Agency for Healthcare Research and Quality

Evidence Report/Technology Assessment

Number 106

Cardiac Resynchronization Therapy for Congestive Heart Failure

Summary

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Introduction

Heart failure is the fastest growing cardiovascular diagnosis in North America, and it carries a poor prognosis.[1,2] To improve survival in heart failure patients, therapies need to reduce either sudden cardiac death (the most common cause of death in patients with New York Heart Association [NYHA] Class I or II symptoms) or progressive heart failure (the predominant cause of death in those with NYHA Class III or IV symptoms).[3,4]

Electrical conduction disturbances are common in heart failure and are associated with increased mortality risk.[5-7] Atrial-synchronized biventricular pacing (cardiac resynchronization therapy [CRT]) addresses many of the pathophysiological changes seen in patients with wide QRS complexes in whom delayed activation of the left free wall results in mechanical dyssynchrony.

The University of Alberta Evidence-based Practice Center conducted a systematic review to examine the success rate and safety of biventricular pacemaker implantation and the efficacy of CRT in patients with heart failure. Further, the researchers used these data in a decision analysis to evaluate the incremental cost-effectiveness of CRT versus medical therapy alone.

Methods

This report addresses the following questions:

1. *In adult patients with symptomatic heart failure, is CRT more effective than optimal medical care alone?*
2. *Is the implantation of a CRT system safe for patients?*
3. *What is the role of CRT in the treatment of heart failure?*
4. *What is the cost-effectiveness of CRT in patients with congestive heart failure?*

Literature Search

Detailed searches were conducted of the Cochrane Heart Group Trial Registry, Cochrane Library, EMBASE, International Pharmaceutical Abstracts, MEDLINE®, Web of Science®, and multiple trial registries. In addition, the researchers contacted the primary authors of included studies, sought U.S. Food and Drug Administration reports, and reviewed the reference lists of all included articles. Additional unpublished data were sought from the companies that produce CRT devices: Medtronic, Inc., Guidant Corporation, and ELA Medical (Montrouge, France). The search was not limited by language or publication status and is considered up to date as of June 30, 2003.

Selection and Data Extraction

Two investigators independently screened all titles and abstracts, and another two investigators independently assessed the full text of potentially relevant studies and extracted data. Disagreements were resolved through third-party adjudication or consensus.

Data Analysis

Intention-to-treat analyses were done using the same standardized endpoint definitions employed in the primary studies. Stata 7.0 (Stata

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Corporation, version 7.0, 2003) was used to pool data and calculate summary risk ratios for dichotomous results and weighted mean differences for continuous variables. Because of expected differences between studies (particularly in control group therapies), the researchers decided a priori to combine results primarily using a random effects model. Fixed effects models were considered in sensitivity analyses. Statistical heterogeneity was assessed by the chi-square test and was quantified and appropriated using the I-squared statistic.[8] Time-to-death data were summarized by the log hazards ratio; Cox proportional hazards and/or Kaplan-Meier curves were generated where appropriate.[9,10]

Simple pooling and exact 95-percent confidence intervals (CIs) were used for the safety analyses. However, given the possibility that reports may not always have reported zero for adverse events that did not occur, the researchers performed sensitivity analyses for safety outcomes in which they assumed that, if a particular event (for example, peri-implantation death) was not mentioned in a report, then it did not occur and assigned a zero for that outcome in that study.

Decision Analysis Methods

A Markov decision model was constructed to compare the lifetime effects and costs of CRT versus medical therapy for patients with symptomatic heart failure. The analysis adopted the U.S. health care perspective (including costs of hospitalization, procedures, ambulatory visits, medications, and laboratory tests), and costs are expressed in 2003 American dollars. Input data were derived from multiple sources:

1. Outcomes with CRT and risks of the procedure were derived from a systematic review with annualization using an exponential approximation.[11,12] Transition probabilities incorporated into the Markov model were adjusted for the cycle length.
2. The health-related quality of life of patients with heart failure was estimated by eliciting utilities. Since the purpose of the decision analytic model was to consider an intervention in the context of resource allocation among different types of interventions, a generic source of preferences was used.[13] A convenience sample (n = 66) was recruited of members of the general public age 40 and over and without underlying cardiac disease. Consenting subjects estimated utilities for standardized health state descriptions (NYHA Class II, III, and IV) by using the standard gamble technique.[14] Hypothetical scenarios describing what one would typically feel and experience if living with each of these health states were developed with input from an expert panel based on descriptors from the Health Utilities Index.[15]
3. The cost of a device capable of CRT was depreciated over its anticipated lifespan. Physician costs related to CRT implantation were based on Current Procedural Terminology codes.[16] The costs of a resynchronization device were based on a survey of manufacturers' list prices. The costs of hospitalizations associated with heart failure were based on estimates derived from a cohort study of health resource use by patients participating in a previous randomized trial of medical therapy for heart failure.[17] All costs were adjusted for inflation by using the U.S. Consumer Price Index.[18]

Structure of Decision Model

The primary analysis considered patients with NYHA Class III symptoms. The analysis considered the lifetime horizon and employed a state-transition Markov model with a cycle length of 1 month. During each cycle, patients who received medical therapy could die of unrelated causes, die of cardiovascular disease, be hospitalized for heart failure, or remain stable. Patients who underwent insertion of a device capable of CRT could die during the initial implantation of the device or experience lead infection, lead failure, battery failure, or any of the health states associated with medical therapy for heart failure.

Decision analyses were performed with DATA Pro™ software (TreeAge Software, Inc., Williamstown, Massachusetts) and Excel 2000 software (Microsoft Corporation, Redmond, Washington).

Assumptions in Decision Analysis

A number of assumptions were necessary because of the paucity of several pieces of data. First, it was assumed that unit costs of heart failure therapy were identical between medical therapy and CRT. Second, it was assumed that the incidence of complications associated with CRT was constant over time. However, since the duration of followup in each trial was relatively short and the incidence of adverse effects in these trials was higher than generally accepted for ICD implantation,[19] the researchers considered lower incidences of device or device-related adverse effects than observed in the trials in the sensitivity analyses. Third, it was assumed that any mechanical malfunction of the device required battery replacement with consequent costs. Finally, age-specific mortality due to unrelated causes was based on life tables.[20]

Uncertainty and Variability Analyses

The analysis distinguished between parameter uncertainty (i.e., variation in costs and effects because of sampling and measurement error) and variability (i.e., heterogeneity in costs and effects between groups of patients with systematic differences in cost or effects). Uncertainty was assessed by using 10,000 probabilistic Monte Carlo simulations.[21,22] Empirical cost variables were assigned log-normal distributions. Empirical probability variables were assigned beta distributions.[21] Variables without a known distributional form (i.e., those with assumed values or those with values based on a range of published reports) were assigned triangular distributions.[23]

Variability was assessed by substituting the value of each variable in the decision model by its upper and lower limits while holding all other values constant.[24-26] For empirical variables, these limits were the 95-percent confidence limits for each variable. For assumed variables (e.g., cost of CRT device insertion and discount rate), these limits were based on reasonable possible limits (i.e., ±50 percent). Threshold analyses identified the value of each variable across its range, if any, at which one should be indifferent between medical therapy alone or CRT (i.e., the incremental cost per quality-adjusted life year was $100,000).[26]

Results

Literature Search

Nine trials reported on the efficacy of CRT; three included implantable cardioverter-defibrillators (ICDs).[27-34] Seventeen studies (eight trials and nine prospective studies without control arms) reported on the safety of CRT. Most of the trials were associated with multiple publications that either expanded on the main results or reported secondary outcomes not included in the primary report. This summary includes the reference to only the primary report for each trial. However, a full listing of all publications is available in the full evidence report.

Description of Included Studies

All nine of the trials enrolled only patients with prolonged QRS duration: ≥120 millisecond (msec) in three trials,[27-29] ≥130 msec in two trials,[30,31] >140 msec in one trial,[32] >150 msec in one trial,[33] >180 msec in one trial, and >200 msec in the remaining trial.[34] Left bundle branch block was present in 64 percent of patients, and 95 percent of patients were in sinus rhythm. All trials also restricted enrollment to patients with reduced ejection fractions (≤35 percent in six trials, ≤25 percent in one trial, and ≤40 percent in the other), and the mean ejection fractions were similar in all trials (from 21 percent to 26 percent).

In total, 3,574 patients were enrolled and 3,216 were randomized to receive CRT (n = 2,063) or control (most commonly pacemaker turned off, n = 1,153) in the nine trials. The mean age was 64 years, 74 percent were male, 75 percent had NYHA Class III symptoms, and 10 percent had NYHA Class IV symptoms. Two trials included some patients with NYHA Class II symptoms.[27,31] Most of the patients in these trials had ischemic etiologies for their heart failure (mean 58 percent, range 29 percent to 69 percent).

Including the nine additional single-arm prospective cohort studies, a total of 3,512 patients who had undergone CRT implantation were included in the safety analyses.

Quantitative Results

All-cause mortality. Based on data pooled from the nine randomized controlled trials, CRT significantly reduced all-cause mortality (relative risk [RR] 0.75, 95-percent CI 0.60 to 0.93). The results were identical when analyses were limited to patients with NYHA Class III or IV symptoms (RR 0.76, 95-percent CI 0.60 to 0.95). There was no significant statistical heterogeneity between trials (p = 0.88, I-squared = 0 percent). The all-cause mortality rate in the control patients was 14.9 percent, and the number needed to treat (NNT) to prevent one death in patients with symptomatic heart failure was 27. A Cox proportional hazards model revealed that the mortality hazard ratio with CRT was 0.59 (95-percent CI 0.43 to 0.81) after the first 3 months.

Cardiac mortality. Seven trials reported progressive heart failure mortality (n = 60 deaths in 1,647 patients); the relative risk favored CRT (random effects RR 0.60, 95-percent CI 0.36 to 1.01; fixed effects RR 0.59, 95-percent CI 0.35 to 0.98). Results were similar when analysis was restricted to patients with NYHA Class III or IV symptoms (random effects RR 0.58, 95-percent CI 0.32 to 1.06). In contrast, CRT did not significantly reduce overall cardiac deaths (n = 91 in 1,628 patients, RR 0.84, 95-percent CI 0.56 to 1.25) because of a nonsignificant excess in sudden cardiac deaths (n = 28 in 1,691 patients, RR 1.99, 95-percent CI 0.95 to 4.16). Data on causes of death for patients in the COMPANION trial[28] were not yet available.

Noncardiac mortality. Using data pooled from the six trials that reported noncardiac death (RR 0.90, 95-percent CI 0.35 to 2.35), results for CRT and control therapy did not significantly differ.

Heart failure hospitalizations. The pooled data revealed benefits with CRT (random effects RR 0.68, 95-percent CI 0.41 to 1.12; fixed effects RR 0.80, 95-percent CI 0.64 to

1.003). This result was heterogeneous (p = 0.01, I-squared = 65 percent). Restricting this analysis to patients with NYHA Class III or IV symptoms revealed homogeneous (p = 0.31, I-squared = 16 percent) and statistically significant reductions in heart failure hospitalizations (RR 0.65, 95-percent CI 0.48 to 0.88; NNT = 12).

Six-minute walk test. CRT was associated with an improved 6-minute walk test, with a weighted mean difference (WMD) of 23 meters (95-percent CI 9 m to 38 m). This improvement was similar in patients with NYHA Class III or IV symptoms (WMD 26 m, 95-percent CI 11 m to 41 m). Although the data from the RD-CHF Trial were not available for pooling, the RD-CHF investigators reported statistically significant improvements in 6-minute walk test distances.[35]

New York Heart Association Functional Class. Combining the data on change in NYHA class from the three studies that reported this endpoint revealed that 57 percent of CRT-treated patients, compared to 34 percent of controls, improved by at least one NYHA class. Thus, CRT was associated with an RR for improving at least one NYHA class of 1.6 (95-percent CI 1.1 to 2.5). Although the data from MIRACLE-ICD[31] and RD-CHF were not reported in a way that they could be pooled with the other trials, both reported statistically significant improvements in NYHA class with CRT.

Quality of life. The minimal clinically important difference for the Minnesota Living With Heart Failure® Questionnaire has been established in placebo-controlled trials as being 5 points.[36-38] Pooled results from the six trials that used the Minnesota Living With Heart Failure Questionnaire showed a statistically and clinically significant improvement with CRT (WMD -5.5 points, 95-percent CI -9 to -2 points). This result was statistically heterogeneous (p = 0.008, I-squared = 68 percent); however, results were consistent in direction in all six trials. Restricting the analysis to only patients with NYHA Class III or IV symptoms increased the difference between the CRT and control groups (WMD -6.4 points, 95-percent CI -9.4 to -3.4 points), and the results were less heterogeneous (p = 0.07, I-squared = 50 percent). Further, although the use of a different scale prevented pooling with the other trials, the RD-CHF investigators reported statistically significant improvements in quality of life with CRT.[35]

Other outcomes. CRT was associated with improvements in peak oxygen consumption (WMD versus control of 0.7 ml/kg/min, 95-percent CI 0.3 to 1.0 ml/kg/min), ejection fraction (WMD 3.5 percent, 95-percent CI 1.5 to 5.5 percent), and QRS interval (WMD 28 msec, 95-percent CI -47 to -9).

Peri-implantation risks. Ten studies reported data on deaths while undergoing implantation of a biventricular pacemaker. There were 13 deaths in 3,113 patients (pooled risk 0.4 percent, 95-percent CI 0.2 percent to 0.7 percent); a sensitivity analysis, in which it was assumed any studies that did not report mortality had zero occurrences, yielded the same result. Device implantation was successful in 90 percent of attempts (95-percent CI 89 percent to 91 percent) in 3,475 patients (16 studies).

Post-implantation risks. Over a median 6 months of followup, mechanical malfunction of the cardiac resynchronization device was noted with 7 percent of successful implants (95-percent CI 5 percent to 8 percent); on sensitivity analysis, in which it was assumed any studies that did not report this outcome had zero occurrences, this rate was 4 percent (95-percent CI 4 percent to 5 percent). Lead dislodgment occurred in 9 percent of patients (95-percent CI 7 percent to 10 percent). There were no differences in lead dislodgment in studies using specially designed left ventricular leads; the estimate was reduced to 8 percent (7 percent to 10 percent) on sensitivity analysis. Post-implantation infection (most commonly in the device pocket) occurred in 1.4 percent of patients (95-percent CI 0.8 percent to 2.3 percent); the estimate was reduced to 0.9 percent (95-percent CI 0.5 percent to 1.4 percent) with sensitivity analysis. Two percent (95-percent CI 1 percent to 3 percent) of patients had arrhythmias in followup.

Sensitivity Analyses for Systematic Review

Using meta-regression (a between-study nonrandomized comparison), the researchers explored the impact of CRT when combined with ICDs. The benefits of CRT on all-cause mortality and heart failure hospitalizations were not appreciably different in patients with an ICD and patients without an ICD. The data from COMPANION were not eligible for this analysis since only one arm in COMPANION received both CRT and an ICD.[39] Indeed, the COMPANION trial data permit the only direct comparison between CRT with/without an ICD. While the chi-square test for all-cause mortality approached significance (p = 0.07) in favor of cardiac defibrillators with CRT, the reductions in heart failure hospitalizations were similar in CRT-treated patients with/without ICDs.[28] However, until detailed data from the COMPANION subanalyses are made available, the most conservative conclusion to make is that the benefits of CRT are similar with/without an ICD.

Cost-Effectiveness of CRT

In patients with NYHA Class III heart failure, medical therapy was associated with a median gain of 2.68 discounted quality-adjusted life years (interquartile range [IQR] = 2.49 to 2.85) and median $34,700 lifetime costs (IQR = $31,100 to $38,100). CRT was associated with a median gain of 3.03

discounted quality-adjusted life years (IQR = 2.82 to 3.27) and median $67,600 lifetime costs (IQR = $62,000 to $73,800). Thus, CRT was associated with an incremental cost of a median $90,700 (IQR = $69,500 to $124,900) per additional quality-adjusted life year. The cost-effectiveness acceptability curve illustrates that the probability that resynchronization is cost effective is less than 59 percent, given a maximum willingness to pay for a quality-adjusted life year of $100,000.

Variability Analyses

The incremental cost-effectiveness of CRT was sensitive to reasonable changes in the values of several variables, particularly the incidence of device-related complications.

Discussion

In summary, when added to medical therapy in patients with symptomatic heart failure who have prolonged QRS duration and reduced left ventricular ejection fraction, CRT reduces all-cause mortality by 25 percent and heart failure hospitalizations by 32 percent. These benefits were particularly marked in heart failure patients at higher risk (i.e., those with NYHA Class III or IV symptoms). These benefits are similar to those reported for ACE inhibitors, beta-blockers, and aldosterone antagonists in recent trials.[40-43] CRT also conferred statistically and clinically significant benefits in a variety of surrogate outcomes. Indeed, a pooled six-point improvement on the Minnesota Living With Heart Failure® Questionnaire is greater than that seen in recent heart failure trials testing pharmacologic therapies.[44,45] However, CRT for patients with heart failure is associated with large uncertainty in the incremental costs per quality-adjusted life year; in particular, the results are sensitive to the incidence of device-related adverse effects.

The survival benefits with CRT appear to be attributable largely to reductions in progressive heart failure deaths and become apparent by 3 months after implantation. This is not surprising, as the benefits of CRT are thought to be mediated through morphometric remodeling of the left ventricle (leading to increased left ventricular filling time, reduced mitral regurgitation, and reduced septal dyskinesis) rather than acute changes in the neurohormonal system.[46]

While the researchers found a nonsignificant trend toward increased sudden cardiac death that was consistent across these trials, it was based on a very small number of events (28 in total). In particular, the lack of difference in the number of ventricular arrhythmia episodes between patients with compared to without CRT in the MIRACLE-ICD Trial (22 percent vs. 26 percent, p = 0.47) suggests that the trend toward excess sudden cardiac deaths may well be due to small numbers.[31] Regardless, the benefits of CRT are similar in patients with or without implantable cardioverter-defibrillators, providing some reassurance that, in those patients who have indications for both a defibrillator and CRT, the two may be administered together. The indications for an ICD in heart failure patients without an ischemic etiology remain uncertain pending completion of the SCD-HeFT Trial.[47]

An important finding of this systematic review is the safety of CRT and its tolerability in patients with advanced heart failure. Peri-implantation mortality rates were less than 1 percent and post-implantation infection rates were also low. Although there were few serious complications, implantation of a biventricular pacemaker (in particular the left ventricular lead) is technically challenging: the systematic review identified a 10-percent failure rate. Furthermore, even if implantation is successful, patients with these devices require close followup, as 7 percent of devices malfunctioned over a median followup of 6 months and 9 percent of left ventricular leads dislodged. Because these complications necessitate another procedure, the failure rates have to be incorporated into any policy decisions.

Although the systematic review results are promising, the results of the decision analysis suggest caution given the magnitude of the uncertainty in the long-term results. Indeed, the researchers believe that there are insufficient long-term effectiveness and cost data to warrant broad implementation of CRT at this time.

Limitations of Research

A substantial limitation of the trials included in this analysis is that randomization occurred after implantation of the device in all but one trial. This design, similar to the run-in period used in some pharmaceutical trials, does not affect the internal validity of the trials but does impact the generalizability of the results, as patients who could not tolerate the procedure or in whom implantation was unsuccessful were not included. As a result, these trials likely overestimate the potential benefits from CRT.[48] Because very few patients in these trials had bradyarrhythmias or atrial fibrillation, the role of CRT in such patients is unknown and is an important area for further study, particularly since almost one-third of CHF patients have atrial fibrillation or indications for conventional pacemakers.[49] Finally, it should be emphasized that only selected cases and experienced providers participated in these trials, so it is plausible that the observed complication rates may not be applicable to other settings and, in particular, clinicians less experienced with device implantation. If so, this decision analysis overestimates survival and underestimates the incremental cost of CRT. Conversely, if adverse effects are less frequent as providers gain experience, the analysis may underestimate survival and overestimate the incremental cost of

CRT. This is particularly important, since the results of the analysis were sensitive to the rate of complications associated with CRT.

The decision analysis also has some limitations. First, although cardiac resynchronization is more costly and more effective than medical therapy, the incremental cost-effectiveness ratio had a large range and there are insufficient data to determine whether to adopt resynchronization therapy for broad use. Second, it is likely that the incidence of complications associated with CRT decreases over time, although for the purposes of our analysis it had to be assumed that they were constant. Thus, the model may underestimate survival and overestimate the incremental cost-effectiveness of CRT. Long-term followup of patients enrolled in the previously completed trials will determine whether the incidence of complications does indeed decline over time. Third, it is unlikely that the relative benefits of CRT will be constant, as the severity of heart failure varies. Therefore, as results from other trials and registries become available, the analysis should be revised to reflect better estimates of the true effectiveness and costs of the program in patients with other classes of CHF. Fourth, it was assumed that heart failure costs were constant even though CRT will decrease heart failure costs if ventricular remodeling decreases the frequency of use of outpatient pharmaceuticals or duration of hospitalization. Finally, the input data were derived from several sources and may be confounded by information that was not incorporated into the model. For example, the effectiveness of CRT was not adjusted for the patient's comorbid illnesses.

Conclusions

CRT exerts a 24-percent relative reduction in all-cause mortality (largely driven by a 42-percent reduction in progressive heart failure deaths) and a 35-percent reduction in heart failure hospitalizations in patients with reduced ejection fractions, NYHA Class III or IV symptoms despite medical management, and a prolonged QRS duration on electrocardiogram. While preliminary data suggest similar relative benefits in patients with NYHA Class II symptoms, this is based on very few events. Further data are required before extending the device indications beyond those currently authorized by the U.S. Food and Drug Administration (i.e., patients with NYHA Class III or IV symptoms). Moreover, as very few such patients were enrolled in the trials, the role of CRT in patients with indications for conventional pacemakers or with atrial fibrillation remains uncertain and requires further study. Approximately 10 percent of heart failure patients have NYHA Class III or IV symptoms, reduced ejection fraction, and a prolonged QRS duration, and up to one-half of these patients may also have indications for an implantable cardioverter-defibrillator.[50]

While CRT should join the list of proven efficacious therapies for selected patients with heart failure, it is an expensive therapy and cost-effectiveness analysis reveals uncertainty in the incremental costs per quality-adjusted life year. In particular, there are insufficient long-term effectiveness and cost data to determine whether CRT is sufficient value for money to warrant its broad implementation at this time. This is in contradistinction to ACE inhibitors, beta-blockers, and spironolactone for patients with advanced symptomatic heart failure.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the University of Alberta Evidence-based Practice Center under Contract No. 290-02-0023. It is expected to be available in November 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 106, *Cardiac Resynchronization Therapy for Congestive Heart Failure*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

Suggested Citation

McAlister F, Ezekowitz J, Wiebe N, Rowe B, Spooner C, Crumley E, Hartling L, Kaul P, Nichol G, Klassen T. Cardiac Resynchronization Therapy for Congestive Heart Failure. Summary, Evidence Report/Technology Assessment No. 106. (Prepared by the University of Alberta Evidence-based Practice Center under Contract No. 290-02-0023.) AHRQ Publication No. 05-E001-1. Rockville, MD: Agency for Healthcare Research and Quality. November 2004.

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AHRQ Pub. No. 05-E001-1
November 2004

ISSN 1530-440X