



## FEP Medical Policy Manual

### FEP 2.02.10 Biventricular Pacemakers (Cardiac Resynchronization Therapy) for the Treatment of Heart Failure

**Effective Policy Date: October 1, 2021**

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**Related Policies:**

None

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

#### Description

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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).

#### OBJECTIVE

The objective of this evidence review is to determine whether cardiac resynchronization therapy improves the net health outcome in individuals with heart failure.

## POLICY STATEMENT

Biventricular pacemakers with or without an accompanying implantable cardiac defibrillator (ie, a combined biventricular pacemaker plus implantable cardiac defibrillator) may be considered **medically necessary** as a treatment of heart failure in patients who meet all of the following criteria:

For New York Heart Association class III or IV,

- Left ventricular ejection fraction  $\leq 35\%$
- Sinus rhythm
- Patients treated with guideline-directed medical therapy (see Policy Guidelines section)

AND

- Either left bundle branch block OR QRS interval  $\geq 150$  ms.

For New York Heart Association class II,

- Left ventricular ejection fraction  $\leq 30\%$
- Sinus rhythm
- Patients treated with a guideline-directed medical therapy (see Policy Guidelines section)

AND

- Either left bundle branch block OR QRS interval  $\geq 150$  ms.

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 (ie, a combined biventricular pacemaker plus 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:

- New York Heart Association class I, II, III, or IV heart failure;
- Left ventricular ejection fraction  $\leq 50\%$ ;
- The presence of atrioventricular block with requirement for a high percentage of ventricular pacing (see Policy Guidelines section); and
- Patients treated with guideline-directed medical therapy (see Policy Guidelines section).

Biventricular pacemakers, with or without an accompanying implantable cardiac defibrillator (ie, a combined biventricular pacemaker plus implantable cardiac defibrillator), are considered **not medically necessary** as a treatment for patients with New York Heart Association class I heart failure who do not meet the above criteria.

Biventricular pacemakers, with or without an accompanying implantable cardiac defibrillator (ie, a combined biventricular pacemaker plus implantable cardiac defibrillator), are considered **not medically necessary** as a treatment for heart failure in patients with atrial fibrillation who do not meet the above criteria.

Triple-site (triventricular) cardiac resynchronization therapy, using an additional pacing lead, is considered **not medically necessary**.

An intrathoracic fluid monitoring sensor is considered **not medically necessary** as a component of a biventricular pacemaker.

Cardiac resynchronization therapy with wireless left ventricular endocardial pacing is considered **not medically necessary**.

## POLICY GUIDELINES

### Definitions

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

- Third-degree atrioventricular block; or
- Second-degree atrioventricular block or a PR interval of  $\geq 300$  ms when paced at 100 beats per minute.

Guideline-directed medical therapy for heart failure is outlined in 2013 American College of Cardiology Foundation and American Heart Association guidelines for the management of heart failure (Yancy et al [2013]).

## BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

## FDA REGULATORY STATUS

There are numerous Cardiac Resynchronization Therapy (CRT) devices, combined implantable cardioverter-defibrillator (ICD) plus CRT devices (CRT-D), and combined CRT plus fluid monitoring devices. Some devices are discussed here. For example, in 2001, the InSync Biventricular Pacing System (Medtronic), a stand-alone biventricular pacemaker, was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process for the treatment of patients with New York Heart Association (NYHA) class III or IV heart failure, on a stable pharmacologic regimen, who also have a QRS duration of 130 ms or longer and a left ventricular ejection fraction (LVEF) of 35% or less. Devices by Guidant (CONTAK-CD CRT-D System) and Medtronic (InSync ICD Model 7272) have been approved by the FDA through the premarket approval process for combined CRT defibrillators for patients at high risk of sudden cardiac death due to ventricular arrhythmias and who have NYHA class III or IV heart failure with a LVEF of 35% or less, QRS interval 130 ms or longer ( $\geq 120$  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<sup>1</sup>); in 2013, the company received the FDA approval for updated CRT-D devices (Ilesto/Iforia series).<sup>2</sup> 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<sup>1</sup>:

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

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

Several CRT devices have incorporated a fourth lead, providing quadripolar pacing. The Medtronic Viva™ Quad XT and the Viva Quad S have a fourth lead, and the Medtronic Attain Performa has a left ventricular lead, which received clearance for marketing from the FDA in August 2014. The Dynagen™ X4 and Inogen™ X4 devices (Boston Scientific) also incorporate a fourth lead. Other CRT devices with quadripolar leads have been approved for use outside of the U.S. (eg, 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. Evidence review 2.02.24 addresses the use of external bioimpedance devices as stand-alone devices to assess cardiac output noninvasively.

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

FDA product code: NIK.

## RATIONALE

### Summary of Evidence

For individuals who have NYHA class III or IV heart failure with an left ventricle 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 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, 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 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 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, quality of life, 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 trial. 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 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, quality of life, 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 (ICD) plus CRT devices versus ICD 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 net health outcome.

For individuals who have NYHA class I, II, III or IV heart failure with LVEF of 50% or less and 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, quality of life, hospitalizations, and treatment-related morbidity. 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 left ventricular (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. 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 AF who receive CRT with or without defibrillator, the evidence includes 5 RCTs and a registry study. Relevant outcomes are OS, symptoms, functional outcomes, quality of life, hospitalizations, and treatment-related morbidity. Results from RCTs have been conflicting, with 2 reporting improvements for patients with AF and others reporting no significant improvements. A registry study reported significant improvements in mortality and hospitalizations for patients with heart failure and AF treated with CRT plus defibrillator compared with ICD alone. The evidence is insufficient to determine that the technology results in an improvement in the net 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, quality of life, 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 an 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 OS, symptoms, functional outcomes, quality of life, hospitalizations, and treatment-related morbidity. The available RCTs have reported improved outcomes on at least 1 measure of functional status or quality of life 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 post-implantation. 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 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, quality of life, 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.

## SUPPLEMENTAL INFORMATION

### Practice Guidelines and Position Statements

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

#### American College of Cardiology et al

The American College of Cardiology (ACC), American Heart Association, and Heart Rhythm Society (2019) published joint guidelines on the evaluation and management of patients with bradycardia and cardiac conduction delay.<sup>84</sup> These guidelines included the following recommendations on CRT (see Table 1).

**Table 1. 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."	Ila	B-R <sup>SR</sup>
"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)."	Ila	B-R

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

The ACC and American Heart Association (2013) published guidelines for the management of heart failure.<sup>85</sup> 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 outlined next.

A focused update to 2008 guidelines<sup>86</sup> for device-based treatment of cardiac rhythm abnormalities was published jointly by ACC Foundation, American Heart Association, and Heart Rhythm Society in 2012.<sup>87</sup> These guidelines included the following recommendations on CRT for heart failure (see Table 2).

**Table 2. 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	A <sup>a</sup> B <sup>b</sup>
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
CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class III/ambulatory class IV symptoms on GDMT	IIa	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
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	C
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	C
CRT may be considered for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with QRS duration 120 to 149 ms, and NYHA class III/ambulatory class IV on GDMT	IIb	B
CRT may be considered for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class II symptoms on GDMT	IIb	B
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 <sup>c</sup>	B
CRT is not indicated for patients whose comorbidities and/or frailty limit survival with good functional capacity to less than 1 year	III <sup>c</sup>	C

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

<sup>a</sup> For NYHA class III or IV heart failure.

<sup>b</sup> For NYHA class II heart failure.

<sup>c</sup>No benefit.

## Heart Failure Society of America

The Heart Failure Society of America (2010) released comprehensive guidelines on the management of heart failure.<sup>88</sup> The guidelines included the following recommendations on the use of CRT (see Table 3).



**Table 3. Guidelines on Management of Heart Failure**

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

HF: heart failure; LOE: level of evidence; LV: left ventricular; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

## National Institute for Health and Care Excellence

The NICE (2014) guidance provided recommendations on CRT for heart failure.<sup>89</sup> The recommendations for patients with left ventricular ejection fraction of 35% or less are list in Table 4.

**Table 4. 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 $\geq 150$ ms (with or without LBBB)	CRT-D recommended
NYHA class III-IV with QRS interval $\geq 150$ ms (with or without LBBB)	CRT-P recommended

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

## U.S. Preventive Services Task Force Recommendations

Not applicable.

## Medicare National Coverage

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

## REFERENCES

1. Food and Drug Administration. Summary of Safety and Effectiveness Data (SSED): Cardiac Resynchronization Therapy Defibrillator (CRT-D). 2010; [https://www.accessdata.fda.gov/cdrh\\_docs/pdf/P010012S230b.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf/P010012S230b.pdf). Accessed March 31, 2021.
2. Food and Drug Administration. Approval Order: Biotronic PMA P050023. 2013; [https://www.accessdata.fda.gov/cdrh\\_docs/pdf5/P050023S058A.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf5/P050023S058A.pdf). Accessed April 8, 2021.
3. Al-Majed NS, McAlister FA, Bakal JA, et al. Meta-analysis: cardiac resynchronization therapy for patients with less symptomatic heart failure. *Ann Intern Med.* Mar 15 2011; 154(6): 401-12. PMID 21320922
4. Ezekowitz JA, Rowe BH, Dryden DM, et al. Systematic review: implantable cardioverter defibrillators for adults with left ventricular systolic dysfunction. *Ann Intern Med.* Aug 21 2007; 147(4): 251-62. PMID 17709759
5. McAlister FA, Ezekowitz JA, Wiebe N, et al. Systematic review: cardiac resynchronization in patients with symptomatic heart failure. *Ann Intern Med.* Sep 07 2004; 141(5): 381-90. PMID 15353430
6. Adabag S, Roukoz H, Anand IS, et al. Cardiac resynchronization therapy in patients with minimal heart failure: a systematic review and meta-analysis. *J Am Coll Cardiol.* Aug 23 2011; 58(9): 935-41. PMID 21851882
7. Bertoldi EG, Polanczyk CA, Cunha V, et al. Mortality reduction of cardiac resynchronization and implantable cardioverter-defibrillator therapy in heart failure: an updated meta-analysis. Does recent evidence change the standard of care?. *J Card Fail.* Oct 2011; 17(10): 860-6. PMID 21962425
8. Nery PB, Ha AC, Keren A, et al. Cardiac resynchronization therapy in patients with left ventricular systolic dysfunction and right bundle branch block: a systematic review. *Heart Rhythm.* Jul 2011; 8(7): 1083-7. PMID 21300176
9. Tu R, Zhong G, Zeng Z, et al. Cardiac resynchronization therapy in patients with mild heart failure: a systematic review and meta-analysis of randomized controlled trials. *Cardiovasc Drugs Ther.* Aug 2011; 25(4): 331-40. PMID 21750900
10. Santangeli P, Di Biase L, Pelargonio G, et al. Cardiac resynchronization therapy in patients with mild heart failure: a systematic review and meta-analysis. *J Interv Card Electrophysiol.* Nov 2011; 32(2): 125-35. PMID 21594629
11. Wells G, Parkash R, Healey JS, et al. Cardiac resynchronization therapy: a meta-analysis of randomized controlled trials. *CMAJ.* Mar 08 2011; 183(4): 421-9. PMID 21282316
12. Chen S, Ling Z, Kiuchi MG, et al. The efficacy and safety of cardiac resynchronization therapy combined with implantable cardioverter defibrillator for heart failure: a meta-analysis of 5674 patients. *Europace.* Jul 2013; 15(7): 992-1001. PMID 23419662
13. Woods B, Hawkins N, Mealing S, et al. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. *Heart.* Nov 2015; 101(22): 1800-6. PMID 26269413
14. Sun WP, Li CL, Guo JC, et al. Long-term efficacy of implantable cardiac resynchronization therapy plus defibrillator for primary prevention of sudden cardiac death in patients with mild heart failure: an updated meta-analysis. *Heart Fail Rev.* Jul 2016; 21(4): 447-53. PMID 27043219
15. Ali-Hassan-Al-Saegh S, Mirhosseini SJ, Karimi-Bondarabadi AA, et al. Cardiac resynchronization therapy in patients with mild heart failure is a reversal therapy. *Indian Heart J.* Jan 2017; 69(1): 112-118. PMID 28228294
16. Lozano I, Bocchiardo M, Achteik M, et al. Impact of biventricular pacing on mortality in a randomized crossover study of patients with heart failure and ventricular arrhythmias. *Pacing Clin Electrophysiol.* Nov 2000; 23(11 Pt 2): 1711-2. PMID 11139906
17. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med.* Mar 22 2001; 344(12): 873-80. PMID 11259720
18. Garrigue S, Bordachar P, Reuter S, et al. Comparison of permanent left ventricular and biventricular pacing in patients with heart failure and chronic atrial fibrillation: prospective haemodynamic study. *Heart.* Jun 2002; 87(6): 529-34. PMID 12010933
19. Leclercq C, Walker S, Linde C, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J.* Nov 2002; 23(22): 1780-7. PMID 12419298
20. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med.* Jun 13 2002; 346(24): 1845-53. PMID 12063368
21. Auricchio A, Stellbrink C, Sack S, et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol.* Jun 19 2002; 39(12): 2026-33. PMID 12084604
22. Auricchio A, Stellbrink C, Butter C, et al. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol.* Dec 17 2003; 42(12): 2109-16. PMID 14680736
23. Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol.* Oct 15 2003; 42(8): 1454-9. PMID 14563591
24. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA.* May 28 2003; 289(20): 2685-94. PMID 12771115
25. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* May 20 2004; 350(21): 2140-50. PMID 15152059
26. Abraham WT, Young JB, Leon AR, et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation.* Nov 02 2004;



- 110(18): 2864-8. PMID 15505095
27. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* Apr 14 2005; 352(15): 1539-49. PMID 15753115
  28. Gasparini M, Bocchiardo M, Lunati M, et al. Comparison of 1-year effects of left ventricular and biventricular pacing in patients with heart failure who have ventricular arrhythmias and left bundle-branch block: the Bi vs Left Ventricular Pacing: an International Pilot Evaluation on Heart Failure Patients with Ventricular Arrhythmias (BELIEVE) multicenter prospective randomized pilot study. *Am Heart J.* Jul 2006; 152(1): 155.e1-7. PMID 16824846
  29. Kindermann M, Hennen B, Jung J, et al. Biventricular versus conventional right ventricular stimulation for patients with standard pacing indication and left ventricular dysfunction: the Homburg Biventricular Pacing Evaluation (HOBIPACE). *J Am Coll Cardiol.* May 16 2006; 47(10): 1927-37. PMID 16697307
  30. Piccirillo G, Magri D, di Carlo S, et al. Influence of cardiac-resynchronization therapy on heart rate and blood pressure variability: 1-year follow-up. *Eur J Heart Fail.* Nov 2006; 8(7): 716-22. PMID 16513420
  31. Rao RK, Kumar UN, Schafer J, et al. Reduced ventricular volumes and improved systolic function with cardiac resynchronization therapy: a randomized trial comparing simultaneous biventricular pacing, sequential biventricular pacing, and left ventricular pacing. *Circulation.* Apr 24 2007; 115(16): 2136-44. PMID 17420340
  32. Leclercq C, Cazeau S, Lellouche D, et al. Upgrading from single chamber right ventricular to biventricular pacing in permanently paced patients with worsening heart failure: The RD-CHF Study. *Pacing Clin Electrophysiol.* Jan 2007; 30 Suppl 1: S23-30. PMID 17302711
  33. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med.* Dec 13 2007; 357(24): 2461-71. PMID 17986493
  34. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J.* Aug 2013; 34(29): 2281-329. PMID 23801822
  35. Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol.* Dec 02 2008; 52(23): 1834-1843. PMID 19038680
  36. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med.* Oct 01 2009; 361(14): 1329-38. PMID 19723701
  37. Pinter A, Mangat I, Korley V, et al. Assessment of resynchronization therapy on functional status and quality of life in patients requiring an implantable defibrillator. *Pacing Clin Electrophysiol.* Dec 2009; 32(12): 1509-19. PMID 19765233
  38. Boriani G, Kranig W, Donal E, et al. A randomized double-blind comparison of biventricular versus left ventricular stimulation for cardiac resynchronization therapy: the Biventricular versus Left Univentricular Pacing with ICD Back-up in Heart Failure Patients (B-LEFT HF) trial. *Am Heart J.* Jun 2010; 159(6): 1052-1058.e1. PMID 20569719
  39. Martinelli Filho M, de Siqueira SF, Costa R, et al. Conventional versus biventricular pacing in heart failure and bradyarrhythmia: the COMBAT study. *J Card Fail.* Apr 2010; 16(4): 293-300. PMID 20350695
  40. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med.* Dec 16 2010; 363(25): 2385-95. PMID 21073365
  41. Thibault B, Ducharme A, Harel F, et al. Left ventricular versus simultaneous biventricular pacing in patients with heart failure and a QRS complex 120 milliseconds. *Circulation.* Dec 20 2011; 124(25): 2874-81. PMID 22104549
  42. van Geldorp IE, Vernooy K, Delhaas T, et al. Beneficial effects of biventricular pacing in chronically right ventricular paced patients with mild cardiomyopathy. *Europace.* Feb 2010; 12(2): 223-9. PMID 19966323
  43. Foley PW, Patel K, Irwin N, et al. Cardiac resynchronisation therapy in patients with heart failure and a normal QRS duration: the RESPOND study. *Heart.* Jul 2011; 97(13): 1041-7. PMID 21339317
  44. Gillis AM, Kerr CR, Philippon F, et al. Impact of cardiac resynchronization therapy on hospitalizations in the Resynchronization-Defibrillation for Ambulatory Heart Failure trial. *Circulation.* May 20 2014; 129(20): 2021-30. PMID 24610807
  45. Goldenberg I, Hall WJ, Beck CA, et al. Reduction of the risk of recurring heart failure events with cardiac resynchronization therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). *J Am Coll Cardiol.* Aug 09 2011; 58(7): 729-37. PMID 21816309
  46. Goldenberg I, Kutyla V, Klein HU, et al. Survival with cardiac-resynchronization therapy in mild heart failure. *N Engl J Med.* May 01 2014; 370(18): 1694-701. PMID 24678999
  47. Hosseini SM, Moazzami K, Rozen G, et al. Utilization and in-hospital complications of cardiac resynchronization therapy: trends in the United States from 2003 to 2013. *Eur Heart J.* Jul 14 2017; 38(27): 2122-2128. PMID 28329322
  48. Yu CM, Abraham WT, Bax J, et al. Predictors of response to cardiac resynchronization therapy (PROSPECT)--study design. *Am Heart J.* Apr 2005; 149(4): 600-5. PMID 15990740
  49. Chung ES, Leon AR, Tavazzi L, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation.* May 20 2008; 117(20): 2608-16. PMID 18458170
  50. Thibault B, Harel F, Ducharme A, et al. Cardiac resynchronization therapy in patients with heart failure and a QRS complex 120 milliseconds: the Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial. *Circulation.* Feb 26 2013; 127(8): 873-81. PMID 23388213
  51. Sipahi I, Carrigan TP, Rowland DY, et al. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. *Arch Intern Med.* Sep 12 2011; 171(16): 1454-62. PMID 21670335
  52. Bryant AR, Wilton SB, Lai MP, et al. Association between QRS duration and outcome with cardiac resynchronization therapy: a systematic review and meta-analysis. *J Electrocardiol.* Mar-Apr 2013; 46(2): 147-55. PMID 23394690

53. Stavrakis S, Lazzara R, Thadani U. The benefit of cardiac resynchronization therapy and QRS duration: a meta-analysis. *J Cardiovasc Electrophysiol.* Feb 2012; 23(2): 163-8. PMID 21815961
54. Sipahi I, Chou JC, Hyden M, et al. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. *Am Heart J.* Feb 2012; 163(2): 260-7.e3. PMID 22305845
55. Kang SH, Oh IY, Kang DY, et al. Cardiac resynchronization therapy and QRS duration: systematic review, meta-analysis, and meta-regression. *J Korean Med Sci.* Jan 2015; 30(1): 24-33. PMID 25552880
56. Shah RM, Patel D, Molnar J, et al. Cardiac-resynchronization therapy in patients with systolic heart failure and QRS interval 130 ms: insights from a meta-analysis. *Europace.* Feb 2015; 17(2): 267-73. PMID 25164431
57. Peterson PN, Greiner MA, Qualls LG, et al. QRS duration, bundle-branch block morphology, and outcomes among older patients with heart failure receiving cardiac resynchronization therapy. *JAMA.* Aug 14 2013; 310(6): 617-26. PMID 23942680
58. Kutyifa V, Stockburger M, Daubert JP, et al. PR interval identifies clinical response in patients with non-left bundle branch block: a Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy substudy. *Circ Arrhythm Electrophysiol.* Aug 2014; 7(4): 645-51. PMID 24963007
59. Stockburger M, Moss AJ, Klein HU, et al. Sustained clinical benefit of cardiac resynchronization therapy in non-LBBB patients with prolonged PR-interval: MADIT-CRT long-term follow-up. *Clin Res Cardiol.* Nov 2016; 105(11): 944-952. PMID 27318807
60. Friedman DJ, Bao H, Spatz ES, et al. Association Between a Prolonged PR Interval and Outcomes of Cardiac Resynchronization Therapy: A Report From the National Cardiovascular Data Registry. *Circulation.* Nov 22 2016; 134(21): 1617-1628. PMID 27760795
61. Hawkins NM, Petrie MC, MacDonald MR, et al. Selecting patients for cardiac resynchronization therapy: electrical or mechanical dyssynchrony?. *Eur Heart J.* Jun 2006; 27(11): 1270-81. PMID 16527827
62. Muto C, Solimene F, Gallo P, et al. A randomized study of cardiac resynchronization therapy defibrillator versus dual-chamber implantable cardioverter-defibrillator in ischemic cardiomyopathy with narrow QRS: the NARROW-CRT study. *Circ Arrhythm Electrophysiol.* Jun 2013; 6(3): 538-45. PMID 23592833
63. Ruschitzka F, Abraham WT, Singh JP, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med.* Oct 10 2013; 369(15): 1395-405. PMID 23998714
64. Brignole M, Pokushalov E, Pentimalli F, et al. A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. *Eur Heart J.* Dec 01 2018; 39(45): 3999-4008. PMID 30165479
65. Brignole M, Botto G, Mont L, et al. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur Heart J.* Oct 2011; 32(19): 2420-9. PMID 21606084
66. Kalscheur MM, Saxon LA, Lee BK, et al. Outcomes of cardiac resynchronization therapy in patients with intermittent atrial fibrillation or atrial flutter in the COMPANION trial. *Heart Rhythm.* Jun 2017; 14(6): 858-865. PMID 28323173
67. Healey JS, Hohnloser SH, Exner DV, et al. Cardiac resynchronization therapy in patients with permanent atrial fibrillation: results from the Resynchronization for Ambulatory Heart Failure Trial (RAFT). *Circ Heart Fail.* Sep 01 2012; 5(5): 566-70. PMID 22896584
68. Khazanie P, Greiner MA, Al-Khatib SM, et al. Comparative Effectiveness of Cardiac Resynchronization Therapy Among Patients With Heart Failure and Atrial Fibrillation: Findings From the National Cardiovascular Data Registry's Implantable Cardioverter-Defibrillator Registry. *Circ Heart Fail.* Jun 2016; 9(6): 617-626. PMID 27296396
69. Curtis AB, Worley SJ, Adamson PB, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med.* Apr 25 2013; 368(17): 1585-93. PMID 23614585
70. Curtis AB, Worley SJ, Chung ES, et al. Improvement in Clinical Outcomes With Biventricular Versus Right Ventricular Pacing: The BLOCK HF Study. *J Am Coll Cardiol.* May 10 2016; 67(18): 2148-2157. PMID 27151347
71. Yu CM, Chan JY, Zhang Q, et al. Biventricular pacing in patients with bradycardia and normal ejection fraction. *N Engl J Med.* Nov 26 2009; 361(22): 2123-34. PMID 19915220
72. Chan JY, Fang F, Zhang Q, et al. Biventricular pacing is superior to right ventricular pacing in bradycardia patients with preserved systolic function: 2-year results of the PACE trial. *Eur Heart J.* Oct 2011; 32(20): 2533-40. PMID 21875860
73. Yu CM, Fang F, Luo XX, et al. Long-term follow-up results of the pacing to avoid cardiac enlargement (PACE) trial. *Eur J Heart Fail.* Sep 2014; 16(9): 1016-25. PMID 25179592
74. Doshi RN, Daoud EG, Fellows C, et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol.* Nov 2005; 16(11): 1160-5. PMID 16302897
75. Anselme F, Bordachar P, Pasquie JL, et al. Safety, feasibility, and outcome results of cardiac resynchronization with triple-site ventricular stimulation compared to conventional cardiac resynchronization. *Heart Rhythm.* Jan 2016; 13(1): 183-9. PMID 26325531
76. Bencardino G, Di Monaco A, Russo E, et al. Outcome of Patients Treated by Cardiac Resynchronization Therapy Using a Quadripolar Left Ventricular Lead. *Circ J.* 2016; 80(3): 613-8. PMID 26821688
77. Lenarczyk R, Kowalski O, Sredniawa B, et al. Implantation feasibility, procedure-related adverse events and lead performance during 1-year follow-up in patients undergoing triple-site cardiac resynchronization therapy: a substudy of TRUST CRT randomized trial. *J Cardiovasc Electrophysiol.* Nov 2012; 23(11): 1228-36. PMID 22651239
78. Pappone C, Calovic Z, Vicedomini G, et al. Improving cardiac resynchronization therapy response with multipoint left ventricular pacing: Twelve-month follow-up study. *Heart Rhythm.* Jun 2015; 12(6): 1250-8. PMID 25678057
79. Rogers DP, Lambiase PD, Lowe MD, et al. A randomized double-blind crossover trial of triventricular versus biventricular pacing in heart failure. *Eur J Heart Fail.* May 2012; 14(5): 495-505. PMID 22312038
80. Zhang B, Guo J, Zhang G. Comparison of triple-site ventricular pacing versus conventional cardiac resynchronization therapy in patients with systolic heart failure: A meta-analysis of randomized and observational studies. *J Arrhythmia.* 2018;34:55-64. PMID 29811111
81. Domenichini G, Rahneva T, Diab IG, et al. The lung impedance monitoring in treatment of chronic heart failure (the LIMIT-CHF study). *Europace.* Mar 2016; 18(3): 428-35. PMID 26683599

82. Luthje L, Vollmann D, Seegers J, et al. A randomized study of remote monitoring and fluid monitoring for the management of patients with implanted cardiac arrhythmia devices. *Europace*. Aug 2015; 17(8): 1276-81. PMID 25983310
83. Bohm M, Drexler H, Oswald H, et al. Fluid status telemedicine alerts for heart failure: a randomized controlled trial. *Eur Heart J*. Nov 01 2016; 37(41): 3154-3163. PMID 26984864
84. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. *J Am Coll Cardiol*. Aug 20 2019; 74(7): 932-987. PMID 30412710
85. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. Oct 15 2013; 128(16): 1810-52. PMID 23741057
86. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Circulation*. May 27 2008; 117(21): e350-408. PMID 18483207
87. Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. [corrected]. *Circulation*. Oct 02 2012; 126(14): 1784-800. PMID 22965336
88. Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail*. Jun 2010; 16(6): e1-194. PMID 20610207
89. National Institute for Health and Care Excellence (NICE). Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure [TA314]. 2014; <https://www.nice.org.uk/guidance/ta314>. Accessed April 5, 2021.

## POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2011	New policy	
September 2013	Replace policy	Policy updated with literature review. Cardiac resynchronization therapy added to title. Numerous new references added, others reordered and/or removed. Cardiac resynchronization as treatment of heart failure in patients with atrial fibrillation is not medically necessary is added as a policy statement. Added investigational policy statement for triple-site (triventricular) CRT.
June 2014	Replace policy	Policy updated with literature review through March 6, 2014; references 11, 19, 25, 30, 31, 38, 41, 47, 49, 50, 51, 52, 53, added. Policy statements unchanged. Rationale reorganized and edited for clarity. Policy updated with literature review through March 6, 2014; references 11, 19, 25, 30, 31, 38, 41, 47, 49, 50, 51, 52, 53, added. Policy statements unchanged. Rationale reorganized and edited for clarity.
June 2015	Replace policy	Policy updated with literature review through March 11, 2015; references 1, 4, 11-12, 14, 30, 32-33, 49, 60, and 62 added. Policy statements for CRT in class II and II/IV heart failure changed to include presence of LBBB (and QRS >120- 130 ms) OR QRS >150 ms as medically necessary criteria. Policy statement added that CRT in patients with heart failure and AV block may be considered medically necessary with criteria.
	Replace policy	Policy updated with literature review through March 24, 2016. References 15, 51-53, 54-55, 57, and 60-61 added. No change to policy statements.
September 2018	Replace policy	Policy updated with literature review through March 5, 2018; References 5, 11, 14-38, 40-42, 44-46, 52, 65-67, 74, 78, 80, 90, 92, 98 added; reference 30 updated. Policy statement added that cardiac resynchronization therapy with wireless left ventricular endocardial pacing is considered not medically necessary.
September 2019	Replace policy	Policy updated with literature review through April 2, 2019; reference added. Policy statements unchanged.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

Date	Action	Description
September 2020	Replace policy	Policy updated with literature review through March 31, 2020; no references added. Policy statements unchanged.
September 2021	Replace policy	Policy updated with literature review through March 31, 2021; references added and updated. Policy statements unchanged.