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

Policy # 00009
Original Effective Date: 06/05/2002
Current Effective Date: 07/11/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Cardiac Hemodynamic Monitoring for the Management of Heart Failure in the Outpatient Setting is addressed separately in medical policy 00287.

When Services May Be Eligible for Coverage
Based on review of available data, the Company may consider biventricular pacemakers with or without an accompanying implantable cardiac defibrillator (ICD) (i.e., a combined biventricular pacemaker plus cardiac defibrillator) as a treatment of heart failure to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for biventricular pacemakers with or without an accompanying ICD as a treatment of heart failure for New York Heart Association (NYHA) class III or IV will be considered in patients who meet all of the following criteria:

- Left ventricular ejection fraction (LVEF) ≤35%, AND
- Sinus rhythm, AND
- Patients treated with guideline-directed medical therapy before implant, such as an angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin receptor blocker) and a beta blocker, digoxin, and/or diuretics, AND
- Either left bundle branch block (LBBB) OR QRS duration ≥150 ms***

Coverage eligibility for biventricular pacemakers with or without an accompanying ICD as a treatment of heart failure for NYHA class II will be considered in patients who meet all of the following criteria:

- LVEF ≤30%, AND
- Sinus rhythm, AND
- Patients treated with guideline-directed medical therapy before implant, such as an ACE inhibitor (or an angiotensin receptor blocker) and a beta blocker, digoxin, and/or diuretics, AND
- Either LBBB OR QRS duration ≥150 ms***

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

Based on review of available data, the Company may consider biventricular pacemakers with or without an accompanying ICD (i.e., a combined biventricular pacemaker plus ICD) for patients who do not meet the criteria outlined above, but who have an indication for a ventricular pacemaker to be **eligible for coverage** as an alternative to a right ventricular pacemaker.

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Patient Selection Criteria
Coverage eligibility for biventricular pacemakers with or without an accompanying ICD (i.e., a combined biventricular pacemaker plus ICD) as an alternative to a right ventricular pacemaker for patients who do not meet the criteria outlined above, but who have an indication for a ventricular pacemaker will be considered when the following criteria are met:

- NYHA class I, II, III or IV heart failure; AND
- LVEF ≤50%; AND
- The presence of atrioventricular (AV) block with requirement for a high percentage of ventricular pacing****; AND
- Patients treated with guideline-directed medical therapy before implant, such as an ACE inhibitor (or an angiotensin receptor blocker) and a beta blocker, digoxin, and/or diuretics.

**** *AV block with a requirement for a high percentage of ventricular pacing is considered to be present when there is either 3rd degree AV block or 2nd degree AV block or a PR interval of 300ms or more when paced at 100 beats per minute.*

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of biventricular pacemakers, with or without an accompanying ICD (i.e., a combined biventricular pacemaker plus ICD) as a treatment for patients with NYHA class II, III or IV heart failure when patient selection criteria are not met to be **investigational**.*

Based on review of available data, the Company considers the use of biventricular pacemakers, with or without an accompanying ICD (i.e., a combined biventricular pacemaker plus ICD) as a treatment for patients with NYHA class I heart failure who do not meet the above criteria to be **investigational.***

Based on review of available data, the company considers biventricular pacemakers, with or without an accompanying ICD (i.e., a combined biventricular pacemaker plus ICD), as a treatment for heart failure in patients with atrial fibrillation (AF) who do not meet the above criteria to be **investigational.***

Based on review of available data, the Company considers triple-site (triventricular) cardiac resynchronization therapy (CRT), using an additional pacing lead, to be **investigational.***

Based on review of available data, the Company considers an intrathoracic fluid monitoring sensor is considered to be **investigational*** as a component of a biventricular pacemaker.

Based on review of available data, the Company considers CRT with wireless left ventricular (LV) endocardial pacing is considered to be **investigational***.

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Background/Overview

HEART FAILURE

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 CRT, have been investigated as a technique to coordinate the contraction of the ventricles, thus improving patients' hemodynamic status. 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.

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 LV pacing leads, which can deliver pacing stimuli at multiple sites. Wireless LV endocardial pacing is also being evaluated for patients who are not candidates for or do not respond to standard epicardial pacing leads.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

There are numerous CRT devices, combined ICD plus CRT devices (CRT-D), and combined CRT plus fluid monitoring devices. Some devices are discussed here. For example, in 2001, the InSync®‡ Biventricular Pacing System (Medtronic), a stand-alone biventricular pacemaker, was approved by the U.S. FDA through the premarket approval process for the treatment of patients with NYHA class III or IV heart failure, on a stable pharmacologic regimen, who also have a QRS duration of 130 ms or longer and a LVEF of 35% or less. Devices by Guidant (CONTAK-CD®‡ CRT-D System) and Medtronic (InSync®‡ ICD Model 7272) have been approved by FDA through the premarket approval process for combined CRT defibrillators for patients at high risk of sudden cardiac death due to ventricular arrhythmias and who have NYHA class III or IV heart failure with a LVEF of 35% or less, QRS interval 130 ms or longer (≥120 ms for the Guidant device), and remain symptomatic despite a stable, optimal heart failure drug therapy. In 2006, Biotronik Inc. received premarket approval from FDA for its combined ICD-D device with ventricular pacing leads (Tupos LV/ATx CRT-D/Kronos LV-T CRT-D systems); in 2013, the company received FDA approval for updated ICD-D devices (Ilesto/Iforia series).

In September 2010, FDA expanded indications for some CRT devices to include patients with class I and II heart failure. Based on data from the 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:

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- Moderate-to-severe heart failure (NYHA class III-IV) with an ejection fraction less than 35% and QRS interval greater than 120 ms.
- LBBB 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, FDA further expanded indications for multiple Medtronic CRT devices to include patients with NYHA class I, II, or III heart failure, who have a LVEF of 50% or less on stable, optimal heart failure medical therapy, if indicated, and have 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 BLOCK HF study, a Medtronic-sponsored randomized controlled trial (RCT) 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 LV lead, which received clearance for marketing from 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 United States (e.g., St. Jude Quartet™‡ LV 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 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. Medical policy 00287 addresses the use of external bioimpedance devices as stand-alone devices to assess cardiac output noninvasively.

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

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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Rationale/Source

Evidence reviews 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 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

Systematic Reviews

Use of biventricular pacemakers with or without an accompanying 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. The 5 systematic reviews published after 2010 that include meta-analyses with comparisons of 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.

Trial characteristics can be found in the following section in Table 3. The majority of patients included in RCTs had NYHA functional class II or III with a LVEF of less than 35%, prolonged QRS interval (≥120 ms), and 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. 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.

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Randomized Controlled Trials

At least 30 RCTs have evaluated CRT have been published and are included in at least one of the meta-analyses listed above. Table 3 shows the baseline characteristics of the RCTs. The 2 largest RCTs (MADIT-CRT, RAFT) are described below.

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)	Through 2015	NYHA class I/II	• CRT-D • ICD alone	3 RCTs (N=3858) with ≥12-mo follow-up	REVERSE, MADIT-CRT, RAFT	**CRT-D vs ICD** Heart failure hospitalizations • OR=0.67 (95% CI, 0.50 to 0.89) Mortality • OR=0.78 (95% CI, 0.63 to 0.96)
Woods et al (2015)	1990-2015	LVEF ≤40%	• CRT or CRT-D • Drug therapy alone or ICD alone	13 RCTs (N=12,638)	CARE-HF, MIRACLE, REVERSE, MUSTIC-SR, RESPONSE, VECTOR, COMPANION, CONTAK-CD, MADIT-CRT, RAFT, REThinQ, REVERSE CRT, Piccirillo (2006), Pinter (2009), RHYTHM-ICD, DEFINITE[a], MADIT[a], MADIT II[a], SCD HeFT[a], AMIOVIRT[a], CAT[a]	**CRT-D vs drug therapy** Mortality • HR=0.58 (95% CrI, 0.50 to 0.68) **CRT-D vs ICD** • Mortality HR=0.82 (95% CrI, 0.72 to 0.93)
Chen et al (2013)	Through 2012	LVEF ≤35%; QRS interval ≥120 ms	• CRT-D • ICD alone	8 RCTs (N=5674)	Lozano (2000), CONTAK-CD, MIRACLE-ICD, MIRACLE-ICD II, RHYTHM-ICD, REVERSE, MADIT-CRT, RAFT	**CRT-D vs ICD** Hospitalization • OR=0.70 (95% CI, 0.60 to 0.81) Mortality • OR=0.80 (95% CI, 0.67 to 0.95)
Wells et al (2011)	1980-2010	QRS interval ≥120 ms	• CRT or CRT- D • ICD alone or drug therapy alone	12 RCTs (N=7538)	Lozano (2000), MUSTIC, MIRACLE, MIRACLE-ICD, MIRACLE-ICD II, COMPANION, RHYTHM-ICD, CARE-HF, VECTOR, REVERSE, MADIT-CRT, RAFT	**CRT vs no CRT** Mortality • RR=0.78 (95% CI, 0.70 to 0.87) **CRT vs drug therapy** Mortality • RR=0.73 (95% CI 0.62 to 0.85) **CRT-D vs ICD** Mortality • RR=0.83 (95% CI, 0.72 to 0.96)
Bertoldi et al (2011)[8]		LV systolic dysfunction	• CRT or CRT-D • ICD alone	12 RCTs (N=8284)	MUSTIC-SR, MUSTIC-AF, MIRACLE, CONTAK-CD, MIRACLE-ICD, MIRACLE-ICD II, COMPANION, CARE-HF, HOBIPACE, REVERSE, MADIT-CRT, RAFT	**CRT vs drug therapy** Mortality • RR=0.76 (95% CI, 0.64 to 0.90) **CRT-D vs ICD alone** Mortality • RR=0.83 (95% CI, 0.72 to 0.96)

CI: confidence interval; CrI: credible interval; CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy with implantable cardioverter defibrillator; HR: hazard ratio; ICD: implantable cardioverter defibrillator; LV: left ventricular; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk.
[a] Trials of ICD vs medical therapy; used in the indirect comparisons in the network meta-analysis.

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

Study	A Priori Design	Duplicate Selection/ Extraction	Comp Literature Search	Search for Gray Literature	Included/ Excluded Studies Provided	Study Characteristics Provided	Study Scientific Quality Assessed and Documented	Scientific Quality Used in Formulated Conclusions	Appropriate Methods for Synthesis	Publication Bias Assessed	COI Included
Sun (2016)	Can't answer	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
Woods (2015)	Can't answer	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Chen (2013)	Can't answer	Can't answer	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
Wells (2011)	Can't answer	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Bertoldi (2011)	Can't answer	Yes	Yes	No	No	Yes	No	No	Yes	Yes	No

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

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

Study	Dur	Funding Source	Treatment Groups	N	Percent NYHA Class				Mean LVEF (SD), %	Mean QRS (SD), ms	Percent ECG Pattern		% AF
					I	II	III	IV			LBBB	RBBB	
Lozano (2000)	3 mo	Unclear	• CRT-D • ICD	• 109 • 113	NA	• 35	• 57	• 8	• 22 (7)	• NR	NR	NR	NR
Lozano (2000)	3 mo	Unclear	• CRT-D • ICD	• 109 • 113	NA	• 35	• 57	• 8	• 22 (7)	• NR	NR	NR	NR
MUSTIC-SR (2001)	3 mo	Industry	• CRT first • Inactive first	• 29 • 29	NA	NA	• 100 • 100	NA	• 23 (7)	• 172 (22) • 175 (19)	• 87	NR	Ex
Garrigue (2002)	2 mo	Unclear	• CRT first • LV first	• 6 • 7	NA	NA	• 77	• 23	• 25 (8)	• 208 (15)	NR	NR	• 100
MUSTIC-AF (2002)	3 mo	Industry	• CRT first • RV first	• 25 • 18	NA	NA	• 100 • 100	NA	• 23 (7) • 30 (12)	• 209 (21) • 208 (12)	NR	NR	• 100 • 100
MIRACLE (2002)	6 mo	Industry	• CRT • Inactive	• 228 • 225	NA	NA	• 90 • 91	• 10 • 9	• 22 (6) • 22 (6)	• 167 (21) • 165 (20)	NR	NR	Ex
PATH-CHF (2002)	1 mo	Industry	• CRT first • Uni-V first	• 24 • 17	NA	NA	• 88 • 82	• 12 • 18	• 21 (6) • 20 (7)	• 174 (30) • 178 (34)	• 87 • 100	• 13 • 0	Ex
PATH-CHF II (2003)	3 mo	Industry	• CRT first • Inactive first	• 43 • 43	NA	• 37 • 28	NA	• 63 • 72	• 23 (7) • 23 (8)	• 154 (18) • 157 (23)	• 91 • 86	NR	Ex
CONTAK-CD (2003)	3 mo	Industry	• CRT-D • ICD	• 245 • 245	NA	• 32 • 33	• 60 • 57	• 8 • 10	• 21 (7) • 22 (7)	• 160 (27) • 156 (26)	• 54 • 55	• 14 • 12	Ex
MIRACLE-ICD (2003)	6 mo	Industry	• CRT-D • ICD	• 187 • 182	NA	NA	• 88 • 89	• 12 • 11	• 24 (7) • 24 (6)	• 165 (22)	• NR	• 13 • 13	Ex
COMPANION (2004)	15 mo	Industry	• CRT • Usual care	• 617 • 308	NA	NA	• 87 • 82	• 13 • 18	• 20[a] • 22[a]	• 160[a] • 158[a]	• 69 • 70	NR	Ex

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MIRACLE-ICD II (2004)	**6 mo**	**Industry**	**• CRT-D • ICD**	**• 85 • 101**	**NA**	**• 100 • 100**		**NA**	**• 24 (7) • 25 (7)**	**• 166 (25) • 165 (23)**	**NR**	**• 12 • 21**	**Ex**
CARE-HF (2005)	29 mo	Industry	• CRT • Usual care	• 409 • 404	NA		• 94 • 93	• 6 • 7	• 25[a] • 25[a]	• 160[a] • 160[a]	NR	NR	Ex
RHYTHM-ICD (2004)	12 mo	Industry	• CRT-D • ICD	• 119 • 59	• 1 • 2	• 5 • 6	• 87 • 87	• 7 • 6	• 26 (8) • 23 (6)	• 169 (16) • 167 (15)	NR	NR	Ex
VecTOR (2005)	6 mo	Industry	• CRT • Inactive	• 59 • 47		• 29	• 65	• 6	• <35	• >140	NR	NR	Ex
BELIEVE (2006)	12 mo	Unclear	• CRT-D • LV-ICD	• 33 • 36	NA	• 42 • 33	• 58 • 67	NA	• 26 (6) • 25 (6)	• 176 (25) • 169 (31)	NR	NR	Ex
HOBIPACE (2006)	3 mo	Govt	• CRT • RV	• 15 • 15	Mean (SD), 3.0 (0.6)				• 26 (08)	• 174 (42)	• 63	NR	• 37
Piccirillo (2006)	1 y	Unclear	• CRT-D • ICD	• 16 • 15	NA	NA	• 33 • 31	• 67 • 69	• 22 (8) • 23 (4)	• 159 (8) • 160 (4)	NR	NR	NR
DECREASE-HF (2007)	6 mo	Industry	• BiV-ICD[b] • LV-ICD	• 205 • 101	NA	NA	• 98 • 97	• 2 • 3	• 23 (7) • 23 (7)	• 167 (16) • 165 (15)	• 94 • 93	• 0 • 1	Ex
RD-CHF (2007)	3 mo	Unclear	• CRT first • RV first	• 25 • 19	Mean (SD), 3.2 (0.4)				• 24 (10) • 27 (9)	• 212 (28) • 199 (21)	NR	NR	• 56 • 63
RethinQ (2007)	6 mo	Industry	• CRT-D • ICD	• 87 • 85	NA	NA	• 100 • 99	NA	• 25 (5) • 26 (6)	• 107 (12) • 106 (13)	Ex	Ex	Ex
Piepoli (2008)	12 mo	Unclear	• CRT • Usual care	• 44 • 45	NA	NA	• 90 • 89	• 10 • 11	• 24 (1) • 23 (7)	• 164 (18) • 160 (20)	NR	NR	Ex
REVERSE (2008)	12 mo	Industry	• CRT on • CRT off	• 419 • 191	• 18 • 17	• 82 • 83	NA	NA	• 27 (7) • 26 (7)	• 153 (21) • 154 (24)	NR	NR	Ex
MADIT-CRT (2009)	2.4 y	Industry	• CRT-D • ICD	• 1089 • 731	• 14 • 16	• 86 • 85	NA	NA	• 24 (5) • 24 (5)	• >150, 64% • >150, 65%	• 70 • 71	• 13 • 13	Ex
Pinter (2009)	6 mo	Unclear	• CRT-D • ICD	• 36 • 36	NR	NR	NR	NR	• 21 (8) • 24 (8)	• NR	NR	NR	NR
B-LEFT HF (2010)	6 mo	Industry	• CRT-D • LV-ICD	• 90 • 86	NA	NA	• 93 • 94	• 7 • 6	• 26 (6) • 25 (6)	• 160 (19) • 162 (20)	• 90 • 87	NR	Ex
COMBAT (2010)	3 mo	Industry	• RV-BiV-RV • BiV-RV-BiV	• 27 • 27	NA	• 16 • 17	• 52 • 52	• 32 • 31	• 29 (7) • 30 (9)	• 154 (13) • 148 (16)	NR	NR	Ex
RAFT (2010)	40 mo	Govt, industry	• CRT-D • ICD	• 894 • 904	NA	• 79 • 81	• 21 • 19	NA	• 22 (5) • 22 (5)	• 157 (24) • 158 (24)	• 73 • 71	• 8 • 10	• 13 • 13
Greater-EARTH (2011)	6 mo	Govt	• BiV-ICD first • LV-ICD first	• 61 • 60	• 8 • 8	• 59 • 63	• 33 • 28	NA	• 24 (7) • 24 (6)	• 157 (25) • 153 (22)	NR	NR	NR
van Geldorp (2010)	6 mo	Industry	• CRT first • RV first	• 19 • 18	• 26 • 24	• 47 • 59	• 26 • 18	NA	• 36 (9) • 36 (11)	• 196 (29) • 193 (23)	NR	NR	• 63 • 41
RESPOND (2011)	6 mo	Unclear	• CRT • Usual care	• 29 • 31	NA	NA	• 65 • 84	• 35 • 16	• 22 (8) • 22 (10)	• 92 (11) • 98 (13)	NR	NR	NR

Adapted from Al-Majed et al (2011).
AF: atrial fibrillation; BiV: biventricular; CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy with implantable cardioverter defibrillator; Dur: duration; ECG: electrocardiogram; ex: excluded; Govt: government; ICD: implantable cardioverter defibrillator; LBBB: left bundle branch block; LV: left ventricle; LVEF: left ventricular ejection fraction; NA: not applicable; NR: not reported; NYHA: New York Heart Association; RBBB: right bundle branch block; RV: right ventricle; Uni-V: univentricular.

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MADIT-CRT Trial

The largest trial published to date is the single-blind Multicenter Automatic Implantation Trial–Cardiac Resynchronization (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. The MADIT-CRT trial reported a reduction for the CRT-D group on 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 [RR] 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. 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 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. Follow-up was available for a median 5.6 years among all 1691 surviving patients enrolled in the trial, and beyond that for 854 subjects enrolled in posttrial registries. Seventy-three percent and 75% of the ICD-only and CRT-D groups, respectively, had LBBB; 69% of each group had a QRS interval of a least 150 ms. At 7-year follow-up, the cumulative rate of death from any cause among patients with LBBB was 29% in the ICD-only group compared with 18% in the CRT-D group (p=0.002; adjusted HR in the CRT-D group, 0.59; 95% CI, 0.43 to 0.80; p<0.001). The benefit associated with ICD-CRT was consistent in subgroup analysis among patients with a prolonged QRS interval (≥150 ms) and a shorter QRS interval (<150 ms). In multivariable analysis, there was no significant interaction between QRS interval and 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.

RAFT Trial

A second, large RCT was the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT), which randomized 1798 patients with class II or III heart failure and an LVEF of 30% or less to CRT-D or ICD alone, with a mean follow-up 40 months. 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.

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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). 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 rate for class II patients in the CRT-D group was 15.5% vs 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 the 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). 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. Of these factors, the QRS interval was the strongest. Patients with a QRS interval of 150 ms or more had a RR for the primary outcome of approximately 0.50, compared with an RR of approximately 1.0 for patients with a QRS interval less than 150 ms (p=0.003 for the difference between the RRs). There was a trend for greater improvement in patients with sinus rhythm compared with patients with atrial arrhythmias, but this difference was not statistically significant.

Safety of CRT Placement

Several systematic reviews have reported on complication rates. Three reviews published after 2010 are shown in Table 4. Van Rees et al (2011) focused on complications from CRT treatment. This analysis included 7 trials of CRT that reported on in-hospital mortality and complications related to device placement. In all 7 CRT trials, the device was placed percutaneously without a thoracotomy. In-hospital mortality occurred at a rate of 0.3%, and 30-day mortality was 0.7%. The most common complications related to placement of the LV lead. Lead dislodgement occurred in 5.9% of patients. Other LV lead placement complications included coronary vein dissection (1.3%) and coronary vein perforation (1.3%). Pneumothorax occurred in 0.9% of patients, and hematoma at the insertion site occurred in 2.4% of patients. Other systematic reviews have reported similar implant success rates, 30-day mortality, and lead problems.

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Table 4. Systematic Reviews Assessing the Safety of CRT for Treatment of Heart Failure

Study	Dates	Population	Studies (N)	Designs	Outcome Measures	Results (95% CI), %
CRT						
van Rees et al (2011)	Through 2010	Undergoing elective CRT	7 RCTs (N=4512)	RCTs	• Implant success rate • In-hospital mortality • Mortality within 30 days • Pneumothorax • Coronary dissection • Coronary perforation • Pocket hematoma • Lead dislodgement	92.5 0.3 0.7 0.9 1.3 1.3 2.4 5.9
Al-Majed et al (2011)	1950-2010	EF ≤40%	23 RCTs (N=8374)	RCTs	• Implant success rate • Mechanical complications • Device malfunction • Lead problems • Infections • Peri-implantation death)	94.4 (93.8 to 94.8) 3.2 (2.8 to 3.6) 1.9 (1.5 to 2.4) 6.2 (5.6 to 6.8) 1.4 (1.1 to 1.7) 0.3 (0.2 to 0.5)
CRT vs ICD						
Adabag et al (2011)	1960-2010	• NYHA class I/II • EF ≤40% • QRS interval ≥120 ms	4 studies (N=4414)	RCTs	• In-hospital death • Pneumothorax • Lead dislodgment • Coronary sinus dissection • Implant failure • Any adverse event	0.05 vs 0.06 1.5 vs 0.8 5.1 vs 0 0.8 vs 0 6.6 vs <0.1 18 vs 4

CI: confidence interval; CRT: cardiac resynchronization therapy; EF: ejection fraction; NYHA: New York Heart Association: RCT: randomized controlled trial.

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 United States. 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.

Predictors of Response to CRT

For patients who meet indications for CRT treatment, there is a large variability in the magnitude of response. Some patients do not respond at all, while others have very substantial benefit. As a result, there is interest in defining the clinical features that predict response to better target therapy to those who will

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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 (PROSPECT) trial. 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. 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. Three additional selection factors are reviewed here: QRS interval /morphology, 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. LESSER-EARTH 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. This trial was terminated early after 85 patients had been enrolled. Interim analysis revealed futility in achieving benefit on the primary outcomes and a trend toward greater adverse events.

A more controversial issue is whether patients with 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 (>150-160 ms) or LBBB. Several meta-analyses of the association between QRS interval and outcomes have been published. Two patient-level meta-analyses have evaluated QRS duration. In a patient-level meta-analysis of data from 3 RCTs (total N=4076 patients), Zusterzeel et al (2014) evaluated whether women with LBBB benefit from combined CRT-D implantation at a shorter QRS interval than men with LBBB. For patients with LBBB and a QRS interval from 130 to 149 ms, women experienced a significant reduction in risk of heart failure or death (absolute risk difference between CRT-D and ICD alone, 23%; HR=0.24; 95% CI, 0.11 to 0.53; p<0.001), while men had no significant reduction in risk of heart failure or death (absolute risk difference, 4%; HR=0.85; 95% CI, 0.60 to 1.21; p=0.38). Men and women with LBBB and QRS durations longer than 150 ms benefited from CRT-D therapy, while neither men nor women with LBBB and QRS intervals shorter than 130 ms benefited. This trial's conclusion is strengthened because of the patient-level data examined, but somewhat limited because not all RCTs had patient-level data available.

In a second review including individual patient data, Woods et al (2015) performed a network meta-analysis of ICDs to inform a National Institute for Health and Care Excellence guidance. 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; QRT interval ≥120 ms to <150 ms vs ≥ 150 ms; LBBB vs no LBBB; see Table 5). 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

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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 with QRS intervals ranging from 120 ms to 150 ms and LBBB, and women older than 60 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 5. 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).
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

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. In one of these studies, the benefit of CRT was confined to patients with LBBB. 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.

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. 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).

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

Kutyifa et al (2014) evaluated whether prolonged PR predicts heart failure or death among 537 (30%) of MADIT-CRT trial subjects who did not have an LBBB. 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).

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. 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). 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.

Lin et al (2017) reported on a secondary analysis of mortality and hospitalization including 903 patients stratified by normal (255 patients ≤230 ms) or prolonged PR interval (53 patients >230 ms) from the medical therapy and CRT-D arms of the COMPANION trial. Mortality was significantly reduced in patients with a prolonged PR interval who received CRT-D vs medical therapy (HR=0.37; 95% CI, 0.21 to 0.67). However, the association was smaller and not significantly significant in those with a normal PR interval (HR=0.73; 95% CI, 0.52 to 1.03).

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. This finding prompted investigation of whether ventricular dyssynchrony could discriminate between responders and nonresponders to CRT, for patients who would otherwise qualify for CRT and for those who would not (i.e., those with a narrow QRS interval).

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A small RCT that compared CRT outcomes in patients who had ventricular dyssynchrony with those without was published by Diab et al (2011). A total of 73 patients with NYHA class II, III, IV heart failure were evaluated, 44 of whom had dyssynchrony on echocardiography. These 44 patients were randomized to CRT-D or ICD alone. Outcomes measures were maximal oxygen consumption (VO_2max), NYHA class, and echocardiographic parameters. At 6-month follow-up, more patients in the CRT group had an increase of at least 1 mL/kg/min in VO_2max (62% vs 50% p=0.04). There were significant within-group improvements in NYHA class and echocardiographic measures, but between-group comparisons with the no CRT group were not statistically significant.

The 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. 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 postimplantation (41% vs 16%, p=0.004). Patients in the CRT group had higher rates of avoiding the combined end point of heart failure hospitalization, heart failure death, and spontaneous ventricular fibrillation (p=0.028).

The EchoCRT study 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). Four hundred four patients were randomized to the CRT group and 405 to the control group. The primary efficacy outcome (death from any cause or hospitalization for worsening heart failure) occurred in 116 (28.7%) of 404 patients in the CRT group and 102 (25.2%) of 405 in the control group (HR with CRT, 1.20; 95% CI, 0.92 to 1.57; p=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. 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_2peak]). A subset of patients with QRS intervals of 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: Cardiac Resynchronization Therapy 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.

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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. However, when mild heart failure is considered as a group (class I or II), these data are sufficient to determine that outcomes are improved for patients with mild heart failure.

Predictors of Response

The presence of dyssynchrony on echocardiography may risk-stratify patients, but it is not a good discriminator of responders from nonresponders. A QRS interval of more than 150 ms or the presence of LBBB appears to discriminate well between responders and nonresponders and represents a potential factor in selecting patients for CRT treatment. Subgroup analyses across multiple RCTs, corroborated by pooling of these subgroups in meta-analyses, have reported that QRS intervals of 150 to 160 ms or more or the presence of LBBB are accurate in discriminating responders from nonresponders. Subgroup analyses of 2 RCTs and 1 registry study have provided inconsistent results on the role of prolonged PR interval. Two patient-level meta-analyses reported that women might benefit at a shorter QRS interval than men.

CRT FOR HEART FAILURE AND ATRIAL FIBRILLATION

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 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, 2 trials (APAF, MUSTIC-AF) have examined CRT specifically in this population, and other RCTs have reported subgroup analyses in patients with permanent or intermittent AF. Systematic reviews of observational studies have also been performed, and analysis from the National Cardiovascular Data Registry is available.

Randomized Controlled Trials

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 COMPANION. 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 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

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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).

The 2011 Ablate And Pace Therapy for Permanent Atrial Fibrillation (APAF) RCT compared CRT with right ventricular (RV) pacing alone in patients with AF. A total of 186 patients had AV nodal ablation, implantation of a CRT device, and were then randomized to echo-optimized CRT or RV pacing alone and followed for a median of 20 months. 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, 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. The primary outcome was the 6-minute walk distance; secondary outcomes were Vo_2max, QOL, hospitalizations, patients' preferred study period and mortality. Only 37 patients completed both crossover periods. In intention-to-treat analyses, no significant differences were observed between assigned groups.

A post hoc analysis of patients with AF enrolled in RAFT was published by Healey et al (2012). Randomization in this trial was stratified for the presence of AF, allocating 114 patients with AF to the CRT plus defibrillator group and 115 patients with AF to the defibrillator 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 in the defibrillator-alone group, but the difference was not statistically significant.

Systematic Reviews

A systematic review by Wilton et al (2011) compared outcomes of CRT in patients with and without AF. This analysis included 23 observational studies enrolling 7495 patients, 1912 of whom had AF. Outcomes in patients with AF were less favorable on all measures. They included overall mortality (RR=1.5; 95% CI, 1.08 to 2.09; p=0.015), nonresponse to CRT (RR=1.32; 95% CI, 1.12 to 1.55; p=0.001), change in Minnesota Living with Heart Failure Questionnaire QOL score (mean difference, -4.1; 95% CI, -1.7 to -6.6; p=0.001), and change in 6-minute walk distance (mean difference, -14.1 meters; 95% CI, -28.2 to 0.0 meters; p=0.05). Five studies compared outcomes of patients with AF who had or did not have AV nodal ablation. A pooled analysis from these studies indicated that AV nodal ablation was associated with a lower rate of nonresponse (RR=0.40; 95% CI, 0.28 to 0.58; p<0.001).

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A systematic review by Ganesan et al (2012) evaluated the role of AV node ablation in patients with AF treated with CRT. Reviewers included nonrandomized studies that reported on outcomes for CRT and medical therapy. Six studies were included, enrolling 768 patients, 339 of whom underwent AV node ablation and 429 of whom did not. AV nodal ablation was associated with improvements in the outcomes of all-cause mortality (RR=0.42; 95% CI, 0.26 to 0.68), cardiovascular mortality (RR=0.44; 95% CI, 0.24 to 0.81), and change in NYHA class (mean difference, -0.34; 95% CI, -0.56 to -0.13; p=0.002).

Yin et al (2014), in another systematic review and meta-analysis, evaluated the effects of AV nodal ablation; it included 13 observational studies (total N=1256 patients) of CRT patients with AF who received AV nodal ablation or medical therapy. In pooled analysis of patients with inadequate biventricular pacing (<90% biventricular pacing), AV nodal ablation was associated with lower risk of all-cause mortality than no ablation (RR=0.63; 95% CI, 0.42 to 0.96), along with a reduced risk of CRT nonresponse (RR=0.41; 95% CI, 0.31 to 0.54). In contrast, among patients with adequate biventricular pacing (>90% biventricular pacing), AV nodal ablation was not significantly associated with risk of CRT nonresponse (RR=0.97; 95% CI, 0.72 to 1.32).

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. 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. 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
There is insufficient evidence to determine whether CRT improves outcomes for patients with AF and heart failure. Data from 2 RCTs enrolling only patients with AF showed different results, with one reporting improvements for patients with AF 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. Similarly, systematic reviews of observational studies have reported conflicting results. 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
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.

In 2014, the U.S. 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

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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 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. Patients with permanent atrial arrhythmias and intrinsic AV block or AV block due to AV node ablation could be enrolled if they met other enrollment criteria. At baseline, patients met the requirement for ventricular pacing, either because of documented third-degree AV block or a second-degree AV block or a PR interval of 300 ms or more when paced at 100 beats per minute.

Nine-hundred eighteen patients were enrolled, 691 of whom underwent randomization after 30 to 60 days of RV pacing, during which time appropriate pharmacologic therapy was established. Approximately half of all enrolled patients (51.6% of the CRT group, 54.1% of the RV pacing group) had AF. After accounting for censored data due to missing measures of LVESV index, the primary outcome (first event of death from any cause, an urgent care visit for heart failure requiring intravenous therapy, or an increase in the LVESV index of ≥15%) occurred in 160 (45.8%) of 349 patients in the biventricular pacing group and in 190 (55.6%) of 342 in the RV pacing group. In a hierarchical Bayesian proportional hazards model, the HR for the primary outcome was 0.74 for the comparison between biventricular pacing and RV pacing (95% CI, 0.60 to 0.90; posterior probability of HR being ≤1, 0.9978, which is greater than the prespecified threshold for superiority of biventricular to RV pacing of 0.9775). The prespecified secondary outcomes of an urgent care visit for heart failure, death or hospitalization for heart failure, and hospitalization for heart failure were less likely in the biventricular pacing group; however, the secondary outcome of death alone did not differ significantly between groups. LV 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). 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 the an earlier trial (PACE), 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). In the trial's main results, at 12 months postenrollment, subjects who underwent standard pacing had lower mean LVEF than those randomized to biventricular pacing (54.8% vs 62.2%; p<0.001) and higher mean LVESV (35.7 mL vs 27.6 mL; p<0.001). No significant differences were reported for QOL or functional measures or rates of heart failure hospitalization. In long-term follow-up over a mean duration of 4.8 years among 149 subjects, biventricular pacing continued to be associated with improved LV functioning and less LV remodeling. 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).

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Several other RCTs have also corroborated the results of the BLOCK and PACE trials. These trials reported improvements in physiologic parameters of LV function and improvements in functional status measured by the 6-minute walk test. 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 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. To demonstrate improved outcomes, RCTs are needed that compare outcomes of triple-site CRT with conventional CRT.

Five RCTs were identified for this review and are summarized in Table 6. 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 (TRUST CRT). 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%; $p<0.05$). Implantation success was similar in the triple-site (94%) and conventional groups (98%; p=*NS*), 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%, $p<0.05$).

The other 4 trials were smaller, enrolling between 43 and 76 patients. Follow-up in these studies was generally short, with the longest being 1 year. Outcomes reported varied across studies and were a mix of physiologic measures, functional status, and QOL. No outcome measures reported were common across all studies. Three of the 4 studies reported significant improvements on at least 1 outcome measure, and the fourth study reported no significant differences for the 3 outcomes measured. Adverse events were not well-reported.

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Table 6. Randomized Controlled Trials Comparing Triple-Site CRT With Standard CRT

Study	N	Group	Outcomes					
			6MWT, m	MLHFQ, points	NYHA Class	Response Rate	Ejection Fraction	QOL, points
Rogers et al (2012)	43[a]	Triple-site CRT	+91	-24	NR	NR	NR	NR
		Standard CRT	+65	-18				
p			0.008	<0.001				
Lenarczyk et al (2012)	100	Triple-site CRT	NR	NR	12.5%[b]	NR	NR	NR
		Standard CRT			30%			
p					<0.05			
Bencardino et al (2016)	43	Triple-site CRT	NR	NR	96%[c]	NR	+10%	NR
		Standard CRT			60%		+4%	
p					<0.05		<0.001	
Anselme et al (2016)	76	Triple-site CRT	+50	NR	NR	78.8%	NR	-8.4
		Standard CRT	+73			81.6%		-15.0
p			0.40			0.90		0.20
Pappone et al (2015)	44	Triple-site CRT	NR	NR	NR	76%	+15%	NR
		Standard CRT				57%	+5%	
p						0.33	<0.001	

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 (total N=251 patients) that evaluated similar outcomes. The meta-analysis included 1 RCT (Anselme et al [2016]; 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<0.001) and NYHA classes (weighted mean difference, -0.27; 95% CI, -0.42 to -0.11; p=0.001). However, there were no significant differences in LV end-diastolic volume or LVESV, 6-minute walk distance, or Minnesota Living with Heart Failure Questionnaire.

Section Summary: Triple-Site CRT

For the use of CRT with triple-site pacing requiring implantation of an additional lead, 5 small RCTs with limited follow-up and a meta-analysis that included nonrandomized studies were identified. All trials except one reported improved outcomes on at least 1 measure of functional status and QOL 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.

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CRT COMBINED WITH REMOTE FLUID MONITORING

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

Randomized Controlled Trials

Three RCTs were identified that compared management of patients with heart failure using remote fluid monitoring to usual monitoring; these trials are summarized in Table 7. Luthje et al (2015) was an unblinded, single-site RCT sponsored by the manufacturer of the OptiVol device. Patients in the remote monitoring group had alarms set for a rising fluid index, with most patients having their diuretic increased by 50% in response to an alert. Median follow-up was not reported. Outcomes were reported as 1-year estimates using Cox proportional hazards. Four patients were lost to follow-up. Domenichini et al (2016) was an unblinded, single-site RCT sponsored by the U.K. National Health Service. Patients in the remote monitoring group had alarms set for a rising fluid index, with most patients having their diuretic increased by 50% in response to an alert. Median follow-up was 375 days (range, 350-430 days). One patient was lost to follow-up, and 71 (89%) of 80 patients had complete data on patient-reported outcomes. Bohm et al (2016) was an unblinded, multicenter RCT conducted in Germany and also sponsored by the device manufacturer. One thousand two patients with NYHA class II or III heart failure and an LVEF of 35% or less were randomized to have their ICD or CRT-D devices automatically transmit fluid index telemedicine alerts or not. Alerts were triggered by intrathoracic fluid index threshold crossing, which was programmed at the investigator's discretion. Patients were followed for a mean of 1.9 years. All patients were included in the intention-to-treat Cox proportional hazard analyses.

None of the 3 RCTs reported improvements for the remote monitoring group on any outcome measures (see Table 7). In the Domenichini study, there were no significant differences reported between groups for hospitalizations rates, functional status, or QOL. Luthje reported no differences in mortality or hospitalizations. Also, Luthje reported a HR for time to the first hospitalization that was not significant at 1.23 (95% CI, 0.62 to 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 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).

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Table 7. Randomized Controlled Trials of Remote Monitoring With Combined Cardiac Resynchronization Therapy and Fluid Monitoring Device

Study	N	Group	Outcomes			
			Mortality	Hospitalizations	6MWT	MLHFQ
Bohm et al (2016)	1002	Remote fluid monitoring	11.7%	21%		
		Usual care	12.7%	25%		
Domenichini et al (2016)	80	Remote fluid monitoring		0.3 (SD=0.9) per patient[b]	+1.5 m	-3 points
		Usual care		0.2 (SD=0.4) per patient	-53.5 m	+10 points
p				0.95	0.83	0.07
Luthje et al (2015)	176	Remote fluid monitoring	8.6%[a]	27% (20/73)		
		Usual care	4.6%	27% (22/82)		
p			0.51	NR		

MLHFQ: Minnesota Living with Heart Failure Questionnaire; NR: not reported; 6MWT: 6-minute walk test.
[a] Kaplan-Meier estimate of 1-year mortality rate.
[b] Total hospitalizations per patient over study period.

Section Summary: CRT Combined With Remote Fluid Monitoring
Three RCTs have reported no improvements in outcomes associated with remote fluid monitoring for patients with heart failure. These RCTs do not a support a benefit from remote monitoring of fluid status vs usual care.

SUMMARY OF EVIDENCE
For individuals who have NYHA class III or IV heart failure with a LVEF of 35% 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 overall survival, symptoms, functional outcomes, 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 QOL 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 interval greater than 150 ms. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have 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 who receive CRT with or without defibrillator, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are overall survival, 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 RAFT. None of the other 3 RCTs reported a mortality difference, but a subgroup analysis of the MADIT-CRT trial reported a mortality benefit for patients with LBBB. Among other outcome measures, hospitalizations for heart failure showed consistent reductions, but QOL 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

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greater than 150 ms. The evidence is sufficient to determine that the technology results in a meaningful 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 overall survival, 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 CRT-D devices vs ICD alone for class I patients, the CI was large and included a 25% to 30% increase in events. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have heart failure and AF who receive CRT with or without defibrillator, the evidence includes 4 RCTs and observational studies. Relevant outcomes are overall survival, symptoms, functional outcomes, QOL, hospitalizations, and treatment-related morbidity. Results from RCTs have been conflicting, with one reporting improvements for patients with AF and others reporting no significant improvements. Results from observational studies are also conflicting. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have heart failure and AV nodal block who receive CRT, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are overall survival, 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 LV dysfunction, results of a small RCT have suggested that biventricular pacing is associated with improvement in 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 a meaningful improvement in the net 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 overall survival, 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 with 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 postimplantation. Larger, high-quality RCTs are needed to define better the benefit-risk ratio for triple-site CRT compared with conventional CRT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have heart failure who receive CRT combined with remote fluid monitoring, the evidence includes 3 RCTs. Relevant outcomes are overall survival, symptoms, functional outcomes, QOL, hospitalizations, and treatment-related morbidity. Three RCTs have reported no improvement in outcomes

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associated with remote fluid monitoring for patients with heart failure. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 06/05/2002
Current Effective Date: 07/11/2018

04/18/2002	Medical Policy Committee review
06/05/2002	Managed Care Advisory Council approval
06/24/2002	Format revision. No substance change to policy.
06/01/2004	Medical Director review. Format revision. Clinical criteria revision.
06/15/2004	Medical Policy Committee review
06/28/2004	Managed Care Advisory Council approval
11/02/2004	Medical Director review. Clinical criteria revision
11/16/2004	Medical Policy Committee review
11/29/2004	Managed Care Advisory Council approval
04/05/2005	Medical Director review
04/18/2005	Medical Director review
04/22/2005	Medical Director review

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04/27/2005	Medical Policy Committee review. Clinical criteria revision. Combination automatic implantable cardiac defibrillators (AICD) and biventricular pacemakers criteria further defined; "patients with New York Heart Association (NYHA) Class III or IV CHF, with a QRS duration of >120-130 msec". FDA labeled indication for the InSync device and CONTAK CD® CRT-D System added. Investigational statement added to address cases not meeting clinical criteria.
04/04/2007	Medical Director review
04/18/2007	Medical Policy Committee approval. Policy statements revised indicating that intrathoracic bioimpedance is considered investigational as a component of a biventricular pacemaker; patient selection criteria for combined biventricular pacemaker/ACID revised to indicate that a combined device would be considered medically necessary in patients who meet the criteria for a biventricular pacemaker alone. Rationale /Source and Background/Overview updated.
04/02/2008	Medical Director review
04/16/2008	Medical Policy Committee approval. No changes to policy statement.
04/02/2009	Medical Director review
04/15/2009	Medical Policy Committee approval. No changes to policy statement.
04/08/2010	Medical Policy Committee approval
04/21/2010	Medical Policy Implementation Committee approval. Added statement "Based on review of available data, the Company considers biventricular pacemakers with or without an accompanying implantable cardiac defibrillator as a treatment of NYHA class I or II heart failure to be investigational to the policy.
04/07/2011	Medical Policy Committee approval
04/13/2011	Medical Policy Implementation Committee approval. Sinus rhythm added to the list of patient selection criteria.
04/12/2012	Medical Policy Committee review
04/25/2012	Medical Policy Implementation Committee approval. Cardiac resynchronization therapy use in patients with NYHA class II heart failure meeting specific criteria now may be considered eligible for coverage; all other uses in mild heart failure (e.g., class I) considered investigational. The term "congestive" was removed from the title and text.
02/04/2013	Coding revised
04/03/2014	Medical Policy Committee review
04/23/2014	Medical Policy Implementation Committee approval. Additional investigational statement added for triple-site (triventricular) CRT.
04/02/2015	Medical Policy Committee review
04/20/2015	Medical Policy Implementation Committee approval. Updated rationale/source and references. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. Coverage statement with criteria added for CRT in patients with heart failure and AV block. Existing coverage criteria changed to include presence of LBBB (and QRS >120-130 ms) OR QRS >150 ms.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
04/06/2017	Medical Policy Committee review
04/19/2017	Medical Policy Committee approval. Coverage eligibility unchanged.
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. Changed "a combined biventricular pacemaker/implantable cardiac defibrillator" to "a combined biventricular pacemaker plus implantable cardiac defibrillator" where it appears in the coverage section. Replaced "a stable

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	pharmacologic medical regimen" with "guideline-directed medical therapy" for patients treated before implant in the Patient Selection Criteria. Coverage eligibility unchanged.
07/05/2018	Medical Policy Committee review
07/11/2018	Medical Policy Implementation Committee approval. Policy statement added that cardiac resynchronization therapy with wireless left ventricular endocardial pacing is considered investigational.

Next Scheduled Review Date: 07/2019

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	33211, 33213, 33217, 33220, 33222, 33223, 33224, 33225, 33226, 33228, 33229, 33230, 33231, 33233, 33235, 33237, 33238, 33241, 33243, 33244, 33249, 93280, 93640, 93641
HCPCS	C1721, C1785, C2619, C2621
ICD-10 Diagnosis	I50.1 I50.20-I50.23 I50.30-I50.33 I50.40-I50.43 I50.9

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

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

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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