 million adults in the United States 20 years of age and older had heart failure between 2017 and 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.

**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 United States (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 milliseconds (ms) or longer and a 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 LVEF of 35% or less, QRS duration 130 ms or longer (≥120 ms for the Guidant device), and remain symptomatic despite a stable, optimal heart failure drug therapy. In 2006, Biotronik Inc. received 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) (4); in 2013, the company received FDA approval for updated CD-CRT 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 (4):

- Moderate-to-severe heart failure (NYHA class III-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 (AV) 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 AV 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.

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

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life (QOL), 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 one 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. RCTs 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.

**Cardiac Resynchronization Therapy for Heart Failure**

Clinical Context and Therapy Purpose

The purpose of cardiac resynchronization therapy (CRT) in individuals 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 policy.

*Populations*

The relevant population of interest is individuals 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 a 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.

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 vs 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) vs ICD alone and/or CRT vs 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 vs ICD alone and a 25% reduction in mortality of CRT vs drug therapy. Reviews providing results stratified by NYHA class I or II vs 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 vs 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<br>• ICD alone | 3 RCTs (N=3858) with ≥12-mo follow-up | REVERSE, MADIT-CRT, RAFT | **CRT-D vs ICD**<br>Heart failure hospitalizations<br>• OR=0.67 (95% CI, 0.50 to 0.89)<br>Mortality<br>• OR=0.78 (95% CI, 0.63 to 0.96) |
| Woods et al. | 1990-2015 | LVEF ≤40% | • CRT or CRT-D | 13 RCTs (N=12,638) | CARE-HF, MIRACLE, | **CRT-D vs drug therapy** |

| | | | | | | |
|---|---|---|---|---|---|---|
| (2015) (16) | | | • Drug therapy alone or ICD alone | | 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] | Mortality<br>• HR=0.58 (95% CrI, 0.50 to 0.68)<br>**CRT-D vs ICD**<br>Mortality<br>• 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; N: number; RCT: randomized controlled trial; RR: relative risk.

[a] Trials of ICD vs medical therapy; used in the indirect comparisons in the network meta-analysis.

**Table 2a. AMSTAR Quality of Systematic Reviews of CRT**

| Study | A Priori Design | Duplicate Selection/ Extraction | Comp Literature Search | Search for Gray Literature | Included/ Excluded Studies Provided | Study Characteristics Provided |
|---|---|---|---|---|---|---|
| Sun (2016) (17) | Can't answer | Yes | Yes | Yes | No | Yes |

| | | | | | | |
|---|---|---|---|---|---|---|
| Woods (2015) (16) | Can't answer | Yes | Yes | No | No | Yes |

For a description of AMSTAR items, see <https://amstar.ca>.
AMSTAR: A MeaSurement Tool to Assess Systematic Reviews; Comp: comprehensive.

**Table 2b. AMSTAR Quality of Systematic Reviews of CRT**

| Study | Study Scientific Quality Assessed and Documented | Scientific Quality Used in Formulated Conclusions | Appropriate Methods for Synthesis | Publication Bias Assessed | COI Included |
|---|---|---|---|---|---|
| Sun (2016) (17) | Yes | Yes | Yes | No | No |
| Woods (2015) (16) | Yes | Yes | Yes | No | Yes |

For a description of AMSTAR items, see <https://amstar.ca>.
AMSTAR: A MeaSurement Tool to Assess Systematic Reviews; COI: conflict of interest.

Randomized Controlled Trials

At least 30 RCTs that have evaluated CRT have been published and are included in at least one of the meta-analyses listed above. (4, 19-46) 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 3a. RCTS of CRT for the Treatment of Heart Failure**

| Study | Dur | Treatment Groups | N | Percent NYHA Class | | | |
|---|---|---|---|---|---|---|---|
| | | | | I | II | III | IV |
| Lozano (2000) (19) | 3 mo | • CRT-D<br>• ICD | • 109<br>• 113 | NA | • 35 | • 57 | • 8 |
| MIRACLE (2002) (23) | 6 mo | • CRT<br>• Inactive | • 228<br>• 225 | NA | NA | • 90<br>• 91 | • 10<br>• 9 |
| CONTAK-CD (2003) (26) | 3 mo | • CRT-D<br>• ICD | • 245<br>• 245 | NA | • 32<br>• 33 | • 60<br>• 57 | • 8<br>• 10 |
| MIRACLE-ICD (2003) (27) | 6 mo | • CRT-D<br>• ICD | • 187<br>• 182 | NA | NA | • 88<br>• 89 | • 12<br>• 11 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| COMPANION (2004) (28) | 15 mo | • CRT<br>• Usual care | • 617<br>• 308 | NA | NA | • 87<br>• 82 | • 13<br>• 18 |
| CARE-HF (2005) (30) | 29 mo | • CRT<br>• Usual care | • 409<br>• 404 | NA | NA | • 94<br>• 93 | • 6<br>• 7 |
| DECREASE-HF (2007) (34) | 6 mo | • BiV-ICD<br>• LV-ICD | • 205<br>• 101 | NA | NA | • 98<br>• 97 | • 2<br>• 3 |
| REVERSE (2008) (38) | 12 mo | • CRT on<br>• CRT off | • 419<br>• 191 | • 18<br>• 17 | • 82<br>• 83 | NA | NA |
| MADIT-CRT (2009) (39) | 2.4 yr | • CRT-D<br>• ICD | • 1089<br>• 731 | • 14<br>• 16 | • 86<br>• 85 | NA | NA |
| RAFT (2010) (43) | 40 mo | • CRT-D<br>• ICD | • 894<br>• 904 | NA | • 79<br>• 81 | • 21<br>• 19 | NA |

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; DUR: duration; 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 lnSync Randomized Clinical Evaluation; MIRACLE-ICD: Multicenter lnSync 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; REVERSE: REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction; SD: standard deviation.

**Table 3b. RCTS of CRT for the Treatment of Heart Failure**

| Study | Treatment Groups | Mean LVEF (SD), % | Mean QRS (SD), ms | Percent ECG Pattern | | % AF |
|---|---|---|---|---|---|---|
| | | | | LBBB | RBBB | |
| Lozano (2000) (19) | • CRT-D<br>• ICD | • 22 (7) | NR | NR | NR | NR |
| MIRACLE (2002) (23) | • CRT<br>• Inactive | • 22 (6)<br>• 22 (6) | • 167 (21)<br>• 165 (20) | NR | NR | Ex |
| CONTAK-CD (2003) (26) | • CRT-D<br>• ICD | • 21 (7)<br>• 22 (7) | • 160 (27)<br>• 156 (26) | • 54<br>• 55 | • 14<br>• 12 | Ex |
| MIRACLE-ICD (2003) (27) | • CRT-D<br>• ICD | • 24 (7)<br>• 24 (6) | • 165 (22) | NR | • 13<br>• 13 | Ex |
| COMPANION (2004) (28) | • CRT<br>• Usual care | • 20[a]<br>• 22[a] | • 160[a]<br>• 158[a] | • 69<br>• 70 | NR | Ex |

| | | | | | | |
|---|---|---|---|---|---|---|
| CARE-HF (2005) (30) | • CRT<br>• Usual care | • 25[a]<br>• 25[a] | • 160[a]<br>• 160[a] | NR | NR | Ex |
| DECREASE-HF (2007) (34) | • BiV-ICD<br>• LV-ICD | • 23 (7)<br>• 23 (7) | • 167 (16)<br>• 165 (15) | • 94<br>• 93 | • 0<br>• 1 | Ex |
| REVERSE (2008) (38) | • CRT on<br>• CRT off | • 27 (7)<br>• 26 (7) | • 153 (21)<br>• 154 (24) | NR | NR | Ex |
| MADIT-CRT (2009) (39) | • CRT-D<br>• ICD | • 24 (5)<br>• 24 (5) | • >150, 64%<br>• >150, 65% | • 70<br>• 71 | • 13<br>• 13 | Ex |
| RAFT (2010) (43) | • CRT-D<br>• ICD | • 22 (5)<br>• 22 (5) | • 157 (24)<br>• 158 (24) | • 73<br>• 71 | • 8<br>• 10 | • 13<br>• 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; DUR: duration; 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 lnSync Randomized Clinical Evaluation; MIRACLE-ICD: Multicenter lnSync 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; REVERSE: REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction; SD: standard deviation.
[a] Median.

*New York Heart Association Class II or III Heart Failure - Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT 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 of 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<0.001). (43) There were significant reductions in both individual components of the primary outcome, overall mortality (20.8% vs 26.1%; p=0.003) and hospitalizations (19.5% vs 26.1%, p<0.001), all respectively. When restricted to patients with NYHA class II heart failure, improvements in the outcomes of mortality and hospitalizations remained significant. The mortality for class II patients in the CRT-D group was 15.5% versus 21.1% in the ICD-alone group (HR=0.71; 95% CI, 0.56 to 0.91;

p<0.006). 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<0.003).

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=0.003). (47) Although the total number of hospitalizations for any cause was lower in the CRT-D group (1448 vs 1553; p=0.042), patients randomized to CRT-D had more hospitalizations for device-related indications (246 vs 159; p<0.001).

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=0.003 for the difference between the HRs). There was a trend for greater improvement in patients with sinus rhythm compared to patients with atrial arrhythmias, but this difference was not statistically significant.

Sapp et al. (2024) published long-term results of the RAFT trial. (48) The median follow-up was 7.7 years in the entire study population and 13.9 years among individuals who survived (interquartile range, 12.8 to 15.7 years). Death from any cause occurred in 76.4% of the ICD alone group and 71.2% of the CRT-D group.

*New York Heart Association Class I or II Heart Failure - Multicenter Automatic Implantation Trial-Cardiac Resynchronization Trial (MADIT-CRT)*

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 (i.e., death or acute heart failure exacerbation). The primary end point 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 on the primary composite outcome. The death rate was similar between groups. Subgroup analyses found significantly reduced mortality of CRT-D vs 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. (49) This analysis supplemented the original MADIT-CRT outcome of time to first heart failure event, by comparing total heart failure events during

an average follow-up of 2.6 years. Over this time period there was a 38% relative reduction in heart failure events in the CRT group (hazard ratio [HR], 0.62; 95% confidence interval [CI], 0.45 to 0.85; p=0.003). On subgroup analysis, the benefit was evident in patients with left bundle branch block (LBBB; HR=0.50; 95% CI, 0.33 to 0.76; p=0.001) but not in patients without LBBB (HR=0.99; 95% CI, 0.58 to 1.69; p=0.96).

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. (50) 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 post-trial registries. Seventy-three percent and 75% of the ICD-only and CRT-D groups, respectively, had LBBB; 69% of each group had QRS duration 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=0.002; adjusted HR in the CD-CRT group, 0.59; 95% CI, 0.43 to 0.80; p<0.001). The benefit associated with ICRT-D was consistent in subgroup analysis among patients with prolonged QRS (≥150 ms) and a shorter QRS interval (<150 ms). In multivariable analysis, there was no significant interaction between QRS interval and overall survival. 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 (CRT) 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. (51) 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=0.01) for CRT-D and from 5.46% to 7.11% (p=0.01) 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. (52) 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. (53) 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 (120-150 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 left bundle branch block (LBBB).

The Evaluation of Resynchronization Therapy for Heart Failure 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. (54) 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. CRT-D significantly reduced mortality compared with ICD alone for women younger than 60 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 | 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 |
| 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. (55-61) In one of these studies, the benefit of CRT was confined to patients with LBBB. (58) 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. (62) 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 a LBBB. (63) 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<0.001). 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=0.078). In long-term follow-up of MADIT-CRT, the reduction in mortality for CRT-D vs 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 vs ICD in normal PR was larger than in the short-term results (HR=2.27; 95% CI, 1.16 to 4.44). (64)

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 vs ICD-only, and outcomes. (65) 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<0.001) 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=0.17). 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<0.001) but not with PR interval of 230 or more (HR=1.01; 95% CI, 0.87 to 1.17; p=0.90). 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 LV end-systolic volume (LVESV), ejection fraction, or clinical criteria. (66) This finding prompted investigation of whether ventricular dyssynchrony could discriminate between responders and non-responders 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-III) of ischemic origin, ejection fraction of 35% or less, QRS interval less than 120 ms, and marked mechanical dyssynchrony on echocardiogram. (67) 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 were more likely to have improved clinical composite scores at 1-year post implantation (41% vs 16%, p=0.004). Patients in the CRT group had higher rates of avoiding the combined end point of heart failure hospitalization, heart failure death, and spontaneous ventricular fibrillation (p=0.028).

The 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). (68) 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, compared with 102 (25.2%) of 405 in the control group (HR with CRT=1.20; 95% CI, 0.92 to 1.57; p= 0.15). 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=0.02).

The Resynchronization Therapy in Normal QRS Trial (RethinQ study) 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 end point of improvement in exercise capacity [$VO_2$peak]). A subset of patients with QRS intervals 120 to 130 ms or more showed improvement (p=0.02), whereas those with a QRS interval less than 120 ms did not (p=0.45).

Section Summary: CRT for Heart Failure

*NYHA 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 QOL for patients with NYHA class III or IV heart failure.

*NYHA 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 QOL 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 non-responders. A QRS interval of more than 150 ms or the presence of LBBB appears to discriminate well between responders and non-responders 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 non-responders. A subgroup analyses 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 individuals 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 policy.

*Populations*

The relevant population of interest is individuals 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.

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 RCT's 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. (69) 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. (70) 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 14% and 41% at 4 years. 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 Ablate and Pace Therapy for Permanent Atrial Fibrillation (APAF) (2011) RCT compared CRT with right ventricular (RV) pacing alone in patients with AF. (71) A total of 186 patients had AV nodal ablation and 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 end point 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=0.005). For the individual outcome measures, there was no significant reduction in mortality (HR=1.57; 95% CI, 0.58 to 4.27; p=0.37), but there were significant reductions in hospitalizations (HR=0.20; 95% CI, 0.06 to 0.72; p=0.013) and worsening heart failure (HR=0.27; 95% CI, 0.12 to 0.58; p=0.37). There were no differences in outcomes on subgroup analysis, including analysis by ejection fraction, NYHA class, and/or QRS interval.

In the MUltisite STimulation In Cardiomyopathies and Atrial Fibrillation (MUSTIC-AF) trial (2002), 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 vs biventricular pacing with 3 months for each period. (22) Race or ethnicity of the participants were not described. The primary outcome was the 6-MWT; secondary outcomes were $VO_2$max, QOL, 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) (70) | 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) (69) | 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) (71) | 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 | May 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) (70)** | 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) (69)** | N=102 | N=102 | N=102 | N=102 | NR |
| 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) (71)** | 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) (70) | 2. Correlation to NYHA classification is unclear | | 3. Drug classes used for background heart failure therapy differed between groups at baseline<br><br>3. Pharmacologic therapy at clinician discretion vs guideline directed medical therapy (U.S.) | | |
| APAF-CRT Morbidity Trial (2018) (69) | 2. Correlation to NYHA classification is unclear | | 3. Drug classes used for background heart failure therapy differed between groups at baseline | | |

| | | | | | |
|---|---|---|---|---|---|
| APAF (2011) (71) | 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) |

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

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.

[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 | Alloca-tion[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| APAF-CRT Mortality Trial (2021) (70) | | | | | | |
| APAF-CRT Morbidity Trial (2018) (69) | | 1. Open label | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| APAF (2011) (71) | | 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 |

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

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.

[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. (72) 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 ($p<0.05$). 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=0.002) and in the composite of death or heart failure hospitalization (HR=0.53; 95% CI, 0.41 to 0.68; $p<0.001$). In contrast, in the intermittent AF and atrial flutter group (n=293), CRT-P did not result in improved outcomes vs medical therapy (death or any hospitalization HR=1.16; 95% CI, 0.83 to 1.63; p=0.38; death or heart failure hospitalization HR=0.97; 95% CI, 0.64 to 1.46; p=0.88).

Daalgard et al. (2023) compared outcomes in patients with and without AF in an analysis of 4 trials of CRT-D or pacemakers (COMPANION, MADIT-CRT, REVERSE, and MIRACLE). (73) A total of 586 patients (14.8%) in the 4 trials had AF. The primary composite endpoint was time to heart failure hospitalization or all-cause mortality. The outcome occurred at a similar rate in patients with AF (HR, 0.78; 95% Cl, 0.55 to 1.10) and without AF (HR, 0.67; 95% Cl, 0.55 to 0.80). The authors identified a lack of power as a possible limitation to their analysis.

A post hoc analysis of patients with AF enrolled in RAFT was published by Healey et al. (2012). (74) 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 in the defibrillator group alone. 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=0.82). 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 with 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. (75) The dataset included 8951 patients with heart failure and AF with a QRS interval of 120 ms or more and a LEVF 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: CRT 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.

**CRT for Heart Failure and AV Nodal Block**

Clinical Context and Therapy Purpose

The purpose of CRT in individuals 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 policy.

*Populations*
The relevant population of interest is individuals 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.

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. (76) 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 3rd-degree AV block or a 2nd-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 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 of 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 death or 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 was not significantly different 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). (77) 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 [PACE] 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). (78, 79) In the trial's main results, at 12 months post enrollment, subjects who underwent standard pacing had lower mean LVEF than those randomized to biventricular pacing (54.8% vs 62.2%; p<0.001) and higher mean LVESV (35.7 mL vs 27.6 mL; p<0.001). No significant differences were reported in QOL or functional measures or rates of heart failure hospitalizations. 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. (80) Also, during long-term follow-up, heart failure hospitalization occurred more frequently in the RV pacing group (23.9% vs 14.6%; p<0.001).

Several other RCTs have also corroborated the results of the BLOCK HF and the PACE trials. (32, 42, 81) These trials reported improvements in physiologic parameters of LV function and improvements in functional status measured by the 6-MWT. Some, but not all, of these trials also reported improvements in QOL for patients treated with CRT.

Section Summary: CRT for Heart Failure and AV Nodal 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 individuals 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 policy.

*Populations*

The relevant population of interest is individuals 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.

To demonstrate improved outcomes, RCTs are needed that compare outcomes of triple-site CRT with conventional CRT. Six RCTs were identified for this policy (82-87) 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. (84) 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 five trials were smaller, enrolling between 43 and 95 patients. Follow-up in these studies was generally short, with the longest being one year. Outcomes reported varied across studies and were a mix of physiologic measures, functional status, and QOL. No outcome measures reported were common across all studies. Three of the five studies reported significant improvements on at least one outcome measure, and the fourth and fifth studies reported no significant differences for the outcomes measured. Adverse events were not well-reported.

**Table 9. RCTs 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) (86) | 43[a] | • Triple-site CRT<br>• Standard CRT | +91m<br><br>+65m<br><br>p=0.008 | -24pts<br><br>-18pts<br><br>p=<0.001 | NR | NR | NR | NR |
| Lenarczyk et al. (2012) (84) | 100 | • Triple-site CRT<br>• Standard CRT | NR | NR | 12.5%[b]<br><br>30%<br><br>p<0.05 | NR | NR | NR |
| Bencardino et al. (2016) (83) | 43 | • Triple-site CRT<br>• Standard CRT | NR | NR | 96%[c]<br><br>60%<br><br>p<0.05 | NR | +10%<br><br>+4%<br><br>p<0.001 | NR |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Anselme et al. (2016) (82) | 76 | • Triple-site CRT<br>• Standard CRT | +50m<br>+73m<br>p=0.40 | NR | NR | 78.8%<br><br>81.6%<br><br>p=0.90 | NR | -8.4 points<br>-15.0 points<br>p=0.20 |
| Pappone et al. (2015) (85) | 44 | • Triple-site CRT<br>• Standard CRT | NR | NR | NR | 76%<br><br>57%<br><br>p=0.33 | +15%<br>+5%<br>p<0.001 | NR |
| Gould et al. (2021) (87) | 95 | • Triple-site CRT<br>• Standard CRT | +31.2<br>-29.9<br>p=.051 | NR | NR | NR | +6.4%<br>+7.3%<br>p=.676 | NR |

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. (88) The meta-analysis included 1 RCT (Anselme et al. [2016] [82]; 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 individuals 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 policy.

*Populations*
The relevant population of interest is individuals 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.

Randomized Controlled Trials
Three RCTs were identified that compared management of patients with heart failure using remote fluid monitoring to usual monitoring. (89-91) Luthje et al. (2015) was an unblinded, single-site RCT sponsored by the manufacturer of the OptiVol device. (90) 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 UK National Health Service. (89) 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. The median follow-up was 375 days (range 350-430 days). One patient was lost to follow-up, and 71/80 (89%) 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. (91) 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 three 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, functional status, or QOL. (89) Luthje et al. (2015) reported no differences in mortality or hospitalizations. (90) Also, Luthje et al. (2015) reported an HR for time to first hospitalization that was not significant at 1.23 (95% CI, 0.62-2.44, p=0.55). Mean number of emergency department visits did not differ between the remote monitoring group (0.10) and the usual care group (0.10; p=0.73), but the mean number of urgent care visits was higher for remote monitoring (0.30) than for usual care (0.10; p=0.03). 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). (91)

Section Summary: CRT Combined With Remote Fluid Monitoring for Heart Failure
Three RCTs have reported no improvements in outcomes associated with remote fluid monitoring for patients with heart failure.

**Summary of Evidence**
For individuals who have New York Heart Association (NYHA) class III/IV heart failure with a left ventricular ejection fraction 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 milliseconds (ms) or more who receive cardiac resynchronization therapy (CRT) with or without defibrillator, the evidence includes randomized controlled trials (RCTs) and systematic reviews of RCTs. Relevant outcomes are overall survival (OS), symptoms, functional outcomes, quality of life (QOL), hospitalizations, and treatment-related morbidity. There is a large body of clinical trial evidence supporting the use of CRT in patients with NYHA class III or IV heart failure. The RCTs have consistently reported that CRT reduces mortality, improves functional status, and improves quality of life for patients with NYHA class III or IV heart failure. Multiple subgroup analyses of RCTs have demonstrated that the benefit of CRT is mainly restricted to patients with LBBB or QRS duration greater than 150 ms. The evidence is sufficient to determine qualitatively that the technology results in an improvement in the net health outcome.

For individuals who have 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 who receive CRT with or without defibrillator, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are OS, symptoms, functional outcomes, QOL, hospitalizations, and treatment-related morbidity. For patients with NYHA class II heart failure, at least 4 RCTs assessing CRT have been published. A mortality benefit was reported in 1 of the 4 trials, the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). None of the other 3 RCTs reported a mortality difference, but a subgroup analysis of the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial reported a mortality benefit for patients with LBBB. Among other outcome measures, hospitalizations for heart failure showed consistent reductions, but quality of life and functional status did not improve. Multiple subgroup analyses of RCTs have demonstrated that the benefit of CRT is mainly restricted to patients with LBBB or a QRS interval greater than 150 ms. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have NYHA class I heart failure who receive CRT with or without defibrillator, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are OS, symptoms, functional outcomes, QOL, hospitalizations, and treatment-related morbidity. Few patients with NYHA class I heart failure have been included in RCTs. The MADIT-CRT trial included 265 patients with class I. While the treatment effect on death and hospitalization favored combined implantable cardiac defibrillator plus CRT devices vs implantable cardiac defibrillator alone for class I patients, the confidence interval was large and included a 25% to 30% increase in events. The evidence is insufficient to determine that the technology results in an improvement in the health outcome.

For individuals who have NYHA class I, II, III or IV heart failure with left ventricular ejection fraction (LVEF) of 50% or less and the presence of atrioventricular (AV) nodal block with requirement for a high percentage of ventricular pacing, treated with guideline-directed medical therapy, who receive CRT with or without defibrillator, the evidence includes RCTs. Relevant outcomes are OS, symptoms, functional outcomes, QOL, hospitalizations, and treatment-related morbidity. For patients who have AV nodal block, some degree of left ventricular 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 left ventricular 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. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have heart failure and atrial fibrillation (AF) who receive CRT with or without defibrillator, the evidence includes 6 RCTs and a registry study. Relevant outcomes are OS, symptoms, functional outcomes, QOL, hospitalizations, and treatment-related morbidity. Results from RCTs have been conflicting, with 3 reporting improvements for patients with AF, including an all-cause mortality benefit, and others reporting no significant improvements. A

registry study reported significant improvements in mortality and hospitalizations for patients with heart failure and atrial fibrillation treated with CRT plus defibrillator compared with implantable cardioverter-defibrillator alone. The evidence is insufficient to determine that the technology results in an improvement in the health outcome.

For individuals who have heart failure and AV nodal block who receive CRT, the evidence includes RCTs. Relevant outcomes are OS, symptoms, functional outcomes, QOL, hospitalizations, and treatment-related morbidity. One large RCT demonstrated that CRT led to reductions in heart failure-related hospitalizations and urgent care visits among patients with heart failure and AV block but who would not necessarily meet conventional criteria for CRT. For patients who require ventricular pacing but have no left ventricular 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. The evidence is sufficient to determine that the technology results in an improvement in the health outcome.

For individuals who have heart failure who receive triple-site CRT, the evidence includes small RCTs and a meta-analysis that included nonrandomized studies. Relevant outcomes are OS, symptoms, functional outcomes, QOL, hospitalizations, and treatment-related morbidity. The available RCTs have reported improved outcomes on at least 1 measure of functional status or QOL with triple-site CRT compared to conventional CRT. However, the trials were small and had methodologic limitations. Also, outcomes reported differed across studies. Triple-site CRT was also associated with higher radiation exposure and a greater number of additional procedures post implantation. Larger, high-quality RCTs are needed to better define the benefit-risk ratio for triple-site CRT compared to conventional CRT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have heart failure who receive CRT combined with remote fluid monitoring, the evidence includes 3 RCTs. Relevant outcomes are OS, symptoms, functional outcomes, QOL, hospitalizations, and treatment-related morbidity. Three RCTs have reported no improvement in outcomes associated with remote fluid monitoring for patients with heart failure. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Practice Guidelines and Position Statements**

American College of Cardiology (ACC) et al.

The ACC, American Heart Association (AHA), and Heart Rhythm Society (2019) published joint guidelines on the evaluation and management of patients with bradycardia and cardiac conduction delay. (92) 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% 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)." | IIa | B-R |

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

A focused update to 2008 guidelines (93) for device-based treatment of cardiac rhythm abnormalities was published jointly by ACC Foundation, AHA, and the Heart Rhythm Society in 2012. (94) The ACC and American Heart Association (2013) subsequently published guidelines for the management of heart failure. (95) 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. (96) 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.

[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. (97) The guidelines were updated in conjunction with the ACC and American Heart Association in 2022 (96); updated recommendations can be found above, in Table 11.

Heart Rhythm Society, et al.

In 2024, the Heart Rhythm Society, European Heart Rhythm Association, Asia Pacific Heart Rhythm Society, and the Latin American Heart Rhythm Society published a guideline on cardiac physiologic pacing, which includes both CRT with biventricular pacing and conduction system pacing (i.e., His bundle pacing or left bundle branch area pacing). (98) In patients with heart failure, the authors stated that there is more evidence supporting the use of CRT than conduction system pacing, and that ongoing studies will address this question. The following patients should receive CRT: left ventricular ejection fraction (LVEF) ≤35%, left bundle branch block, QRS duration ≥150 ms, and New York Heart Association class II to IV symptoms despite guideline-directed therapy. Patients who meet all of the above criteria but have an LVEF ≤30%, or patients who meet all of the above criteria but have a QRS duration of 120 to 149 ms, can also be considered for CRT. Symptom control/functional class and LVEF may improve with CRT in patients with LVEF ≤35%, sinus rhythm, QRS duration ≥150 ms, and New York Heart Association class Ill or ambulatory class IV symptoms despite guideline-directed therapy.

The following patients with cardiovascular implanted electrical devices are appropriate candidates for CRT: decline in left ventricular function or worsening symptoms due to substantial ventricular pacing. Another option for the same patients is switching to a conduction system pacing device.

In the setting of atrial fibrillation, CRT is recommended in patients undergoing ablation who have LVEF ≤50% or who are otherwise eligible for CRT implantation.

National Institute for Health and Care Excellence (NICE)

The NICE (2014) guidance provided recommendations on CRT for heart failure. (99) 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-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-III with QRS interval 120 to 149 ms and with LBBB | CRT-D recommended |
| NYHA class III-IV with QRS interval 120 to 149 ms and with LBBB | CRT-P recommended |
| NYHA class I-III with QRS interval ≥150 ms (with or without LBBB) | CRT-D recommended |
| NYHA class III-IV with QRS interval ≥150 ms (with or without LBBB) | CRT-P recommended |

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

**Ongoing and Unpublished Clinical Trials**

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

**Table 13. Summary of Key Active Trials**

| NCT Number | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| ***Ongoing*** | | | |
| NCT06105580 | Conduction System Pacing vs Biventricular Resynchronization Therapy in Systolic Dysfunction and Wide QRS: Mortality, Heart Failure Hospitalization or Cardiac Transplant | 320 | Nov 2027 |
| NCT05467163 | CONDUCTion System Pacing Versus Biventricular Pacing After Atrioventricular Node Ablation in Heart Failure Patients With Symptomatic Atrial Fibrillation and Narrow QRS (CONDUCT-AF Trial) | 82 | Dec 2026 |

| | | | |
|---|---|---|---|
| NCT05187611 | Conduction System Pacing vs Biventricular Resynchronization Therapy in Systolic Dysfunction and Wide QRS: CONSYST-CRT Randomized Clinical Trial. | 130 | Oct 2024 |
| NCT05572736 | Conduction System Pacing Versus Biventricular Resynchronization in Patients With Chronic Heart Failure (PhysioSync-HF) | 179 | Dec 2024 |
| NCT01994252 | Resynchronization/Defibrillation for Ambulatory Heart Failure Trial in Patients With Permanent Atrial Fibrillation (RAFT-PermAF) | 200 | Feb 2024 |
| NCT04225520 | Assessment of Mechanical Desynchrony as Selection Criterion for Cardiac Resynchronization Therapy | 700 | Dec 2023 |
| 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 |
| NCT02922036[a] | Stimulation Of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in Non-Responders, Previously Untreatable and High Risk Upgrade Patients (SOLVE CRT) | 300 | Apr 2024 |
| NCT05451797 | A Feasibility Study Into the Implant of the WiSE CRT System With an Intracardiac Pacemaker to Achieve Totally Leadless CRT | 40 | Jan 2025 |

NCT: national clinical trial.

[a] Denotes industry sponsored or co-sponsored trials.

## Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

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| **CPT Codes** | 33211, 33213, 33225, 93640, 93641, 93642, 0515T, 0516T, 0517T, 0518T, 0519T, 0520T, 0521T, 0522T, 0861T, 0862T, 0863T |
| **HCPCS Codes** | None |

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## Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

## Policy History/Revision

| Date | Description of Change |
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| 11/15/2024 | Document updated with literature review. Coverage unchanged. References 1, 48, 61, 73, 98 added; some updated; others removed. |
| 09/15/2023 | Reviewed. No changes. |
| 02/01/2023 | Document updated with literature review. The following change was made to Coverage: 1] For NYHA class II, III, and IV medical regimens for biventricular pacemakers updated to state: Individuals treated with guideline-directed medical therapy for heart failure with reduced ejection fraction including 4 medication classes: 1) renin angiotensin system inhibition with angiotensin receptor-neprilysin inhibitors (ARNi), angiotensin-converting enzyme inhibitors (ACRi), or angiotensin (II) receptor blockers |

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| | (ARB) alone; 2) beta blockers; 3) mineralocorticoid receptor antagonists (MRAs); and 4) sodium-glucose cotransporter 2 inhibitor (SGLT2i). 2] Right ventricular pacemaker criteria updated to state: Individuals treated with guideline-directed medical therapy for heart failure with mildly reduced ejection fraction therapy (if indicated). References 1-3, 47, 67, 68, 84, 92 and 93 added. |
| 07/15/2021 | Reviewed. No changes. |
| 09/15/2020 | Document updated with literature review. Coverage unchanged. Reference 83 added; others removed. |
| 09/15/2019 | Reviewed. No changes. |
| 03/01/2019 | Document updated with literature review. The following changes were made to Coverage: 1) Added New York Heart Association (NYHA) class IV to criteria for CRT in patients with heart failure and atrioventricular block; 2) Added experimental, investigational and/or unproven (EIU) statement for NYHA class I heart failure when not meeting stated criteria; 3) Removed EIU statement on galectin-3 and soluble ST2 testing, as it will now be addressed on medical policy MED207.158. Title changed from: Biventricular Pacing. Added references 5, 11, 14-25, 28-31, 33-35, 37, 45-47, 52, 65-67, 72, 78, 80, 90, 93, 99. |
| 01/01/2019 | Document updated with literature review. The following change was made to Coverage: Added "Cardiac resynchronization therapy with wireless left ventricular endocardial pacing is considered experimental, investigational and/or unproven." |
| 08/15/2017 | Reviewed. No changes. |
| 11/01/2016 | Document updated with literature review. 1) The following criteria was added as to the medically necessary coverage statement on biventricular pacemakers, (with or without an accompanying implantable cardiac defibrillator, i.e., a combined biventricular pacemaker/ICD) as a treatment of heart failure (HF) for patients who are New York Heart Association (NYHA) functional class II, III or IV: "Either left bundle branch block OR QRS duration ≥150 ms". This replaced the previous criteria that noted "QRS duration of ≥120–130 msec*", 2) The following was added as a medically necessary coverage statement: "For patients who do not meet the criteria outlined above but have an indication for a ventricular pacemaker, biventricular pacemakers with or without an accompanying implantable cardiac defibrillator (i.e., a combined biventricular pacemaker/implantable cardiac defibrillator) may be considered medically necessary as an alternative to a right ventricular pacemaker in patients who meet all of the following criteria: NYHA functional class I, II, or III, left ventricular ejection fraction (LVEF) of ≤50%; patient on stable optimal HF medical therapy, if indicated; and have atrioventricular (AV) block that is expected to require a high percentage of ventricular pacing that cannot be managed with algorithms to minimize right ventricular pacing. 3) In addition, the following note was added defining |

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| | atrioventricular block. “NOTE: Atrioventricular (AV) block with a requirement for a high percentage of ventricular pacing is considered to be present when there is: third-degree AV block; second-degree AV block or a PR interval of 300 ms or more when paced at 100 beats per minute”, 4) The experimental, investigational and/or unproven coverage statement for biventricular pacemakers, with or without an accompanying implantable cardiac defibrillator (i.e., a combined biventricular pacemaker/ICD) was changed to note experimental, investigational and/or unproven for all other indications not addressed in the coverage section, and 5) The following experimental, investigational and unproven statement added to the coverage section: “Triple-site (triventricular) cardiac resynchronization therapy, using an additional pacing lead, is considered experimental, investigational and/or unproven.” |
| 01/01/2015 | Document updated with literature review. Soluble ST2 testing (growth stimulation expressed gene 2 [Interleukin 1receptor like-1] was added as experimental, investigational and/or unproven for all indications including but not limited to, selection of individuals for biventricular testing and to determine prognosis of heart failure. CPT/HCPCS code(s) updated. |
| 01/01/2013 | Document updated with literature review. The following was added: Galectin-3 testing is considered experimental, investigational and unproven for all indications including but not limited to, selection of individuals for biventricular testing and to determine prognosis of heart failure. CPT/HCPCS code(s) updated |
| 04/15/2012 | Document updated with literature review. The following was added: 1) Biventricular pacemakers (with or without an accompanying implantable cardiac defibrillator, i.e., a combined biventricular pacemaker/ICD) may be considered medically necessary as a treatment of heart failure in patients with New York Heart Association classification II, when meeting the criteria as listed in the coverage including a new criteria listing of sinus rhythm. 2) Biventricular pacemakers, with or without an accompanying implantable cardiac defibrillator (i.e., a combined biventricular pacemaker/ICD) are considered experimental, investigational and unproven as a treatment for patients with New York Heart Association classification I. |
| 05/01/2009 | CPT/HCPCS code(s) updated |
| 02/01/2009 | Revised/updated entire document |
| 04/15/2006 | Revised/updated entire document |
| 09/01/2005 | CPT/HCPCS code(s) updated |
| 03/01/2003 | New medical document originating from position statement |
| 11/13/2002 | Coverage revised |
| 03/01/2000 | New medical document |