Cardiac Resynchronization Therapy for Mild Congestive Heart Failure

Assessment Program
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Executive Summary

Background

Congestive heart failure (CHF) is common, and rapidly increasing in incidence. CHF carries a poor prognosis, with an estimated 30–50% 1-year mortality for patients with advanced disease. It is also associated with a high burden of illness, high resource utilization, and frequent hospitalizations. The current treatment for CHF involves addressing the underlying cause(s), lifestyle modifications, and pharmacologic interventions. In the majority of cases, treatment is not curative, but intended to ameliorate symptoms and improve function.

Approximately 20–30% of patients with CHF exhibit dyssynchronous contractions of the left and right ventricles due to conduction system disease. Dyssynchrony further depresses the already impaired pumping ability of the heart. Cardiac resynchronization therapy (CRT) is intended to correct dyssynchronous ventricular contractions. CRT uses biventricular pacing to simultaneously stimulate both ventricles in order to achieve coordinated contractions.

CRT therapy has demonstrated benefit in class III and class IV CHF. A systematic review of 9 randomized, controlled trials of CRT for class III/IV CHF concluded that CRT reduced mortality, improved quality of life, and improved functional status. Much of the focus of new research in CRT is to evaluate whether the benefits of CRT extend to patients with less severe heart failure.

Objective

To determine whether cardiac resynchronization therapy improves health outcomes for patients with mild congestive heart failure, defined as New York Heart Association (NYHA) class I or II CHF.

Search Strategy

Electronic search of MEDLINE® (via PubMed) was performed using the keywords “CRT,” “resynchronization,” and “biventricular pacing.” These terms were cross-referenced with “CHF,” “congestive heart failure,” and “cardiomyopathy.” Search was performed from January 1995 through December 2009. Electronic search was supplemented with a hand search of relevant bibliographies and use of the “related articles” function in MEDLINE®.

Selection Criteria

Studies were selected for inclusion that had the following characteristics: 1) randomized, controlled trial; 2) included patients with NYHA class I or II CHF, or included a broader population of CHF patients and reported outcomes separately for the group with class I/II CHF; 3) enrolled at least 25 patients per treatment group; and 4) reported on at least one relevant health outcome.

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Main Results

A total of 3 randomized, controlled trials enrolling 2,616 patients met the inclusion criteria, with follow-up ranging from 6 months to 2.4 years. The largest trial published to date was the MADIT-CRT trial, a single-blind trial that randomized 1,820 patients with class I/II CHF to an ICD alone or an ICD-CRT device. The MADIT-CRT trial reported a reduction for the ICD-CRT group on the primary outcome, i.e., death or acute heart failure exacerbation. The primary endpoint was reached by 17.2% of patients in the ICD-CRT group compared to 25.3% of patients in the ICD-alone group. This composite outcome is suboptimal for several reasons. First, death and hospitalizations represent fundamentally different outcome measures and therefore do not lend themselves to combination. Second, the outcomes occur at different rates, with hospitalizations much more frequent. This makes it likely that the results on hospitalizations will drive the overall results. Finally, the relative risks for these outcomes are not similar, with a large reduction in relative risk for hospitalizations, and no reduction for death.

As a result, it is preferable to examine the results on the individual outcome measures rather than rely on the composite outcome. 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 ICD-CRT group and (relative risk reduction [RRR] 39%, absolute risk reduction [ARR] 8.9%, number needed to treat [NNT] =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.

The REVERSE trial enrolled a total of 610 patients, all of whom received a CRT device. Patients were randomized to CRT-ON or CRT-OFF for a period of 12 months in double-blind fashion. The primary outcome was a composite measure that classified patients as improved, unchanged, or worse. There were no significant differences reported on this primary outcome. There was a decrease in hospitalizations for heart failure in the CRT-ON group (4.1%, 17/419) compared with the CRT-OFF group (7.9%, 15/191). Changes in functional status, as measured by the 6-minute walk, were similar between groups. Quality of life (QoL), as measured by the Minnesota Living with Heart Failure Questionnaire, was also similar between groups.

The MIRACLE ICD study was the smallest of the 3 studies, enrolling 186 patients with class II CHF and an indication for an ICD in an unblinded fashion. Patients were randomized to ICD/CRT-ON versus ICD/CRT-OFF and followed for 6 months. There was no difference in the primary outcome of peak oxygen uptake between groups. There were also no differences reported between groups on the secondary outcomes of functional status as measured by the 6-minute walk, QoL, as measured by the Minnesota Living with Heart Failure Questionnaire, and NYHA CHF class.

All 3 randomized, controlled trials reported significant improvements in echocardiographic measures of left-ventricular (LV) pump function. LV ejection fraction improved more in the CRT group in each trial, with a range of improvement of 3.0–11.0%, compared with the control group. There were also substantial improvements in LV end-systolic and end-diastolic volumes (LVESV, LVEDV) in all 3 trials. All 3 trials reported relatively large improvements in the LVESV and the LVEDV in favor of the CRT group.

Complications in these trials were not uniformly reported; however, each trial contained some information on short- and long-term complications. Short-term complication rates ranged from 4–22%, with lead dislodgement and hematoma at the access site most common. Long-term complications were reported by 2 of the trials, with rates of 16% and 35%. The majority of these long-term complications were lead dislodgement.

The MADIT-CRT trial provides data on a limited set of complications of a combined device versus an ICD alone. There were more complications reported for the combined device compared to ICD alone for pneumothorax (1.7% vs. 0.8%), infection (1.1% vs. 0.8%), hematoma requiring evacuation (3.3% vs. 2.5%), coronary venous dissection (0.5% vs. 0.0%), and LV lead dislodgement (4.0% vs. 0%).

Author's Conclusions and Comments

The available evidence reports benefits on some outcomes, but not on others. As a result, the most challenging analytic aspect of evaluating these data is considering the clinical importance of the different outcomes, and determining whether differences in the subset of outcomes that report benefit represent adequate evidence for improvement in health outcomes when weighed against the risks of the procedure.

The most important outcomes for this treatment are mortality from CHF, progression to more advanced disease, functional status, and quality of life. None of these outcomes showed differences in any of the 3 available trials. In the 2 trials reporting mortality outcomes, one showed a slightly lower rate for the CRT group, while the other showed a slightly lower rate for the control group. For the outcomes of functional status and quality of life, the 2 trials including these outcomes did not report any group differences. Therefore, it can be concluded with a moderately high degree of certainty that CRT in patients with mild CHF does not lead to improvements in mortality, quality of life, or functional status over the short to medium term.

The outcome measures that did show improvement were hospitalizations (or acute "CHF events" in the MADIT-CRT trial) and echocardiographic measures of cardiac morphology and function. Hospitalizations for CHF are an important outcome measure, as a reduction in hospitalizations would be of benefit for the individual patient. Reducing hospitalizations will also prevent the iatrogenic complications associated with hospitalization.

However, for several reasons, this evidence is not definitive in determining whether CRT leads to a health outcome benefit. Hospitalizations, or acute heart failure events, are the most subjective of the outcomes reported in these trials. Hospitalization involves a decision by a treating clinician that involves a substantial degree of judgment. These decisions can be influenced by a number of factors and may not be solely the result of exacerbation of disease. Thresholds for admission to the hospital may vary substantially by individual clinicians and/or geographic regions. As a result, the lack of blinding of clinicians in 2 of the 3 trials represents a potential bias in this outcome measure. This leaves only 1 trial, the REVERSE trial, which reports a difference in hospitalizations that is not prone to bias.

Even if the reported difference in hospitalizations is real, this may not represent a large effect, and the benefit may not outweigh the risks. Using the results reported in REVERSE, there is a relative risk reduction of 48% and an absolute risk reduction of 3.8% for CHF hospitalizations. This translates to a number needed to treat of 26 patients over a period of 1 year to prevent 1 hospitalization. This relatively small benefit in hospitalizations needs to be weighed against the risks of the procedure and the adverse effects of having a CRT device implanted long-term. While the risks of the procedure are uncommon, some may be serious and exceed the benefit of reduced hospitalizations. Minor adverse events, such as lead dislodgement, are more common and may involve some degree of morbidity and repeat procedures.

In the 2 trials that report rates of lead dislodgement, the MIRACLE trial reported a rate of 5.8% over a 6 month period and the REVERSE trial reported a rate of 10.6% over a 1-year period. This would translate roughly to 1 in 10 patients experiencing lead dislodgement over a 1-year period, which is equivalent to a number needed to harm of approximately 10. Thus it appears more likely that a patient will develop lead dislodgement, or another long-term complication, than would prevent a hospitalization.

For patients with indications for an ICD, a combined ICD/CRT device is often used. In this situation, the additional risk of CRT implantation compared to ICD alone is the proper comparison to determine the risks of CRT, and the risk/benefit ratio is shifted more favorably toward CRT use. However, the evidence is not sufficient to estimate the precise rates of incremental complications of a combined device compared with an ICD alone.

The echocardiographic outcomes reported in these trials show consistent, large improvements associated with CRT therapy. However, the clinical importance of these intermediate outcomes is uncertain. While LVEF and other echocardiographic parameters do correlate with mortality in CHF, this correlation has not been shown for patients with a CRT device. It is possible that CRT induces changes in these parameters when measured on echocardiography, but that they do not translate to physiologic improvements.

Finally, if the CRT device is actually leading to better pump function of the heart, this should be evident in other measures of quality of life and functional status. Since none of the available studies report any differences in functional status or quality of life, there is further concern that the improvements in the echocardiographic measures may not be translating into real improvements in health outcomes.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether the use of cardiac resynchronization therapy for class I/II congestive heart failure meets the Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC) criteria.

1. **The technology must have final approval from the appropriate government regulatory bodies.**

U.S. Food and Drug Administration (FDA) indications are limited to patients with class III/IV failure, none of the approved devices currently available have indications for treatment of patients with class I and/or II CHF. Use in mild heart failure, therefore, meets this criterion as an off-label use of an approved device.

One stand-alone biventricular pacemaker (InSync® Biventricular Pacing System, Medtronic) has received approval by the FDA 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 msec and a left ventricular ejection fraction of ≤35%. Biventricular pacemakers have also been combined with implantable cardiac defibrillators (ICDs). Both Guidant (CONTAK CD® CRT-D System) and Medtronic (InSync® ICD Model 7272) have received FDA approval for combined cardiac resynchronization therapy 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 left ventricular ejection fraction of 35% or less, QRS duration ≥130 msec (≥120 msec for the Guidant device) and remain symptomatic despite a stable, optimal heart failure drug therapy.

At the time this Assessment went to press, the FDA Circulatory System Devices Advisory Panel voted unanimously to recommend approval of CRT devices for use in mild heart failure. The indications proposed by the FDA Advisory Panel include patients in NYHA functional class II or in patients with class I ischemic heart failure with an LVEF <30% and a QRS duration >130 ms. Also added was a requirement that eligible patients also have left-bundle-branch block (LBBB). Note that recommendation of approval does not constitute final approval.

2. **The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

The evidence is sufficient to permit conclusions concerning the effect of CRT on mortality, functional status and quality of life. For each of these 3 outcome measures, at least 2 of the 3 randomized, controlled trials reported on this outcome. For each outcome, there were no group differences, and there was no apparent trend toward improvement in the CRT group. Therefore, conclusions on these outcome measures can be made over the period of time covered by the study.

The evidence is also sufficient to determine the effect of CRT therapy on echocardiographic parameters while the device is on. The evidence from the included studies is consistent in reporting an improvement in LVEF and LV volumes over the first year of therapy with the CRT device continuously on. The evidence is not sufficient to determine whether these changes represent structural changes in the heart that would persist in absence of the CRT device turned on.

The evidence is not sufficient to permit conclusions on the effect of CRT on hospitalizations. Although this outcome was reported by 2 trials, it is a more subjective outcome that can be influenced by knowledge of group assignment. The MADIT-CRT trial was the largest trial and was single blinded. As a result, there is potential for bias on the outcome of hospitalizations, leaving only one trial that was double blinded and thus avoided this potential bias.

3. The technology must improve the net health outcome.

For the outcomes of mortality, functional status, and quality of life, the evidence does not support the conclusion that the net health outcome is improved. For these outcomes, there were no improvements associated with CRT therapy. Therefore, it can be concluded with a moderately high degree of certainty that there is not improvement in these outcomes over the 1- to 2-year time period covered by these studies.

For the outcome of hospitalizations, the evidence is not sufficient to permit conclusions. For the echocardiographic outcomes, the evidence is not sufficient to conclude that the net health outcome is improved. This is because it is not certain that these changes in cardiac morphology and function translate to physiologic benefits that can be experienced by the patient.

4. The technology must be as beneficial as any established alternatives.

The evidence is not sufficient to determine whether the net health outcome is improved, therefore it cannot be determined whether the technology is as beneficial as alternatives.

5. The improvement must be attainable outside the investigational settings.

Whether CRT for mild heart failure improves health outcomes has not been demonstrated in the investigational setting.

For the above reasons, the use of cardiac resynchronization therapy for class I/II congestive heart failure does not meet the TEC criteria.

Contents

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Assessment Objective

The overall objective of this Assessment is to determine whether cardiac resynchronization therapy (CRT) improves health outcomes for patients with mild congestive heart failure (CHF). For the purposes of this Assessment, mild CHF will be defined as patients with New York Heart Association (NYHA) class I and II heart failure. Current treatment for mild CHF consists of lifestyle modifications and medications.

CRT is intended to improve pump function in patients with CHF and dyssynchronous ventricular contractions. Dyssynchrony occurs in approximately 20–30% of patients with CHF as a result of damage to the conduction system of the heart. The CRT device consists of a small pulse generator implanted subcutaneously, connected to pacemaker leads in the right atrium and both ventricles. CRT therapy has demonstrated benefit for patients with advanced CHF (NYHA class III and IV), with prior randomized, controlled trials reporting improvements in mortality, functional status, and quality of life (QoL).

The most important health outcome measures in research on CHF are mortality, improvement in functional status and QoL, and delay of progression to more advanced disease. In addition, CRT may lead to "reverse remodeling," or favorable changes in cardiac morphology and function. Most research on CRT has incorporated measures of cardiac morphology and function determined by echocardiography, in order to assess whether there is evidence for reverse remodeling. These echocardiographic parameters are physiologic measures that may or may not be linked to health outcomes. If so, these improvements in pump function would then be expected to lead to improvements in functional status and QoL, and a decrease in acute CHF exacerbations and hospitalizations. If reverse remodeling occurs, progression to more advanced classes of CHF may be delayed. These echocardiographic outcomes are not sufficient to demonstrate clinical benefit in the absence of improvement in health outcomes.

Background

CHF is a disorder of abnormal pump function, in which the heart is unable to generate sufficient output to meet physiologic needs. It is characterized by poor tissue perfusion, organ hypoxemia, and fluid retention. A variety of symptoms can occur, which result from poor oxygen delivery, fluid retention, and congestion of visceral organs. For example, shortness of breath with exertion results from poor oxygen delivery and fluid accumulation in the lungs. Peripheral edema represents leakage of fluid into the extravascular space with accumulation in dependent regions of the body. A variety of other symptoms are related to these physiologic abnormalities, including progressive organ dysfunction of the liver, kidney, and central nervous system.

The severity of CHF is usually assessed using the NYHA class system (Table 1). This classifies patients into class I–IV CHF based on symptoms and functional status. As shown in this table, patients with class I CHF are essentially asymptomatic, while patients with class IV CHF are symptomatic even at rest. Class III/IV CHF is often considered advanced disease, while class I/II can be considered mild disease.

CHF is common, and rapidly increasing in incidence, despite a reduction in the incidence and mortality of heart disease overall (NHLBI Chartbook 2007). There are over 500,000 cases of CHF diagnosed each year in the U.S. and more than 5 million individuals are living with CHF (Tang et al. 2008). CHF carries a poor prognosis, with an estimated 30–50% 1-year mortality for patients with advanced CHF (McAlister et al. 2004a, 2004b). The majority of deaths in CHF arise from ventricular arrhythmias. Progressive pump failure is the other main reason for death in CHF.

CHF is also associated with a high burden of illness. CHF leads to major impairments in functional status. Patients with advanced CHF (class III/IV) are unable to perform even simple activities of daily living without symptoms. Symptoms and decreased functional status lead to impaired QoL. CHF is also associated with high degrees of resource utilization. There are over 1 million hospitalizations each year, and CHF is currently the most common discharge diagnosis in the U.S. for elderly patients (Tang et al. 2008).

The current treatment for CHF involves addressing the underlying cause(s), lifestyle modifications, and pharmacologic interventions. Underlying causes of CHF may be related to chronic ischemia, valvular abnormalities, and/or myocardial disease. Treating the underlying cause of CHF, if possible, is crucial to optimal management of these patients. Lifestyle

Table 1. New York Heart Association Classification of CHF

Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

changes are recommended for all patients with CHF; these include salt and fluid restriction, and sometimes exercise therapy. Medications with established benefit in CHF include ACE inhibitors, angiotensin-receptor blockers, beta-blockers, diuretics, and aldosterone antagonists. For advanced heart failure, other treatment options exist, such as left-ventricular assist devices and cardiac transplantation. However, for mild heart failure, these aggressive interventions are generally not an option.

Some patients with CHF also have abnormalities in the conduction system of the heart. In the normal heart, the electrical system coordinates contractions of the atria and ventricles through the sinus node, the AV node, and the His-Purkinje system in the ventricles. Coordinated contractions of the atria and ventricle maximize pump function and ejection fraction.

Approximately 20–30% of patients with CHF exhibit dyssynchronous ventricular contractions due to conduction system disease. The EKG in these patients will generally show a prolonged QRS complex, indicating intraventricular conduction delay. Dyssynchrony further depresses the already impaired pumping ability of the heart. Abnormal contraction reduces diastolic filling and causes an increase in left ventricular volume, leading to progressive ventricular dilatation (Hasan and Abraham 2007). This phenomenon of progressive ventricular dilatation and worsening pump function in CHF is called "structural remodeling." Dyssynchrony may further impair pump function by inducing mitral regurgitation, or exacerbating pre-existing mitral regurgitation (Hasan and Abraham 2007).

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is intended to correct dyssynchronous contractions of the left and right ventricles in patients with CHF. CRT uses biventricular pacing to simultaneously stimulate both ventricles in order to achieve coordinated contractions.

The CRT device involves 3 pacemaker leads, one in the right atrium and one in each ventricle. The pacer leads are connected to a pulse generator implanted subcutaneously in the chest wall. The procedure to implant a CRT device differs from a simple pacemaker in that an additional pacer lead is placed in the left ventricle. The placement of a pacemaker in the left ventricle can sometimes be technically difficult, since it involves cannulation of the coronary sinus.

There are risks of device implantation, many of which similar to implantation of a simple pacemaker or ICD. These include local complications at the site of percutaneous access such as bleeding, hematoma and infection. There are also small risks of more serious cardiac complications. Perforation of the myocardial wall can lead to pericardial effusion, which may cause tamponade requiring intervention. Irritation of the myocardium can lead to arrhythmias. Myocardial infarction and thromboembolism can also occur as a complication of this procedure. However, CRT is likely to have additional complications related to LV pacer lead placement.

CRT therapy has demonstrated benefit in class III and class IV CHF. A summary of the larger trials of CRT in advanced heart failure is given in Table 2. The COMPANION trial (Bristow et al. 2004), which had the highest enrollment and the longest follow-up, reported a significant improvement in mortality. The other trials reported lower mortality for the CRT group that did not reach statistical significance. Four of the 5 trials reported changes on functional status, with all 4 reporting significant improvements for

Table 2. Summary of Larger Randomized, Controlled Trials Evaluating CRT in NYHA Class III/IV CHF

				Outcomes			
Study/year	Follow-up	Group	N	Mortality	Hospitalizations	Δ MLWHF score*	Δ 6-min walk (m)
Cleland et al. 2005 (CARE-HF)	29.4 months	CRT	409	20.0% (82/409)	17.6% (72/409)	31 ± 22**	NR
		Medical therapy	404	29.7% (120/404)	32.9% (133/404)	40 ± 22**	NR
				p<0.002	p<0.001	p<0.001	
Bristow et al. 2004 (COMPANION)	12 months	CRT	617	21.2% (131/617)	NR	-25 ± 26	+40 ± 96
		Medical therapy	308	25.0% (77/308)	NR	-12 ± 23	+1 ± 93
				NS		p<0.001	p<0.001
Higgins et al. 2003 (CONTAK-CD)	6 months	CRT + ICD	245	4.5% (11/245)	13.1% (32/245)	NR	+35 ± 7
		ICD alone	245	6.5% (16/245)	15.9% (39/245)	NR	+15 ± 7
				NS	NS		p=0.04
Young et al. 2003 (MIRACLE-ICD)	6 months	CRT + ICD	187	7.5% (14/187)	45.5% (85/187)	-17 (-21 to -13)	+54.5 (+40 to +75)
		ICD alone	182	8.2% (15/182)	42.9% (78/182)	-11 (-16 to -6)	+52 (+40 to +74)
				NS	NS	p<0.02	NS
Abraham et al. 2002 (MIRACLE)	6 months	CRT-ON	228	5.3% (12/228)	7.9% (18/228)	-18 (-22 to -12)	+39 (+26 to +54)
		CRT-OFF	225	7.1% (16/225)	15.1 % (34/225)	-9 (-12 to -5)	+10 (0 to +25)
				NS	p<0.05	p<0.001	p<0.005

* Minnesota Living with Heart Failure (MLWHF) QoL scale, 0-100 score with higher scores reflecting worse QoL
** Final score on the MLWHF questionnaire
Abbreviations: NR: not reported; NS: not significant

the CRT group. Similarly, 4 of the trials reported QoL measures, with all 4 showing significant improvements for the CRT group. Hospitalizations were reduced in 2 of the 4 trials, with an additional 2 trials reporting no difference in hospitalizations.

A systematic review of 9 randomized, controlled trials of CRT in class III/IV CHF was published in 2004 (McAlister et al. 2004a, 2004b). This quantitative analysis revealed the following conclusions: 1) improvement of 3.5% in LVEF; 2) improved QoL, with weighted mean difference on the Minnesota Living with Heart Failure Questionnaire of 7.6 points (0–100 scale); 3) improved functional capacity and a reduction in all-cause mortality of 21%. This analysis also found some evidence that cardiac morphology may be improved, suggesting that CRT may prevent, delay, or even reverse the anatomic changes that result from chronic CHF (reverse remodeling).

There is a current trend in clinical care to use a combined CRT/ICD device, as the indications for both devices often overlap. A combined device can be implanted in a single procedure, and is thus an attractive option for clinicians and patients who have indications for these interventions.

Much of the focus of new research in CRT is to evaluate whether the benefits of CRT extend to patients with less severe heart failure. The rationale behind implantation of CRT in early heart failure is to delay or prevent the progression to more advanced stages by optimizing pump function and preventing structural remodeling of the ventricles. CRT may also improve symptoms and functional status in patients with mild heart failure. However, by definition, patients with mild heart failure may be asymptomatic or have only mild symptoms, thus reducing the potential for improvement on these parameters.

FDA Status. One stand-alone biventricular pacemaker (InSync® Biventricular Pacing System, Medtronic) has received approval by the U.S. Food and Drug Administration (FDA) 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 msec and a left ventricular ejection fraction of ≤35%. Biventricular pacemakers have also been combined with implantable cardiac defibrillators (ICDs). Both Guidant (CONTAK CD® CRT-D System) and Medtronic (InSync® ICD Model 7272) have received FDA approval for combined cardiac resynchronization therapy 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 left ventricular ejection fraction of 35% or less, QRS duration ≥130 msec (≥120 msec for the Guidant device) and remain symptomatic despite a stable, optimal heart failure drug therapy.

At the time this Assessment went to press, the FDA Circulatory System Devices Advisory Panel voted unanimously to recommend approval of CRT devices for use in mild heart failure (Stiles 2010). The indications proposed by the FDA Advisory Panel include patients in NYHA functional class II or in patients with class I ischemic heart failure with an LVEF <30% and a QRS duration >130 ms. Also added was a requirement that eligible patients also have left-bundle-branch block (LBBB). Note that recommendation of approval does not constitute final approval.

Methods

Search Methods

Electronic search of MEDLINE® (via PubMed) was performed using the keywords "CRT," "resynchronization," and "biventricular pacing." These terms were cross-referenced with "CHF," "congestive heart failure," and "cardiomyopathy." Search was performed from January 1995 through December 2009. Electronic search was supplemented with a hand search of relevant bibliographies and use of the "related articles" function in MEDLINE®.

Study Selection

Studies were selected for inclusion that had the following characteristics:

- randomized, controlled trial
- included patients with NYHA class I or II CHF, or included a broader population of CHF patients and reported outcomes separately for the group with class I/II CHF
- enrolled at least 25 patients per treatment group
- reported on at least one relevant health outcome

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory

Panel (MAP) on December 17, 2009. In order to maintain the timeliness of the scientific information in this Special Report, literature searches were performed subsequent to the Panel's review (see "Search Methods"). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no studies that would change the conclusions of this Assessment.

Formulation of the Assessment

Patient Indications

For the purpose of this Assessment, patient indications are individuals with mild CHF. This is defined as having NYHA class I or II CHF. For more advanced stages of CHF, benefit of CRT has already been demonstrated, and patients with advanced heart failure will not be addressed as part of this Assessment.

Technologies to be Compared

CRT therapy will be compared to optimal medical therapy. For advanced heart failure, other treatment options exist, such as left-ventricular assist devices and cardiac transplantation. However, for mild heart failure, these other interventions are not an option and treatment consists of medical therapy and lifestyle changes.

Health Outcomes

Evidence will be sought for the effect of CRT on health outcomes that are most important for the patient with CHF. These include:

- mortality from heart failure
- progression to more advanced stages of CHF
- functional status
- quality of life
- hospitalizations for exacerbations of heart failure

Echocardiographic parameters are physiologic measures that may or may not be linked to important health outcomes. These measures can be confirmation that treatment affects the physiologic parameter for which it is intended, and can corroborate that differences in are the result of changes in cardiac function. However, these outcomes alone are not sufficient evidence of a health outcome benefit in the absence of improvements in clinical parameters. The most common echocardiographic outcomes reported in these trials are measures of pump function and ventricular dilatation:

- left-ventricular ejection fraction (LVEF)
- left-ventricular end-systolic volume (LVESV)
- left-ventricular end-diastolic volume (LVEDV)

Specific Assessment Question

In patients with class I or II CHF and dyssynchronous ventricular contractions, does CRT improve health outcomes, as compared to optimal medical therapy?

Review of Evidence

There were a total of 3 randomized, controlled trials that met the inclusion criteria for this Assessment (Abraham et al. 2004; Linde et al. 2008; Moss et al. 2009; Tables 3 and 4). Total enrollment in these trials was 2,616 participants, with the respective individual trials enrolling 186, 610, and 1,820 participants. Follow-up ranged from 6 months to 2.4 years. Each trial reported similar, but not identical, outcome measures. These outcome measures included mortality, acute exacerbations of CHF, functional status, quality of life (QoL), and echocardiographic measures of pump function.

Table 3. Randomized, Controlled Trials of CRT in Mild CHF: Study Characteristics

Study/yr	Patient Population	Protocol	Age	LVEF	MLWHF Score	6-min Walk	Outcomes	Comments
Abraham et al. 2004	▪ NYHA class II CHF for at least 3 months ▪ Sinus rhythm with QRS duration ≥130 msec ▪ LVEF ≤35% ▪ LV end-diastolic diameter ≥55 mm ▪ Indication for ICD	▪ All pts implanted with dual ICD/CRT device ▪ Pts randomized to CRT on or off ▪ Double-blinded; independent MD performed all tests that could reveal device status ▪ Follow-up at 1, 3, 6 months	63.1	24.5%	40.7	370.2 m	**Primary** Change in peak oxygen uptake with exercise **Secondary** NYHA class 6-minute walk QOL LVEF LV volume Composite response*	
Linde et al. 2008 (REVERSE)	▪ NYHA class I or II CHF for at least 3 months ▪ Sinus rhythm with QRS duration ≥120 msec ▪ LVEF ≤40% ▪ LV end-diastolic diameter ≥55mm ▪ On optimal medical therapy including ACE inhibitors and beta-blockers	▪ All pts had CRT inserted at baseline ▪ Pts randomized to CRT-ON or CRT-OFF in 2:1 ratio ▪ Double-blinded; independent MD performed all tests that could reveal device status ▪ Follow-up at 1,3, 6, and 12 months ▪ CRT status maintained for 12 months ▪ Crossover allowed for chronic worsening of CHF to NYHA III or IV	62.6	26.7 ± 7.0%	27.6 (0–100 score)	396 m	**Primary** Classified into 1 of 3 response groups: improved, unchanged or worsened** **Secondary** Left-ventricular end-systolic volume index	Implantation success rate of 97%

* Pt assigned to 1 of 3 response categories: improved, unchanged, worsened. Criteria for assigning categories not reported.
** Improved – demonstrated improvement in NYHA functional class, and/or reported moderately or markedly improved heart failure symptoms at 12-month follow-up
Unchanged – did not meet criteria for either improved or worsened
Worsened – died, were hospitalized anytime during 12mth follow-up, crossed over to alternate treatment, permanently discontinued double-blind treatment because of worsening CHF, demonstrated worsening in NYHA class at 12-month follow-up, or reported moderately or markedly worse heart failure symptoms

Table 3. Randomized, Controlled Trials of CRT in Mild CHF: Study Characteristics (cont'd)

Study/yr	Patient Population	Protocol	Age	LVEF	MLWHF Score	6-min Walk	Outcomes	Comments
Moss et al. 2009 (MADIT-CRT)	▪ Ischemic cardiomyopathy with NYHA class I or II CHF, or nonischemic cardiomyopathy with class II CHF ▪ Sinus rhythm with QRS duration ≥130 msec ▪ LVEF ≤30%	▪ Pts randomized to CRT-ICD or ICD alone in 3:2 ratio ▪ Single-blinded, treating physicians not blinded to treatment assignment ▪ Follow-up at 1, 3, 6, 9, 12 months	64.6	24 ± 5%	NR	361 m	**Primary** Composite of death from any cause or nonfatal heart failure events*** **Secondary** LVEF LV end-diastolic volume LV end-systolic volume	Implantation success rate of 98.4% for device. 7.5% of pts assigned to CRT-ICD could not have CRT implanted due to technical difficulties, analyzed in ICD group

*** Heart failure events – Signs and symptoms consistent with congestive heart failure that was responsive to intravenous decongestive therapy on an outpatient basis or an augmented decongestive regimen with oral or parenteral medications during an inpatient stay

Table 4. Randomized, Controlled Trials of CRT in Mild CHF: Outcomes

Study/yr	F/U	Group	N	Primary Endpoint		Death	Hospitalization for CHF	Δ6-min Walk	ΔQOL	Echocardiographic Parameters		
Abraham et al. 2004	6 months			Δoxygen uptake						Δ LVEF	Δ LVESV	Δ LVEDV
		ICD-CRT	85	0.5 ± 3.2		NR	NR	38 ± 109	-13.3 ± 25.1	3.8 ± 8.0	-42 ± 77	-41 ± 76
		ICD alone	101	0.2 ± 3.2		NR	NR	33 ± 98	-10.7 ± 21.7	0.8 ± 6.2	-14 ± 57	-16 ± 62
		p value		NS				NS	NS	0.02	0.01	0.04
Linde et al. 2008 (REVERSE)	12 months			Worse Impr/Unch						Δ LVEF	ΔLVESV	ΔLVEDV
		CRT-ON	419	16% (67/419)	84% (352/419)	2.2% (9/419)	4.1% (17/419)	13 ± 102 m	-8.4 ± 17	+4.1%	-18.4 ± 30 mL/m2	-22 mL/m2
		CRT-OFF	191	21% (40/191)	79% (151/191)	1.6% (3/191)	7.9% (15/191)	19 ± 105 m	-6.7 ± 16	+0.6%	-1.3 ± 23 mL/m2	-1 mL/m2
		p value		NS		NS	0.03	NS	NS	<0.0001	<0.0001	<0.0001
Moss et al. 2009 (MADIT-CRT)	2.4 yrs (echo results done at 12-month follow-up visit)			Death/heart failure			CHF events					
		ICD-CRT	1089	17.2% (187/1089)		6.8% (74/1089)	13.9% (151/1089)	NR	NR	+11%	-57 mL	-52 mL
		ICD alone	731	25.3% (185/731)		7.3% (53/731)	22.8% (167/731)	NR	NR	+3%	-18 mL	-15 mL
		p value		<0.001		NS	<0.001*			<0.001	<0.001	<0.001

LVESV – left ventricular end-systolic volume; LVEDV – left ventricular end-diastolic volume
* Calculated unadjusted chi-square value; statistical test not reported in publication

The largest trial completed to date is the MADIT-CRT trial (Moss et al. 2009), which randomized 1,820 patients with class I/II CHF to an ICD alone or an ICD-CRT device. The trial was single-blinded, with patients unaware of group assignment but clinicians aware of group assignment. Patients were followed for an average of 2.4 years. There were a fairly high percent of patients (14.9%) who dropped out or crossed over, with a total of 173 crossovers (9.5%) and 99 dropouts (5.4%). These dropouts/crossovers were not equally balanced between groups. The ICD-alone group had a dropout/crossover rate of 20% (146/731) compared to a rate of 11.6% (126/1,089) for the ICD-CRT group. This trial received a quality rating of fair (Appendix Table A), due to the limitations of no double blinding and high dropouts/crossover.

The MADIT-CRT trial reported a reduction for the ICD-CRT group on the primary outcome, i.e., death or acute heart failure exacerbation. The primary endpoint was reached by 17.2% of patients in the ICD-CRT group compared to 25.3% of patients in the ICD-alone group. This represents a relative risk reduction (RRR) of 32%, an absolute risk reduction (ARR) of 8.1%, and a number needed to treat (NNT) of 12.3 over a period of 2.4 years to prevent 1 event.

The difference in the primary composite outcome was due entirely to differences in acute heart failure events, which occurred in 13.9% of patients in the ICD-CRT group compared to 22.8% of patients in the ICD-alone group (RRR 39%, ARR 8.9%, NNT=11.2). The death rate was similar between groups, 3.3 % (36/1,089) of patients in the ICD-CRT group compared to 2.5% (18/731) of patients in the ICD-alone group. Death at any time was also similar between groups, with 8.9% (53/1,089) of patients in the ICD-CRT group dying at any time during the trial compared to 8.7% (35/731) of patients in the ICD-alone group.

Although MADIT-CRT collected data on functional status and QoL, these data had not been reported at the time of this Assessment. Echocardiographic outcomes were reported for a subset of 1,366 patients (746 in ICD-CRT and 620 in ICD-alone) at the 1 year follow-up time point. These paired echocardiographic measures performed at baseline and at 1 year follow-up reported significant improvements in LVEF, LVESV, and LVEDV.

Complications reported in this trial are summarized in Tables 5 and 6. The most common periprocedural complications reported were hematoma at the access site (4.0%) and lead dislodgement (3.3%). Less common complications were pneumothorax, coronary dissection, and infection. Long-term complications were not reported for each complication, rather a composite rate of 4.5/100 device-months was provided. This complication rate would equal roughly 1 event per patient for every 2 years of device implantation.

The REVERSE trial (Linde et al. 2008) enrolled a total of 610 patients, all of whom received a CRT-device. Patients were randomized to CRT-ON or CRT-OFF for a period of 12 months in double-blind fashion, with both patients and treating clinicians unaware of group assignment. This trial met all of the quality parameters and was assigned a good rating (Appendix Table A).

The primary outcome was a composite measure that classified patients as improved, unchanged, or worse. There was no significant difference reported on this primary outcome. The percent of patients who were worse at the end of the trial was 16% in CRT-ON group compared with 21% in the CRT-OFF group (p=0.10).

There was a decrease in hospitalizations for heart failure in the CRT-ON group (4.1%, 17/419) compared with the CRT-OFF group (7.9%, 15/191). There was a significant decrease in time to first hospitalization for heart failure in the CRT-ON group (HR 0.47, p=0.03).

Changes in functional status, as measured by the 6-minute walk, were similar between groups. QoL, as measured by the Minnesota Living with Heart Failure Questionnaire, was also similar between groups.

The overall periprocedural complication rate reported by patient was 4.0% (Table 5). The most common complication reported was arrhythmia, which occurred at a rate of 1.2%. Other complications that occurred at a rate of less than 1% were pneumothorax, coronary dissection, pericardial effusion, and tamponade. Long-term complications, occurring between 30 days and 12 months post-implantation, were present for 16% of patients (Table 6). The majority of these long-term complications were lead dislodgements, which occurred in 10.6% of patients. Other reported long-term

Table 5. Short-term Complications of CRT Device Implantations (<30 days)

Study/yr	Total Periop	Hematoma	Pneumo-thorax	Thrombo-embolism	Coronary Dissection	Arrhythmia	Lead Dislodge	Pericard Effusion	Tamponade	Infection
Moss et al. 2009*	NR	3.3% (36/1089)	1.7% (18/1089)	NR	0.5% (5/1089)	NR	4.0% (44/1089)	NR	NR	1.1% (12/1089)
Linde et al. 2008**	4% (26/642)	NR	0.6% (4/621)	NR	0.5% (3/621)	1.2% (8/621)	NR	0.2% (1/621)	0.2% (1/621)	NR
Abraham et al. 2004**	22% (46/210)	NR	NR	NR	1.4% (3/210)	NR	2.3% (5/210)	1.4% (3/210)	NR	NR

* Complications reported for group of patients receiving ICD-CRT
** Complications reported for entire cohort of patients enrolled in trial (CRT-ON + CRT-OFF)

Table 6. Long-term Complications of CRT Device Implantations (>30 days)

Study/yr	Total Complications	Lead Dislodge	Hematoma	Thrombo-embolism	Diaphragm Irritation	Arrhythmia	Pericardial Effusion
Moss et al. 2009*	4.5/100 device-months	NR	NR	NR	NR	NR	NR
Linde et al. 2008**	16% (101/621)	10.6% (66/621)	0.8% (5/621)	0.5% (3/621)	2.3% (14/621)	1.3% (8/621)	0.6% (4/621)
Abraham et al. 2004**	35% (66/191)	5.8% (11/191)	NR	NR	1.6% (3/191)	NR	0.5% (1/191)

* Complications reported for group of patients receiving ICD-CRT
** Complications reported for entire cohort of patients enrolled in trial (CRT-ON + CRT-OFF)

complications were pneumothorax, hematoma, diaphragmatic irritation, and pericardial effusion.

The MIRACLE ICD study (Abraham et al. 2004) was the smallest of the 3 studies, enrolling 186 patients with class II CHF and an indication for an ICD. Patients were randomized to ICD/CRT-ON versus ICD/CRT-OFF and followed for 6 months. The primary outcome for this study was the change in peak oxygen uptake. Other more clinically relevant outcomes such as functional status and QoL were reported as secondary outcomes. This trial was rated fair (Appendix Table A), with the limitations noted of suboptimal outcome measures and short length of follow-up.

There was no difference in the primary outcome of peak oxygen uptake between groups. There were also no differences reported between groups on the secondary outcomes of functional status as measured by the 6-minute walk, QoL as measured by the Minnesota Living with Heart Failure Questionnaire, and NYHA CHF class.

This trial reported higher complication rates compared to the other 2. A periprocedural complication rate of 22% was reported (Table 5), with the most common events being coronary dissection, lead dislodgement, and pericardial effusion. Long-term complications occurring between 30 days and 6 months post-implantation were reported for 35% of patients. These long-term complications included lead dislodgement, coronary dissection, and diaphragmatic irritation.

All 3 randomized, controlled trials reported significant improvements in echocardiographic measures of LV pump function (Table 4). LV ejection fraction improved more in the CRT group in each trial, with a range of improvement of 3.0–11.0% compared with the control group. There were also substantial improvements in LV end-systolic and end-diastolic volumes (LVESV and LVEDV) in all 3 trials. All 3 trials reported relatively large improvements in the LVESV and the LVEDV in favor of the CRT group.

A separate publication from the REVERSE trial evaluated a subset of patients with repeat echocardiographic measures when the device was turned off (St John Sutton et al. 2009). Paired echocardiographic measures were available for 503 of the 610 patients randomized. Patients in the CRT-ON group had echocardiography repeated after CRT had been off for 10 minutes. At baseline, mean LVEF for patients in the CRT-ON group was 27.2 +/- 6.6%. At 12 months' follow-up, the LVEF had increased by 4.1% to 31.8 +/- 8.8%. Following turning CRT off for 10 minutes, the LVEF decreased slightly to 30.8 +/- 8.8%. Similar findings were found for other echocardiographic outcomes, including LVESV and LVEDV.

Discussion

There is a limited amount of evidence available to evaluate whether CRT therapy improves outcomes in mild CHF (Appendix Table B). The 3 available trials were moderate-sized randomized, controlled trials with follow-up ranging from 6 months to 2.4 years. One of the trials, the REVERSE trial, met all quality indicators and received a quality rating of good, while the other 2 trials had some methodologic limitations and were rated as fair quality.

The available evidence reports benefits on some outcomes, but not on others. As a result, the most challenging analytic aspect of evaluating these data is considering the clinical importance of the different outcomes, and determining whether differences in the subset of outcomes that report benefit represent adequate evidence for improvement in health outcomes when weighed against the risks of the procedure.

The most important outcomes for this treatment are mortality from CHF, progression to more advanced disease, functional status, and quality of life. None of these outcomes showed differences in any of the 3 available trials. While the trials were likely underpowered to detect differences in mortality, there were not any trends suggesting the lack of improvement in mortality was due to lack of power. In the 2 trials that reported mortality outcomes, one showed a slightly lower rate for the CRT group while the other showed a slightly lower rate for the control group.

For the outcomes of functional status and quality of life, the 2 trials including these outcomes did not report any group differences. As with the mortality outcomes, there were no obvious trends noted in the data suggesting that a larger trial with longer follow-up might reveal differences on these outcomes. Therefore, it can be concluded with a moderately high degree of certainty that

CRT in patients with mild CHF does not lead to improvements in mortality, quality of life, or functional status over the short to medium term.

Furthermore, the evidence does not demonstrate benefit on progression of clinical heart failure, although this outcome measure was only evaluated in 1 of the 3 trials. None of the 3 studies reported any improvement in the percent of patients who progressed to more advanced heart failure, nor do the data show an improvement in NYHA class. It is possible that progression to more advanced disease requires studies of longer duration to show an effect; however, this remains to be determined.

The outcome measures that did show improvement in these trials were hospitalizations for CHF (or acute "CHF events" in the MADIT-CRT trial) and echocardiographic measures of cardiac morphology and function. Hospitalization for CHF is an important outcome measure as a reduction in hospitalizations would be of benefit for the individual patient. Reducing hospitalizations will also prevent the iatrogenic complications associated with hospitalization. However, for several reasons, this evidence is not definitive in determining whether CRT leads to a health outcome benefit.

Hospitalizations, or acute heart failure events, are the most subjective of the outcomes reported in these trials. This outcome is dependent on discretionary decisions made by clinicians in the course of clinical care. The decision to hospitalize a patient, or to provide intensive treatment for a heart failure event, can be influenced by a variety of factors. As a result, the lack of blinding of clinicians making this decision in the Moss and colleagues study represents a potential bias in this outcome measure. Thus, the confidence that this reported difference in hospitalizations is valid is reduced for the largest trial to date. This leaves only 1 trial, the REVERSE trial, which reports a difference in hospitalizations that is not prone to bias.

Even if the reported difference in hospitalizations is real, this may not represent a large effect. The relative risk reduction in hospitalizations is fairly large, but the absolute benefit is smaller, since only a minority of patients with mild CHF are hospitalized over a 1- to 2-year period. Using the results reported in REVERSE, there is a relative risk reduction of 48% and an absolute risk reduction of 3.8% for CHF hospitalizations. This translates to a number needed to treat of 26 patients over a period of 1 year to prevent 1 hospitalization.

This relatively small benefit in hospitalizations needs to be weighed against the risks of the procedure and the adverse effects of having a CRT device implanted long-term. While the risks of the procedure are uncommon, some may be serious and exceed the benefit of reduced hospitalizations. These uncommon events, such as coronary dissection and pericardial effusion with tamponade, could lead to a high degree of morbidity for some patients and may even be life-threatening. Minor adverse events, such as lead dislodgement, are more common and may involve some degree of morbidity and repeat procedures.

In the 2 trials that report rates of lead dislodgement, the MIRACLE trial reported a rate of 5.8% over a 6-month period and the REVERSE trial reported a rate of 10.6% over a 1-year period. This would translate roughly to 1 in 10 patients experiencing lead dislodgement, or a number needed to harm (NNH) of 10, over a 1-year period. Thus it appears more likely that a patient will develop lead dislodgement, or another long-term complication, than would prevent a hospitalization.

A further issue to consider in the risk/benefit ratio is whether or not the patient has indications for an ICD. If this is the case, a combined device is most appropriate, and the complications ascribed to CRT might be considered to be the additional complications of a combined device compared to an ICD alone. The additional complications associated with CRT implantation will largely be related to placement of the pacer leads. In this analysis, the benefit/risk ratio will be shifted more favorably towards CRT. However, the precise incremental rate of complications is difficult to determine from the available data. The MADIT-CRT trial provides data on a limited set of complications of a combined device versus an ICD alone. There were more complications reported for the combined device compared to ICD alone for pneumothorax (1.7% vs. 0.8%), infection (1.1% vs. 0.8%), hematoma requiring evacuation (3.3% vs. 2.5%), coronary venous dissection (0.5% vs. 0.0%), and LV lead dislodgement (4.0% vs. 0%). Statistical testing was not performed for any of these adverse event comparisons.

The balance of risks and benefits for this procedure is, therefore, not entirely clear. In order to properly weigh the benefits of reduced hospitalizations against the risks of the procedure, patients' values and utilities should be taken into account. While some patients may decide that the risk is worth the benefit, others may not. A balance table (Appendix Table C) presents the balance of outcomes in tabular form.

The echocardiographic outcomes reported in these trials show consistent, large improvements associated with CRT therapy. The difference in LVEF of 4–11% represents a substantial improvement in ejection fraction for these patients who have a baseline ejection fraction ranging from 24–27%. The improvements in LV volume are also of a relatively large magnitude.

However, the importance of these echocardiographic outcomes is uncertain. These are intermediate outcomes in which the link to the important health outcomes is not definite. While LVEF and other echocardiographic parameters do correlate with mortality in CHF, this correlation has not been shown for patients with a CRT device. It is possible that CRT induces changes in these parameters when measured on echo, but that they do not translate to physiologic improvements.

The hypothesis that CRT prevents structural remodeling in CHF, or that CRT leads to reverse remodeling has not been proven. All of the main outcome data contained in the 3 trials was obtained with the device on. The REVERSE trial did attempt to perform paired echocardiographic measures at baseline and 1 year, the first with the device on and the second with the device off. The authors reported that the morphologic changes and improvement in ejection fraction did not immediately revert to baseline when the CRT device was turned off for a short period of 10 minutes. It is not known, however, whether there would be a more gradual return to baseline if the device was left off for longer periods of time.

Finally, if the CRT device is actually leading to better pump function of the heart, this should be evident in other measures of QoL and functional status. Since none of the available studies report any differences in functional status or QoL, there is further concern that the improvements in the echocardiographic measures may not be translating into real improvements in health outcomes.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether the use of cardiac resynchronization therapy (CRT) for class I/II congestive heart failure meets the Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC) criteria.

1. **The technology must have final approval from the appropriate government regulatory bodies.**

U.S. Food and Drug Administration (FDA) indications are limited to patients with class III/IV failure, none of the approved devices currently available have indications for treatment of patients with class I and/or II CHF. Use in mild heart failure, therefore, meets this criterion as an off-label use of an approved device.

One stand-alone biventricular pacemaker (InSync® Biventricular Pacing System, Medtronic) has received approval by the FDA 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 msec and a left ventricular ejection fraction of ≤35%. Biventricular pacemakers have also been combined with implantable cardiac defibrillators (ICDs). Both Guidant (CONTAK CD® CRT-D System) and Medtronic (InSync® ICD Model 7272) have received FDA approval for combined cardiac resynchronization therapy 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 left ventricular ejection fraction of 35% or less, QRS duration ≥130 msec (≥120 msec for the Guidant device) and remain symptomatic despite a stable, optimal heart failure drug therapy.

At the time this Assessment went to press, the FDA Circulatory System Devices Advisory Panel voted unanimously to recommend approval of CRT devices for use in mild heart failure. The indications proposed by the FDA Advisory Panel include patients in NYHA functional class II or in patients with class I ischemic heart failure with an LVEF <30% and a QRS duration >130 ms. Also added was a requirement that eligible patients also have left-bundle-branch block

(LBBB). Note that recommendation of approval does not constitute final approval.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The evidence is sufficient to permit conclusions concerning the effect of CRT on mortality, functional status, and quality of life. For each of these 3 outcome measures, at least 2 of the 3 randomized, controlled trials reported on this outcome. For each outcome, there were no group differences, and there was no apparent trend toward improvement in the CRT group. Therefore, conclusions on these outcome measures can be made over the period of time covered by the study.

The evidence is also sufficient to determine the effect of CRT therapy on echocardiographic parameters while the device is on. The evidence from the included studies is consistent in reporting an improvement in LVEF and LV volumes over the first year of therapy with the CRT device continuously on. The evidence is not sufficient to determine whether these changes represent structural changes in the heart that would persist in absence of the CRT device turned on.

The evidence is not sufficient to permit conclusions on the effect of CRT on hospitalizations. Although this outcome was reported by 2 trials, it is a more subjective outcome that can be influenced by knowledge of group assignment. The MADIT-CRT trial was the largest trial and was single blinded. As a result, there is potential for bias on the outcome of hospitalizations, leaving only one trial that was double blinded and thus avoided this potential bias.

3. The technology must improve the net health outcome.

For the outcomes of mortality, functional status, and quality of life, the evidence does not support the conclusion that the net health outcome is improved. For these outcomes, there were no improvements associated with CRT therapy. Therefore, it can be concluded with a moderately high degree of certainty that there is not improvement in these outcomes over the 1- to 2-year time period covered by these studies.

For the outcome of hospitalizations, the evidence is not sufficient to permit conclusions. For the echocardiographic outcomes, the evidence is not sufficient to conclude that the net health outcome is improved. This is because it is not certain that these changes in cardiac morphology and function translate to physiologic benefits that can be experienced by the patient.

4. The technology must be as beneficial as any established alternatives.

The evidence is not sufficient to determine whether the net health outcome is improved, therefore it cannot be determined whether the technology is as beneficial as alternatives.

5. The improvement must be attainable outside the investigational settings.

Whether CRT for mild heart failure improves health outcomes has not been demonstrated in the investigational setting.

For the above reasons, the use of cardiac resynchronization therapy for class I/II congestive heart failure does not meet the TEC criteria.

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Appendix

Table A. Quality Assessment for Randomized, Controlled Trials of CRT for Mild Heart Failure: USPSTF Framework (Harris et al. 2001)

Study/yr	Initial Assembly of Comparable Groups	Maintenance of Comparable Groups	Comparable Intervention(s)	Comparable Measurements	Appropriate Analysis of Outcomes	OVERALL QUALITY LEVEL
Abraham et al. 2004	YES	YES	YES	NO*	YES	FAIR Does not met all quality indicators, but no fatal flaws
Linde et al. 2008 (REVERSE)	YES	YES	YES	YES	YES	GOOD Meets all quality indicators
Moss et al. 2009 (MADIT-CRT)	YES	NO**	YES	YES/NO***	YES	FAIR Does not met all quality indicators, but no fatal flaws

*Primary outcome is oxygen uptake, clinical outcomes secondary outcomes
**High rate of withdrawals/crossovers: 20.0% (146/731) in ICD alone group, 11.6% (126/1089) in ICD-CRT group
***Clinicians not blinded to group assignment

Appendix Table B. GRADE Evaluation of Evidence for CRT in Mild CHF

Outcome	Importance	# studies	Study Design	Study Quality	Consistency	Directness	Quality of Evidence
Mortality	Critical	2	RCTs	Some limitations	No important inconsistency	High	Low
Functional status	Critical	2	RCTs	Some limitations	No important inconsistency	High	Low
Quality of life	Critical	2	RCTs	Some limitations	No important inconsistency	High	Low
Hospitalizations	Important	2	RCTs	Some limitations	No important inconsistency	High	Moderate
Echo parameters*	Uncertain	3	RCTs	Important limitations	No important inconsistency	Moderate	High

* Left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV)

Table C. Balance Table for CRT in Mild Heart Failure

Outcome	CRT + Optimal Medical Therapy	Optimal Medical Therapy Alone
Benefits		
Mortality	+ (?)	+ (?)
Quality of life	++	++
Functional status	++	++
Delay of disease progression	+ (?)	+ (?)
Hospitalizations for CHF	++ (?)	+
Harms		
Serious complications, <30 days*	+ (<3%) (?)	—
Minor complications, <30 days**	++ (5–20%) (?)	—
Serious complications, 30 days-1 year***	+ (<1%) (?)	—
Minor complications, 30 days-1 year****	++ (16–35%) (??)	—

(?) some degree of uncertainty present
(??) high degree of uncertainty present

*Coronary dissection, pneumothorax, arrhythmia, tamponade
**Hematoma, localized infection, lead dislodgement, pericardial effusion without tamponade
***Thromboembolism, arrhythmia
****Lead dislodgement, pericardial effusion without tamponade, diaphragmatic irritation, localized infection

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