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Cardiac Resynchronization Therapy for Congestive Heart Failure

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new healthcare technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for healthcare quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.gov.

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Structured Abstract

Context: Congestive heart failure (CHF) is the fastest growing cardiovascular diagnosis in North America.

Objectives: The objectives were to determine the efficacy, safety, and cost-effectiveness of cardiac resynchronization therapy (CRT) in adults with symptomatic CHF.

Data Sources: Electronic databases (the Cochrane Heart Group Trial Registry, Cochrane Library, EMBASE, International Pharmaceutical Abstracts, MEDLINE, PubMed, Web of Science, and Trial Registries) were searched, reference lists and Food and Drug Administration (FDA) reports were checked, and authors of primary studies and manufacturers of CRT devices were contacted.

Study Selection: Randomized controlled trials (RCT) [efficacy review] and/or prospective cohort studies [safety review]. *Population*: patients with symptomatic CHF and reduced left ventricular ejection fraction. *Intervention*: active CRT with medical therapy compared to medical therapy alone or non-active/univentricular pacing. *Outcomes*: mortality, heart failure hospitalizations, six-minute walk test distances, functional status (New York Heart Association [NYHA] Class), quality of life, and peri/post-implantation risks.

Data Extraction: Data were extracted using standardized methods by two independent abstractors.

Data Synthesis: *Efficacy Review*: Data were analyzed using a random effects model in Stata 7.0. Calculations included: Relative risk (RR) for dichotomous data; weighted mean difference (WMD) for continuous data; log hazards ratio for time-to-event data. All results reported with 95% confidence intervals (95% CI). *Safety review*: Simple pooled risks and sensitivity analysis were conducted. *Decision Analysis:* Cost-effectiveness of CRT was estimated using a Markov model adopting a societal perspective. Future costs and effects were discounted at 3%. Monte Carlo simulation and sensitivity analyses were used to assess robustness.

Main Results: *Efficacy*: In nine RCTs (3216 patients, 85% with NYHA Class III or IV symptoms and 100% with prolonged QRS duration), CRT improved peak oxygen consumption (WMD 0.65 ml/kg/min, 95% CI 0.27 to 1.04 ml/kg/min), left ventricular ejection fraction (WMD 3.35%, 95% CI 1.22% to 5.48%), six-minute walk distance (WMD 23 meters, 95% CI 9 m to 38 m), quality of life (WMD reduction of 5.5 points, 95% CI 2 to 9 points on the Minnesota Living with Heart Failure Questionnaire), and functional class (57% improved at least one NYHA class compared to 34% of controls). Heart failure hospitalizations decreased by 32% (RR 0.68, 95% CI 0.41 to 1.12), especially in patients with NYHA III/IV symptoms (RR 0.65, 95% CI 0.48 to 0.88; number needed to treat [NNT]=12). All-cause mortality was reduced by 25% (RR 0.75, 95% CI 0.60 to 0.93, NNT=27), mainly due to 40% fewer progressive heart failure deaths (RR 0.60, 95% CI 0.36 to 1.01). Kaplan Meier curves separated at 3 months, and the risk of death was reduced 41% after the first 3 months (hazard ratio 0.59, 95% CI 0.43 to 0.81). No significant differences were seen in sudden cardiac deaths or non-cardiac deaths. *Safety:* In 17 prospective studies (3512 patients with CRT devices), the implant success rate was 89.9%

(88.8% to 90.9%) and peri-implant death risk was 0.4% (95% CI 0.2% to 0.7%). Over a median 6 months of followup, lead dislodgement occurred in 8.5% (7.4% to 9.9%), mechanical malfunctions in 6.7% (5.4% to 8.2%), arrhythmias in 1.7% (0.8% to 3.4%), and site infections in 1.4% (0.8% to 2.3%) of patients. *Decision Analysis:* Optimal medical therapy for CHF in NYHA Class III patients is associated with a median gain of 2.68 (interquartile range [IQR] 2.49 to 2.85) discounted quality-adjusted life years and median $34,700 (IQR $31,400 to $38,100) cost. CRT was associated with a median gain of 3.03 (IQR 2.82 to 3.27) discounted quality-adjusted life years and median $67,600 (IQR $62,000 to $73,800) cost. The incremental cost-effectiveness of CRT compared to optimal medical therapy was median $90,700 (IQR $69,500 to $124,900) per additional quality-adjusted life year; however, costs were highly sensitive to changes in several variables, particularly the incidence of complications. The cost-effectiveness acceptability curve illustrated that the probability that resynchronization is cost-effective relative to medical therapy alone is less than 59%, given a maximum willingness-to-pay for a quality-adjusted life year of $100,000.

Conclusions: In patients with NYHA Class III or IV CHF despite medical management, reduced ejection fractions, and prolonged QRS duration, CRT improves functional and hemodynamic markers and reduces morbidity/mortality. Given the moderate implantation success rates, biventricular pacemaker insertions should only be done by experienced providers. The cost-effectiveness of CRT remains uncertain; additional effectiveness and cost data surrounding peri-implantation complications are required to determine whether CRT is sufficient value to be widely adopted.

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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.

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Evidence Report

Chapter 1. Introduction and Background

The Problem of Congestive Heart Failure

Congestive heart failure (CHF) leads to significant morbidity and mortality; in 2001 it accounted for almost one million hospitalizations in the United States (as the most responsible diagnosis) and $24.3 billion in direct and indirect costs.[1] CHF is the fastest growing cardiovascular diagnosis in North America: the community prevalence is estimated at 0.4% to 2.4% in adults,[1-4] with the incidence approaching 10 cases/1000 in people over 65 years of age.[1] Indeed, the lifetime risk of developing CHF is estimated at 20% in North America.[5] Despite many advances in diagnosis and therapy over the past two decades, heart failure carries a poor prognosis (30% to 50% mortality rate at 1 year), which has changed little over that time frame.[1,6]

Patients with CHF may be classified on the basis of their functional status using the New York Heart Association (NYHA) Classification. In this system, CHF patients without limitations of physical activity (i.e., ordinary physical exertion does not cause fatigue, palpitations, dyspnea, or chest discomfort) are classified as having NYHA Class I disease. CHF patients who develop fatigue, palpitations, dyspnea, or chest discomfort with ordinary physical activity (defined as walking two blocks or climbing two flights of stairs) are classified as having NYHA Class II disease. Those patients who are comfortable at rest but develop symptoms on less than ordinary activity are categorized as having NYHA Class III disease. Finally, CHF patients who have symptoms at rest or with minimal activity are classified as having NYHA Class IV disease.

Attempts to reduce mortality in heart failure are directed at the two main ways in which death occurs: sudden cardiac death (electrical failure) and progressive heart failure (mechanical failure).[7] Sudden cardiac death accounts for more deaths than progressive "pump" failure in patients with NYHA Class I or II heart failure; on the other hand, progressive heart failure is the predominant cause of death in those with NYHA Class III or IV symptoms.[8] It is important to emphasize that not all therapies that improve functional outcomes (such as symptoms, quality of life, ejection fraction, and other hemodynamic measurements) in CHF patients confer survival benefits.[9] Thus, it is essential that any novel therapies in patients with CHF be evaluated for their impact on clinically important outcomes such as death or hospitalization.

Heart failure is a clinical syndrome characterized by specific symptoms and, in most (but not all) cases, accompanied by a depressed ejection fraction.[10] Coronary artery disease is the cause of heart failure in two-thirds of North American and European patients, with hypertension, valvular dysfunction, viral myocarditis, idiopathic dilated cardiomyopathy, and other diseases causing the remainder.[11] Identification of modifiable risk factors in CHF has lead to the development of treatment options for heart failure including the standard pharmacological, non-pharmacological, and electrically based therapies currently recommended in consensus guidelines for the care of patients with CHF.[10,12,13]

Current Risk Factors and Markers in Congestive Heart Failure

Many prognostic risk factors have been established in CHF (Table 1). Well-validated risk factors for short- and long-term mortality include demographic factors such as older age and male gender;[14] differing ethnic background (black patients have a higher mortality rate than white patients even after adjustment for important covariates);[15,16] co-morbidities such as diabetes mellitus,[17] anemia,[18] and poor renal function;[19] and physical examination findings such as a third heart sound and elevated jugular venous pressure.[20] Biochemical values that predict mortality include decreased serum sodium,[21] elevated aldosterone, angiotensin II, and arginine vasopressin,[22] elevated brain natriuretic peptide,[23] and elevated levels of other neurohormones.[24] Other prognostic risk factors have been explored (such as genetic and echocardiographic markers) and are reviewed elsewhere;[25] electrophysiologic prognostic factors are reviewed below.

Table 1. Prognostic risk factors in congestive heart failure

Demographics:	**Electrophysiologic findings:**
Older age	Ventricular arrhythmias
Male gender	Intraventricular conduction delay
Ethnic background (blacks have poorer outcomes than whites)	Atrial fibrillation T-wave alternans
Comorbidities:	
Diabetes	**Laboratory findings:**
Anemia	Elevated norepinephrine/epinephrine
Renal failure	Low sodium
	Elevated creatinine
Clinical Assessment:	Elevated aldosterone
Advanced symptoms (NYHA Class III or IV)	Elevated B-type natriuretic peptide
Elevated jugular venous pressure	Elevated Tumor Necrosis Factor-alpha
Edema	Elevated InterLeukin-6
Third heart sound	Elevated endothelin-1
	Elevated angiotensin II
Hemodynamics:	Elevated renin
Lower left ventricular ejection fraction	Elevated troponin I/T
Lower right ventricular ejection fraction	Elevated arginine vasopressin
Elevated pulmonary capillary wedge pressure	
Elevated pulmonary vascular resistance	

Source: adapted from Eichhorn EJ. Prognosis determination in heart failure. Am J Med 2001;110 (Suppl 7A);14S-36S[25]
NYHA=New York Heart Association

Current Therapeutic Strategies for Congestive Heart Failure

Current therapy for congestive heart failure incorporates a number of strategies to enhance the quality of life, improve exercise tolerance, and reduce morbidity and mortality. In the past two decades, advances in heart failure management have arisen from randomized clinical trials

of medications, non-pharmacologic interventions (exercise training, care delivery systems), electrophysiologic procedures and devices, and surgery including cardiac transplantation.

Pharmacologic Management

Afterload reduction with the combination of isosorbide dinitrate and hydralazine was one of the first pharmaceutical combinations tested and used to treat heart failure. It achieved a relative risk reduction in mortality of approximately one third when compared to placebo.[26,27] While enalapril (an angiotensin-converting enzyme [ACE]) inhibitor was subsequently proven to be more effective than hydralazine/isosorbide dinitrate, the combination remains useful for management of those heart failure patients intolerant of ACE inhibitors or angiotensin-receptor blockers (ARB), and in those with advanced renal insufficiency.[10]

ACE inhibitors were the first medications to show a reduction in mortality in advanced congestive heart failure patients (those with NYHA Class IV symptoms), with a relative risk reduction for the enalapril group (versus placebo) of 40% at 6 months.[28] Since then, 33 other randomized placebo-controlled trials[29] of ACE inhibitors have confirmed substantial benefits (in the order of 25% to 35% reductions in mortality and 27% to 33% reductions in hospitalization rates) in patients with all classes of heart failure (even asymptomatic patients with reduced ejection fraction). ACE inhibitors are now the cornerstones of treatment for systolic left ventricular dysfunction with or without symptoms.[30]

Beta-blockers are the second choice in the pharmacologic treatment of systolic dysfunction. Twenty-two randomized controlled trials have demonstrated consistent benefits in reducing mortality (relative risk reduction 35%) and morbidity (relative risk reduction 36% in hospitalization),[31] and improving NYHA class and quality of life.[32]

Angiotensin-receptor blockers have been demonstrated to reduce a combined endpoint of morbidity and mortality by 13% when added to ACE inhibitor therapy and have an indication as primary therapy for heart failure in ACE-inhibitor intolerant patients, either alone or with beta-blockers. The reduction in hospitalization alone is 27% when added to an ACE inhibitor. Caution is urged when patients are concomitantly taking an ACE-inhibitor and beta-blocker, as no additional benefit was seen in a group of patients on all three agents.[33,34]

Aldosterone blockade (with spironolactone or eplerenone) is associated with relative risk reductions of 15% to 30% in mortality for patients with NYHA Class III/IV symptoms and an ejection fraction <35%,[35] or patients with an ejection fraction <40% and a recent myocardial infarction.[36] These benefits were largely due to reduced rates of sudden cardiac death. Furthermore, both agents are associated with 27% to 35% relative risk reductions in heart failure hospitalizations.[35,36] Digoxin has also been shown to reduce hospitalization rates, but without significant impact on mortality in patients with CHF.[37]

Non-Pharmacologic Management

Lifestyle modification is important in the management of symptomatic CHF patients. The importance of avoiding non-steroidal anti-inflammatory drugs has been highlighted in numerous studies where use of anti-inflammatory drugs has been associated with a two- to four-fold increase in hospitalizations for acute heart failure.[38,39] Non-compliance with sodium restriction has been identified as the cause of up to 22% of hospitalizations for CHF, highlighting the importance of dietary modification for these patients.[39] Finally, addressing concomitant risk

factors for underlying coronary artery disease (dyslipidemia, tobacco use, hyperglycemia) is important in the secondary prevention of myocardial ischemia in CHF patients. Another non-pharmacologic strategy includes specialty clinics that provide a multidisciplinary disease management approach to this complex disease.[40] While a systematic review of 11 randomized trials showed that patients managed in specialized multidisciplinary heart failure clinics had better processes of care and outcomes,[41] it is unclear whether these benefits can also be expected with "specialist" physicians operating outside the bounds of a multidisciplinary clinic. Exercise training can also result in substantial improvements in functional status for patients with CHF, but existing studies have not reported consistent results or have involved regimens that are not practical in an ambulatory care setting.[42,43]

Surgical Management

There are some surgical interventions for heart failure that may also improve survival when directed to the appropriate patients at risk. Left ventricular assist devices can improve short-term cardiac function and provide a bridge to cardiac transplantation for appropriately selected NYHA Class IV patients. Indeed, they have recently even been approved as destination therapy for patients with end-stage heart failure.[44] Valvular repair or replacement, revascularization of ischemic myocardium,[45] and other surgical approaches to heart failure have been proven or are under investigation to improve both survival and quality of life in selected patients. Finally, cardiac transplantation is effective. However, this is offered to fewer than 2500 individuals per year in the United States and is not a solution for the vast majority of heart failure patients.

Unfortunately, even with the best care using optimal combinations of these non-pharmacologic, pharmacologic, and surgical approaches, the mortality rate remains high and quality of life is usually poor for patients with CHF. As an example, in a specialized heart failure clinic where 86% of patients are on ACE inhibitors or ARB, 46% are on a beta-blocker, and 45% of patients seen since 1999 are on spironolactone, the mortality rates are still 27%, 43%, and 74% at 1, 2, and 5 years.[46]

Clearly, there is a need for additional treatment strategies in CHF that can improve function, diminish symptoms, reduce hospitalizations, and/or increase survival. Recent studies have shown that cardiac resynchronization therapy (CRT) with biventricular pacemakers offers improvements in quality of life, NYHA class, and six-minute walk test results, but have yet to demonstrate a conclusive mortality benefit. Implantable cardioverter defibrillators (ICDs) do not improve functional outcomes, but do provide a substantial mortality benefit (through the prevention of sudden cardiac death) in patients with a history of ventricular arrhythmias or at high risk due to ischemic substrate and poor ejection fraction.[47]

Pacing in CHF

Electrical conduction disturbances are common in heart failure, including atrial or ventricular dysrhythmias, atrioventricular conduction delay, and inter- and intraventricular conduction disturbances. The QRS duration is used as an electrical marker for mechanical activation. In an Italian registry of heart failure patients, left bundle branch block was present in 25% of patients and was associated with an increased one-year mortality (Hazard Ratio 1.70, [95% Confidence

Interval [CI] 1.41 to 2.05]).[48] Intraventricular conduction delay (exact width of QRS not defined) was present in 25% to 50% of the patients in a specialty clinic analysis and was associated with increased mortality after adjustment for other important covariates (Hazard ratio 1.84, 95% CI 1.22 to 2.76).[49] In a third study, the 33% of patients with a QRS duration of >120 msec had the worst survival.[50]

The presence of either left bundle branch block or intraventricular conduction delay are associated with physiological changes in cardiac function, including a reduction in ventricular dP/dt, prolonged duration of mitral regurgitation, and abnormal or paradoxical ventricular septal wall motion. Delay in electrical conduction results in increased duration of mitral regurgitation or the opportunity for pre-systolic mitral regurgitation to develop. There is an increase in the overall ventricular contraction time due to delayed activation of the left free wall and together this results in mechanical dyssynchrony and a reduction in cardiac output.

Original attempts at pacing in heart failure using right-sided dual-chamber atrioventricular (AV) sequential devices produced short-term physiological improvements,[51] but subsequent randomized trials failed to demonstrate a functional or mortality benefit in CHF.[52]

Biventricular pacing (BVP), or CRT, involves pacing simultaneously in the right atrium, right ventricle, and left ventricle. It was first tried as a short-term bridge after cardiac surgery; subsequent physiological studies demonstrated improved cardiac function with reductions in both pulmonary capillary wedge pressure and myocardial oxygen use when compared to dobutamine.[53-56] Since the first attempts at synchronized atrial-biventricular pacing by Cazeau et al.[57] many mechanical improvements in the devices, refinements of the implantation technique, and advances in patient selection have occurred.

Objectives of this Review

The benefits of CRT in congestive heart failure have now been tested in several randomized clinical trials, but due to small numbers of events, no definitive mortality benefit has been demonstrated. Furthermore, surrogate measures were used as the primary endpoint in many of these trials, and the impact of this potentially costly therapy cannot be estimated from the existing data. Through performing a systematic review and meta-analysis of these trials, we sought to determine if CRT reduces mortality (all-cause, progressive heart failure, sudden cardiac death), hospitalization rates, and/or improves functional outcomes and quality of life in patients with symptomatic CHF. We also sought to clarify the safety of these devices within clinical trials and when used in the non-trial setting. Finally, to clarify the effects of CRT on the healthcare system, we performed a decision analysis that incorporated safety, effectiveness, and cost data for biventricular pacemakers, taking into account other proven effective therapies in CHF (such as ACE inhibitors, beta blockers, aldosterone antagonists, digoxin, and multidisciplinary specialty clinics).

Study Questions

The specific questions we attempted to address in this project were:

- In adult patients with symptomatic CHF, is CRT more effective than optimal medical care alone or univentricular pacing?
- Is the implantation of a CRT system safe for patients?
- What is the role of CRT in the treatment of CHF?
- Which patients with CHF would most likely benefit from CRT?
- What is the cost-effectiveness of CRT in patients with CHF?

Chapter 2. Methods

Methods for the Systematic Reviews

Literature Search

A medical librarian identified relevant databases and developed search strategies based on the following terms: biventricular pacing, biventricular pacer, biventricular stimulation, BiV, congestive heart failure, CHF, chronic heart failure, artificial cardiac pacing, heart diseases, chronic cardiac failure resynchronization therapy, dual-chamber pacing, cardiac resynchronization, Medtronic, InSync, ELA medical, randomized controlled trial, controlled clinical trial, meta-analysis, multi-center trial, safety, risk, adverse effects, side effects, harm, etiology, aetiology, contraindications, causation, causality, predict.

These search terms were adapted appropriately to search the following electronic resources: Cochrane Heart Group Trial Registry, Cochrane Library, EMBASE, International Pharmaceutical Abstracts, MEDLINE, PubMed, Web of Science, and Trial Registries (http://www2.umdnj.edu/~shindler/trials/trials_a.html; http://www.nhlbi.nih.gov/index.htm; http://www.controlled-trials.com/; clinicaltrials.gov; http://www.update-software.com/National/; http://www.centerwatch.com/search.asp; and http://www.cardiosource.com). The detailed search strategies can be located in Tables A-1 to A-16, which are available on the AHRQ web site.

In addition, the investigators contacted the primary authors of key studies, sought Food and Drug Administration (FDA) reports, and reviewed the reference lists of all included articles. Additional unpublished data were also sought from the companies that make biventricular devices: Medtronic Inc., Guidant Corporation, and ELA Medical. The search was not limited by language or publication status and is considered up-to-date to June 2003.

Selection and Inclusion

The librarian screened the initial search results to eliminate all duplicates. Following this, we used a two-step eligibility and selection process. First, two heart failure clinicians (JE, FM) independently screened all titles and abstracts to determine if an article met the general inclusion criteria (i.e., clinical trial, biventricular, dual chamber or multisite pacing, resynchronization therapy, human, symptomatic heart failure). Each article was rated as 'include', 'exclude', or 'unclear'. The full text of all articles marked as 'include' or 'unclear' were retrieved. Second, two teams of physicians (JE and FM, and BR and TK) independently assessed the studies using specific inclusion and exclusion criteria for the efficacy and safety reviews, respectively (Table 2). Standard inclusion forms were used for this purpose (Tables B-1 and B-2, available on the AHRQ web site). Disagreements were discussed between reviewers until consensus on inclusion was reached. If needed, the investigators contacted the authors to clarify that individual publications reported on discrete patients. In cases of multiple publications involving the same or a portion of the same patients, the article with the most complete data was selected.

Table 2. Inclusion/exclusion criteria for review on cardiac resynchronization therapy

Criterion	Efficacy review	Safety review
Study Design	Include: RCT (parallel or crossover) > 2 weeks duration. Exclude: non-RCTs, acute physiological studies, studies not involving human subjects	Include: RCT (parallel or crossover) or non-RCT (e.g., registry data, prospective cohort, FDA document, etc.) > 2 weeks duration. Exclude: acute physiological studies, studies not involving human subjects
Participants	Include: symptomatic CHF (NYHA Class ≥ II), decreased LVEF, prolonged QRS. Must be receiving stable optimal drug therapy	Include: symptomatic CHF (NYHA Class ≥ II), decreased LVEF, prolonged QRS. Must be receiving stable optimal drug therapy
Intervention	Treatment with active CRT (also called BVP, multi-site pacing, dual chamber pacer) compared to either placebo pacing or uni-ventricular pacing or optimal drug therapy	Treatment with active CRT (also called BVP, multi-site pacing, dual chamber pacer). Comparison group not necessary
Outcome measures	Mortality (all-cause, CHF, sudden cardiac death, non-cardiac), CHF hospitalizations, 6MWT, NYHA class, QOL	Peri-implant mortality, successful implant rate, risks of /during implantation, risks following implantation

BVP = biventricular pacing; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; QOL = quality of life; RCT = randomized controlled trial; 6MWT = six-minute walk test.

Quality Assessments

Efficacy review. The methodological quality of RCTs was assessed independently by two reviewers (JE, CS) using two quality assessment methods. First, allocation concealment was assessed as adequate, inadequate, or unclear. Second, a five-point scoring system validated by Jadad[58] was used to assess randomization, double blinding, and reporting of withdrawals and dropouts (Table B-3). In addition, the funding source and whether authors reported use of intention-to-treat analysis were noted. Discrepancies were resolved through discussion between the two reviewers.

Safety review. Studies included in the safety review were assessed for quality independently by two reviewers (CS, LH) using a partially validated checklist developed by Downs and Black.[59] The checklist includes 28 questions evaluating five criteria (Table B-4). These five criteria are: Reporting (10 questions, total score 11), External validity (three questions, total score 3), Internal validity – bias (seven questions, total score 7), Internal validity – confounding (six questions, total score 6) and Power (two questions, total score 2). Decision rules regarding application of the tool were developed *a priori* through discussions with a cardiologist and a methodologist. Discrepancies in quality assessment were resolved through discussion.

Data Extraction

Data were extracted using standard forms (Tables B-5 and B-6) designed for either RCTs (efficacy and safety reviews) or cohort studies (safety review) and entered into an Excel spreadsheet. Data were extracted by one reviewer (JE, CS, NW, or LH) and checked for accuracy and completeness by a second (JE, NW, or CS). Extracted data included study characteristics, inclusion/exclusion criteria, baseline drug use, characteristics of participants, procedural data, and outcomes. Efficacy outcomes included mortality (all cause as well as CHF death, sudden cardiac death, non-cardiac death) and time to death; CHF hospitalizations, six-

minute walk test, NYHA class, quality of life, peak oxygen consumption, left ventricular ejection fraction, mitral regurgitation jet area, ECG and echocardiogram results. Safety outcomes included risks during implantation (death, lead misplacement, device-related malfunctions, procedural complications, implant tools, heart function, and patient complaints), risks following implantation (mechanical malfunction, lead dislodgment, infection, pain), and successful implant rate.

Data Analysis

Efficacy review. The following imputations and manipulations were performed to form useable data. Standard errors were converted into standard deviations. Graph extraction was performed using Corel Draw 9.0 (Vector Capital, San Francisco, California) for time to death in the COMPANION trial.[60] Means were approximated by medians, and 95% empirical intervals were used to calculate approximate standard deviations for the MIRACLE trial.[61] Change from baseline data was used wherever possible for continuous data (PATH CHF[62] being the exception); however, since correlations between baseline and endpoint data were never reported, a correlation of 0.5 was assumed[63] to calculate the appropriate standard deviation for change from baseline data. Change from baseline and endpoint data were combined; both entities estimate differences between treatment groups. Efficacy results were extracted rather than intention-to-treat results when provided.

Numerical results were meta-analyzed primarily in Stata 7.0;[64] metagraphs were generated using S-plus 6.0.[65] For dichotomous results (e.g., CHF hospitalizations), the review included relative risks (RR) for each individual study as well as a pooled result among those studies that could be combined. Additionally, risk differences were considered where zero total events occurred in both groups. Increments of one or more across functional classification (e.g., from Class III to Class II) were considered a dichotomous outcome. For continuous variables, mean differences (e.g., six-minute walk test) were calculated for separate studies and the weighted mean difference (WMD) for the pooled estimate. Time-to-event data (i.e., death) were summarized by the log hazards ratio;[66] Kaplan Meier curves were generated. An individual patient dataset for this analysis was constructed using summary monthly mortality tables in the trial manuscripts. The Log Rank test assessed for treatment group differences across curves. All results were reported with 95% confidence intervals (CIs) where reasonable.

Due to the differences expected between studies (particularly in control group therapies), we decided *a priori* to combine results primarily using random effects model;[67] fixed effects models were considered in sensitivity analyses. Statistical heterogeneity was assessed by the Chi-square test; a conservative level of significance ($p<0.10$) was considered heterogeneous.[68] Also, heterogeneity was quantified and appropriated using the I-squared statistic.[69] Inclusion of studies with active control arms[62,70] was assessed in sensitivity analyses. Relevant direct subgroup comparisons were summarized, including effects of CRT in patients with more severe heart failure symptoms (NYHA Class III or IV). Implantable cardioverter defibrillators (ICDs) were considered in an indirect subgroup comparison using meta-regression.

Estimates of carryover effect were extracted from crossover designs. Only period one data were used for irreversible outcomes (i.e., death and CHF hospitalizations). Standard errors for crossover WMD were calculated according to Curtin.[71]

Safety review. Numerical results were meta-analyzed primarily in S-plus 6.0. Risks were simply pooled and all results were reported with 95% CIs. Statistical heterogeneity was assessed by the Chi-square test; $p<0.10$ was considered heterogeneous.[68] Also, heterogeneity was quantified and appropriated using the I-squared statistic.[69] Exclusion of NYHA class II data and studies with active control arms[62,70] was assessed in sensitivity analyses but is not reported here.

The possibility that reports may have been less judicious in reporting adverse events that did not occur was considered. Sensitivity analyses were performed where studies (randomized controlled or cohort) did not report a particular risk (e.g., death); zero adverse events were assumed for these studies. In addition, some implantation risks were reported by event and not by patient. This non-independence was small and would not be expected to affect results importantly.

Methods for the Decision Analysis

The purpose of the decision analysis was to provide policy makers with a better understanding of the role of this new health technology for the treatment of congestive heart failure from a healthcare system perspective. The specific objectives were: 1) to estimate the long-term effects and costs of the use of cardiac resynchronization compared with medical therapy alone in patients with symptomatic congestive heart failure and reduced left ventricular ejection fraction, and 2) to calculate the incremental cost-effectiveness of cardiac resynchronization relative to medical therapy alone. The decision model compares the lifetime effects and costs of two treatment strategies for congestive heart failure: cardiac resynchronization in addition to medical therapy vs. medical therapy alone.

Structure of the Decision Model

The primary analysis considered patients with NYHA III heart failure and prolonged QRS duration. This analysis considered the lifetime horizon, as recommended.[72] A state-transition Markov model compared costs and outcomes of congestive heart failure treated by CRT and medical therapy vs. medical therapy alone. A cycle length of one month was used.

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 (Figure 1 end of chapter). Patients who underwent biventricular pacemaker insertion could die during initial implantation of the device, experience lead infection, lead failure, or battery failure, or experience 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 Inc., Redmond, Washington). Statistical analyses were performed with S-Plus (Insightful Inc., Seattle, Washington).

Input Data

Survival and Hospitalization. Baseline probabilities of adverse events, the probabilities of cardiovascular death, arrhythmic death, heart failure death, hospitalization for heart failure, and

adverse effects associated with the therapy options, as well as estimates of life expectancy associated with each therapy, were derived from the meta-analyses described above. Nine trials were included in the efficacy analysis: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION),[60] CONTAK CD,[73] Garrigue et al.,[70] Multicenter InSync Randomized Clinical Evaluation (MIRACLE),[61] Multicenter InSync Randomized Clinical Evaluation ICD (MIRACLE ICD),[36] Multisite Stimulation in Cardiomyopathies Sinus Rhythm (MUSTIC SR),[74] Multisite Stimulation in Cardiomyopathies Atrial Fibrillation (MUSTIC AF)[75], the Pacing Therapies for Congestive Heart Failure trial (PATH CHF)[62] , and the RD-CHF Trial (Leclerq C, personal communication, December 2003).

The rate of events observed among patients randomized to medical therapy was annualized by using an exponential approximation.[76,77] Transition probabilities incorporated into the Markov Model were adjusted for the cycle length. Pooled relative risks were calculated by using the Dersimonian and Laird random effects model.[67]

The base case analysis considered only the effect of CRT on all-cause mortality since it is difficult to subclassify causes of death in patients with cardiovascular disease. Cardiac and non-cardiac deaths were only considered in secondary analyses that accounted for the patient age at implantation (ie. differences in mortality due to unrelated causes).

Quality of Life. The health-related quality of life of patients with heart failure was estimated by eliciting utilities, since current standards suggest use of such outcome measures, and the relative cost-effectiveness of some cardiac therapies is sensitive to the magnitude of the difference between the utilities associated with either treatment.[78,79] Since the purpose of the decision analytic model was to consider an intervention in the context of resource allocation among different types of interventions, the use of a generic source of preferences was used as recommended.[78] A convenience sample (n=90) of members of the general public was recruited. Inclusion criteria were: fluent in English, provision of informed consent, age greater than 40, and no underlying cardiac disease. Consenting subjects estimated utilities for standardized health state descriptions by using the standard gamble technique.[80] Four health states were considered: NYHA functional class II, III, IV, and congestive heart failure severe enough to require hospitalization. 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.[81]

Costs. The economic analysis was conducted from a health care perspective, including costs of hospitalization, procedures, ambulatory visits, medications, and laboratory tests. Costs are expressed in 2003 American dollars (Table 3, end of chapter). The costs of a CRT device were based on a survey of manufacturers' list prices. Physician costs related to CRT implantation were based on Current Procedural Terminology codes (http://www.naspe.org/pdf_files/cpt_coding_form_0304.pdf - accessed on June 15, 2003). The costs of hospitalizations associated with congestive 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.[82] All costs were adjusted for inflation by using the U.S. Consumer Price Index (http://stats.bls.gov/cpi accessed on May 30, 2003).

Assumptions. We made several assumptions about the costs and effects of CRT. First, unit costs of complications related to CRT are identical to those for implantable cardioverter

defibrillators. Second, unit costs of heart failure therapy (ie. costs of out patient or in patient care) were otherwise identical between medical therapy and CRT. Third, the incidence of complications associated with CRT was constant over time from implantation. Since the duration of study followup in each trial was relatively short and the incidence of adverse effects observed in the randomized trials was higher than is generally accepted for implantable cardioverter defibrillator use (which may reflect relative inexperience with biventricular pacemakers),[83] the primary analysis assumed that the annual probability of each of lead infection, lead failure or mechanical malfunction was 3.0% (range 0% to 10%). We also assumed that any mechanical malfunction of the device required battery replacement with consequent costs and consequences. Fourth, uncomplicated CRT had identical health-related quality of life as that of medical therapy. Fifth, the utility for hospitalization was identical, regardless of the reason for hospitalization. The morbidity of hospitalization was incorporated into the model by assigning the utility for hospitalization to it's duration, and assigning the utility for the health state prior to hospitalization to the remainder of the cycle. Finally, age-specific mortality due to unrelated causes was based on life tables.[84]

An intervention that was more effective and less costly than the other was considered to be "dominant" and hence preferred to the alternative.

Uncertainty and Variability Analyses

The analysis distinguished between parameter uncertainty (i.e., variation in costs and effects due to 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.[85,86] Empirical cost variables were assigned log-normal distributions. Empirical probability variables were assigned beta distributions.[85] Variables without a known distribution form (i.e., those with assumed values, or those with values based on a range of published reports) were assigned triangular distributions.[87] Since there is no absolute cost-effectiveness criterion,[88] the results of the Monte Carlo simulations were illustrated as a scatter plot of incremental effects (in quality-adjusted life years) versus incremental costs. In such a plot, the incremental cost-effectiveness ratio is represented by the slope of incremental costs to incremental effects. The uncertainty in costs and effects was also illustrated as a cost-effectiveness acceptability curve. An acceptability curve is a conditional probability plot showing the proportion of the observed incremental cost-effectiveness density that lies below a threshold ratio, which represents the monetary value of a unit of health gain. The plot is conditional on the threshold ratio, and therefore the decision maker can interpret the data in light of their threshold willingess to pay for the incremental health outcome.

Variability was assessed by using sensitivity analyses as follows. We substituted the upper and lower limits of the value of each variable in the decision model while holding all other values constant (Table 3).[89,90] For empirical variables, these limits were the 95% confidence limits for each variable. For assumed variables (e.g., cost of cardiac resynchronization and discount rate), these limits were based on reasonable possible limits (i.e., $\pm$50%). Threshold analyses identified the value of each variable across its range, if any, at which one should be indifferent between medical therapy or CRT (i.e., the incremental costs per quality-adjusted life year was $100,000).[90]

Multiway sensitivity analyses were also performed. Since the effectiveness of both interventions may be correlated, we varied simultaneously the probability of arrhythmic death with medical therapy, and relative risk of arrhythmic death with CRT. Since the rate of adverse effects observed in the randomized trials was higher than is generally accepted for implantable cardioverter defibrillator use,[83] the incidence of device-related adverse effects observed in the trials was substituted into the model.

A structural sensitivity analysis considered the relative risks of cardiovascular death (heart failure death and sudden cardiac death) disaggregated with CRT versus medical therapy alone (Figure 2, end of chapter). Since it is difficult to classify cardiovascular deaths as arrhythmic or non-arrhythmic,[91] the pooled relative risk of arrhythmic death and non-arrhythmic death were based on retrospective subgroup analyses of data observed in the randomized trials of CRT. There is ongoing debate in the clinical community about whether CRT increases the risk of sudden cardiac death.

Finally, subgroup analyses considered the incremental cost-effectiveness of CRT versus medical therapy alone for patients with NYHA II or NYHA IV heart failure by substituting the appropriate health-related quality of life weight.

Peer Review

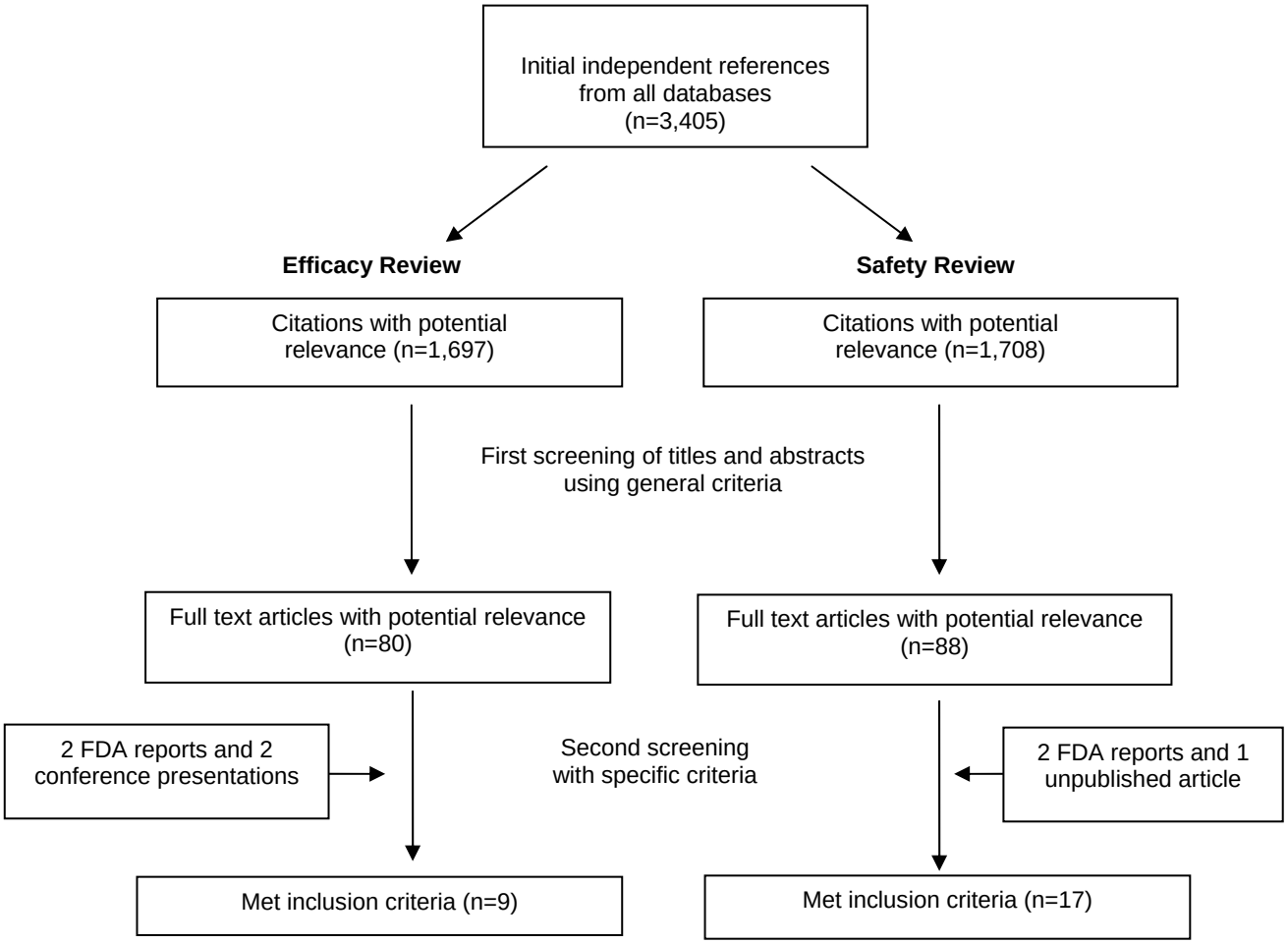
We asked 27 external people to peer review a draft of the report—consisting of the two completed reviews and the decision analysis. Nine agreed to do so, and we received comments from five of them. Authors considered their comments, as well as 6 anonymous peer reviewers from the Annals of Internal Medicine, and amended the analyses and document accordingly. Peer reviewers are listed in Appendix D, available on the AHRQ web site (except of course the anonymous peer reviewers from the Annals of Internal Medicine).

Chapter 3. Results

Literature Search

Of more than 3000 initial references, only nine and 17 studies were accepted for the efficacy and safety reviews, respectively (Figure 3). Two of these were unpublished manuscripts describing studies that met the inclusion criteria. Another was a report submitted to the FDA on the MIRACLE[35] trial to enhance data from the published trial results.[61] Also included were the FDA reports on the MIRACLE ICD[93] and CONTAK CD[73] trials found on the FDA web site. (We used the published report for data on patients with NYHA Class III or IV symptoms in the MIRACLE ICD[94] Trial, and the FDA report for NYHA Class II data since this was not included in the journal publication.) Bristow published the protocol for the COMPANION trial in 2000,[95] and the results were presented at the Annual Scientific Conference of the American College of Cardiology in Chicago, April 2003. Further unpublished data from this trial were made available to us and are included in the analysis.

Figure 3. Flow diagram of study retrieval and selection for cardiac resynchronization therapy



There were three main reasons for exclusion of studies from the review: 1) the intervention studied was not CRT; 2) the article was a review, a protocol, or an editorial; and 3) the study did not report our outcomes of interest. The list of excluded studies and reasons for exclusion are identified at the end of the Reference List.

Most of the included trials were associated with multiple publications that either expanded on the main results or reported secondary outcomes not included in the primary report. We only included the primary report for each trial, but did extract data on secondary outcomes if they were reported only in these secondary publications. Table 4 (end of chapter) identifies the associated publications.

Efficacy Review

Description of Included Studies

Nine randomized trials met the inclusion criteria for the efficacy review:

Abraham 2002: Multicenter InSync Randomized Clinical Evaluation (MIRACLE trial).[61]

Auricchio 2002: Pacing Therapies for Congestive Heart Failure (PATH CHF trial).[62]

Bristow 2003: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION trial).[60]

Cazeau 2001: Multisite Stimulation in Cardiomyopathies Sinus Rhythm (MUSTIC SR trial).[74]

Garrigue et al.[70]

Guidant Corporation: the CONTAK CD trial.[73]

Medtronic 2001: Multicenter InSync Randomized Clinical Evaluation ICD (MIRACLE ICD).[36,93,94]

Leclercq 2000: Multisite Stimulation in Cardiomyopathies Atrial Fibrillation (MUSTIC AF trial).[96]

RD-CHF: presented at the 2003 European Society of Cardiology Meeting and personal communication from Dr. C. Leclerq November, 2003.

Six of these trials have been published, (Garrigue et al., MIRACLE, MIRACLE ICD, MUSTIC AF, MUSTIC SR, and PATH CHF) and three (COMPANION, CONTAK CD, RD-CHF) were located from other sources as mentioned above. The four largest trials were conducted in North America,[36,60, 61,73] and the other five were conducted in the European Community.[62,70,74,75,RD-CHF] Characteristics of the trials are summarized in Table 5 (end of chapter).

In total, 3574 patients were enrolled in these trials and 3216 (90%) were randomized to receive CRT (n=2063) or control (n=1153). The majority of those who were enrolled but not randomized had failed implant attempts. The mean age of enrolled patients was 64 ± 3 years and 74% were male. Approximately 75% were considered NYHA class III (range 55% to 100%) and 10% NYHA class IV (range 6% to33%). Two trials included NYHA class II (range 10% to 38%).[36,73] Ethnic background was available from one trial in which 90% were Caucasian.[61] Further details about baseline characteristics for each trial are presented in Table 6.

No trial specifically recruited patients based on the etiology of their heart failure, although patients with uncorrectable valvular disorders and hypertrophic or restrictive cardiomyopathy were excluded from all trials. In the three trials that evaluated CRT with ICDs, the majority of patients had ischemic etiology (~59%);[36,60,73] in the other trials, ischemic etiology ranged from 37%[74] to 55%.[61] Other comorbidities such as diabetes mellitus, renal failure, previous cardiac history, or a history of sudden cardiac death were reported in only one trial.[93]

All trials (except PATH CHF, which did not specify an ejection fraction criteria)[62] were limited to patients with an ejection fraction < 35% or < 40%. The mean ejection fractions were similar in all trials, and ranged from 21% to 30%. Six trials also specified a left ventricular end diastolic dimension: ≥ 55 mm in two trials[36,61] and ≥ 60 mm in the other four trials.[60,70,74,75] The reported mean left ventricular end diastolic dimension for the trials were similar (68 mm to 73 mm).

QRS width was a criteria for all trials, with three trials specifying ≥ 120 msec,[60,62,73] two trials ≥ 130 msec,[36,61] one trial >140 msec,[70] one trial >150 msec,[74] one trial >180 msec, and one trial >200 msec.[75] Six of the nine trials had a mean QRS between 159 msec and 175 msec, with the MUSTIC AF trial having a mean QRS of 209 msec. Left bundle branch block was present in most patients (mean 64%; range 0 to100%).

Five trials were restricted to patients in normal sinus rhythm,[60,62,73,74] but two were restricted to patients with atrial fibrillation[70,75] In the eighth trial ~14% of patients had atrial fibrillation.[93] Overall, approximately 5% of randomized patients included in this meta-analysis had atrial fibrillation. Three trials reported PR intervals that ranged from 196 msec to 215 msec and two required a prolonged PR interval >150 msec for inclusion.[60,62] Three trials required a six-minute walk test result of less than 450 meters as an inclusion criterion.[61,74,75] The physical exam findings at baseline were similar among trials, with systolic blood pressure (range 113 to 118 mmHg), diastolic blood pressure (range 67 to 69 mmHg), and heart rate (range 71 to 80 bpm) all similar to other trials in heart failure.[97]

In the three trials where implantable cardioverter defibrillators were tested along with cardiac resynchronization therapy,[36,60,73] there was a general requirement that study patients meet indications for ICD placement. Although it was not specified by which ICD criteria patients were evaluated, the indications in MIRACLE ICD[36] and CONTAK CD[73] were consistent with the AHA/ACC/NASPE guidelines for secondary prevention. (Table C-1, available on the AHRQ web site, details the inclusion criteria of the individual trials.)

Medication use was specified in all but the PATH-CHF and RD-CHF trials.[62] ACE inhibitors were required in all trials, beta-blockers were required in three,[60,61,70] and spironolactone was only required in COMPANION.[60] (Baseline medication use in the efficacy review trials is detailed in Table 7 at the end of this chapter.) Importantly, three European trials reported 31% use of amiodarone,[62,70,74] and 38% of patients in the MIRACLE ICD trial were on non-beta-blocker anti-arrhythmic agents.[36] Digoxin was used in 48% to 76% of patients, with the four largest trials having at least 75% of their patients on digoxin.[36,60,61,73]

Four of the trials employed a parallel study design.[36,60,61,73] One of these had planned a crossover period but changed protocol mid-study and excluded crossover data from the analysis;[73] five others completed a crossover design.[62,70,74,75,RD-CHF] The duration of treatment was 4 weeks in PATH CHF,[62] 2 months in Garrigue et al.,[70] 3 months in RD-CHF, 3 months/phase in MUSTIC AF[75] and MUSTIC SR,[74] 6 months in MIRACLE[61] and MIRACLE ICD,[36] and 12 months in the COMPANION[60] trial. Eight of the nine trials used a transvenous

approach for placement of the epicardial leads (54 patients in CONTAK CD[73] required a transthoracic approach), while PATH CHF[62] used a transthoracic approach.

Parallel-arm trials. The MIRACLE trial[61] enrolled 453 patients (NYHA Class III or IV); 228 were randomized to CRT 'on', 225 to CRT 'off' (Table 5). The MIRACLE ICD trial[36] enrolled 659 patients (NYHA Class II to IV; 434 in NYHA Class III/IV); 554 patients were randomized (364 in NYHA Class III/IV): 272 to CRT 'on' and 283 to CRT 'off'. All patients in MIRACLE ICD[36] received an implantable cardioverter defibrillator. For both MIRACLE[61] and MIRACLE ICD,[36] the primary outcomes were quality of life, six-minute walk test, and NYHA class.

COMPANION[60] was a three-arm, parallel-group trial that compared optimal pharmacological therapy (n=308), cardiac resynchronization therapy (n=617), and cardiac resynchronization therapy with cardioverter defibrillator (n=595) randomized in a 1:2:2 fashion before device implantation. The primary outcome was a composite of all-cause mortality and all-cause hospitalization (including emergency room visits or unscheduled office visits requiring >4 hours of intravenous vasoactive or inotropic drug).

CONTAK CD[73] was a two-part trial with an initial pilot crossover involving two 3-month phases (n=205 for first 3 month results). We were not able to obtain complete data from the second phase; hence this part of the trial was excluded from this report. For part two, they conducted a parallel design study with 6-month followup (n=151). The device used also had a cardioverter defibrillator. The primary outcome was a composite of all-cause mortality, heart failure hospitalizations, and ventricular arrhythmias requiring device intervention.

Crossover Trials. In MUSTIC SR,[74] 67 patients were enrolled and implantation attempted, followed by an 8- to 12-week observation phase; 58 patients were then randomized into a 3-month crossover of either CRT 'on' or 'off' (Phase 1: n=29, Phase 2: n=29). In MUSTIC AF,[75] 64 patients were enrolled and implantation attempted, followed by 8 to 12 weeks of observation; 43 were randomized into a 3-month crossover of CRT 'on' or 'off' (Phase 1: n=25, Phase 2: n=18). Both trials used the six-minute walk test as the primary outcome. Neither used a 'washout' period between phases and neither detected a carryover effect.

PATH CHF[62] was a 4-week crossover study in which 42 patients were enrolled and implantation attempted; 41 patients were randomized to CRT 'on' or 'off' in two phases with a 4-week washout period between the two (Phase 1: n=24, Phase 2: n=17). The primary endpoint was peak oxygen uptake on a maximal exercise test. This trial did detect a carryover effect.

Garrigue et al.[70] used a 2-month crossover design in which 13 patients had the device implanted (plus HIS-bundle ablation). The 13 patients were randomized to either CRT or left-univentricular pacing alone. The primary endpoint was peak endocardial acceleration time as measured by an implantable sensor. Patients were crossed over after 2 months without a washout phase. The study did not assess for a carryover effect in the analysis.

Methodological Quality of Included Studies

As a measure of methodological quality for the included trials, (end of chapter) the overall Jadad[58] score (maximum five points) was 5 for one trial,[61] 4 for three trials,[61,62,73] 3 for three others,[60,74,75] and one for the remaining study[70] (Table 8). Insufficient details about the RD-CHF Trial were provided to be able to grade methodologic quality.

All trials were described as randomized; however, the description of randomization detail varied. As far as blinding, two were open-label,[60,70] three were single-blind (i.e., the patient was blinded)[60,74,75] and four were double-blind (patient and the outcome assessor was blinded).[36,61,62,73] In CONTAK CD,[73] MIRACLE,[61] and MIRACLE ICD,[36] the independent events committee was blinded to which arm of the trial the patient was in; no information was available for COMPANION.[60] Notably, five trials randomized patients before implantation.[60,62,73-75] An intention-to-treat statistical analysis was specified in all trials, and MIRACLE[61] and PATH CHF[62] performed an intention-to-treat analysis.[61,62] In the remaining trials, it was either unclear[60,74,75] or multiple analyses were done for the FDA that included an intention-to-treat analysis of all patients involved in the trial program[36,73] Withdrawals and dropouts were clearly described in all trials except COMPANION.[60] Unscheduled crossovers occurred in zero to nine percent of the patients in these trials and were generally balanced between study arms. Withdrawals ranged from zero to 3% for the cardiac resynchronization group and from zero to 2.5% for the control groups. Allocation concealment was unclear for all but the MIRACLE[61] trial.

Industry sponsored seven of the nine trials; two also received funding from government sources.[74,75] Guidant Corporation sponsored three,[60,62,73] Medtronic Inc. sponsored four,[36,61,74,75] and ELA Recherche funded two.[74,75] Garrigue et al.[70] did not report funding sources.

Safety Review

Description of Included Studies

Seventeen randomized (n=8) and cohort studies (n=9) met the inclusion criteria for the review of safety of cardiac resynchronization therapy (Table 9, end of chapter). Eight of the nine trials included in the efficacy review were eligible (Garrigue et al.[70] did not contain any pertinent safety outcomes). The 9 additional studies included one randomized trial that did not report efficacy endpoints of interest[98] and 8 prospective cohort studies,[70,96,99-103] that included one unpublished manuscript submitted to us by an author of another included study.[104] Thirteen studies reported that devices were implanted transvenously, two were transthoracic,[62,98] and two used both approaches.[73,105] Either Medtronic Inc. or Guidant Corporation manufactured all implanted devices; however, the models and leads varied among and within trials.

In total, 3938 patients were enrolled; of these, 3636 patients received CRT. Some patients were excluded or withdrew due to unsuccessful implants, death, heart transplantation, or miscellaneous reasons. The mean age was 65 ± 3 years, and 78% were male. Approximately 75% of each study population was NYHA class III (range 32% to100%), and 17% NYHA class IV (range 4 to 100%) (Table 10). Five studies[73,93,98,101,102] included patients with NYHA class II symptoms (range 4% to 38%). Ethnic background was available from one trial in which 90% were Caucasian.[61]

Kuhlkamp[102] required participants be survivors of a cardiac arrest and have sustained ventricular tachycardia; otherwise no studies specifically based inclusion on the etiology of their heart failure. Patients with correctable valvular disorders, hypertrophic or restrictive cardiomyopathy, unstable angina, or acute myocarditis were excluded. Four studies did not state

exclusion criteria.[99,102,103,106] Ischemic etiology ranged from 29%[62] to 69%.[101] Other comorbidities such as diabetes mellitus or renal failure were reported in only one study.[36]

Eleven studies limited inclusion to patients with an ejection fraction <35%, one restricted it to <30%,[98] one to <25%,[60] and 3 did not specify this criterion.[62,99,101] The mean ejection fraction ranged from 19% to 26%. Nine studies specified a left ventricular end diastolic dimension inclusion criterion of ≥55 mm[60,61,74,75,93,96,100,102,104] or ≥ 60 mm. The reported mean left ventricular end diastolic dimension for the trials ranged from 68 mm to 74 mm.

QRS width was a criterion for 13 studies, with six specifying ≥ 120 msec,[60,62,73,103,107] four studies ≥ 130 msec,[61,93,101,102] two trials >150 msec,[74,100] and one > 200 msec.[75] Ten of the 16 studies reported a mean QRS between 158 msec and 180 msec, and six ranged from 180 msec to 213 msec.[70,75,96,99,104,106] In the nine studies that reported the presence of left bundle branch block, the mean was 68% (range 0 to 100%).

Five studies were restricted to patients in normal sinus rhythm,[60,62,74,100] but two were restricted to patients with atrial fibrillation.[96,106] In the others, 6% to 38% of patients had atrial fibrillation. Eight studies reported PR intervals that ranged from 198 msec to 248 msec, and two required a prolonged PR interval >150 msec for inclusion.[60,62] Three studies required a six-minute walk test result of ≤ 450 meters as an inclusion criterion.[61,74,75] The physical exam findings of systolic blood pressure (range 113 mmHg to 118 mmHg), diastolic blood pressure (range 67 mmHg to 68 mmHg), and heart rate (range 73 to 78 bpm) at baseline were all similar to other studies in heart failure.[97] (The inclusion and exclusion criteria for the individual studies are detailed in Appendix C: Table C-2).

Concomitant medication use was specified in all but the PATH CHF[62] and Molhoek[103] studies (Table 11). ACE inhibitors were required in all studies, beta-blockers were required in three,[60,61,101] and spironolactone was only required in COMPANION.[60] Importantly, four studies reported 31% to 50% use of amiodarone,[62,74,98,100] and 38% of patients in the MIRACLE ICD trial[36] were on non-beta-blocker anti-arrhythmic agents. Eleven studies reported that 32% to 100% of participants were on digoxin and 90% to 100% were taking diuretics. Table 11 (see end of chapter) details baseline medication use by study.

Quality of Included Studies

Overall, the studies were rated as having 'good' quality on the Downs and Black[59] scoring system. Eight studies were described as randomized (three parallel trials,[36,95,108] five crossover trials,[62,73,74,96,98] and the remaining eight were prospective cohort studies.[99,96,100-104,106] Reporting was generally good with 8 of 16 rating 11/11, the rest ranging from 7 to 10. External validity assessment posed some problems because authors did not report the source population for patients or the proportion of eligible patients selected for inclusion, nor compare the distribution of main confounding factors with the source population. (For this review we defined the source population as those with symptomatic CHF.) Since this procedure can only be performed in specialist centers, we determined that all facilities were representative. Internal validity concerning assessment of bias ranged from 5/7 to 7/7; the lack of blinding was the main shortfall. Four studies were double-blind,[36,61,62,73] two were single-blind (i.e., the patient),[74,75] and the remaining trials were open-label. Internal validity assessments concerning confounding ranged between 1/6 to 6/6, with only two studies receiving 2 or less.[96,100] Many authors did not state the period of time over which patients were recruited, the source of patients, or how the randomization code was generated and concealed. Withdrawals and dropouts were clearly

described in all studies except COMPANION.[60] Four studies included a power calculation,[60,61,74,75] and nine had sufficient sample sizes to determine a clinically important effect.[36,60-62,73-75,98,104]

The majority of studies that reported sponsorship received funding from industry. Three were sponsored by Guidant Corporation,[60,62,73] six by Medtronic,[36,61,74,75,102,106] and three received technical support from ELA Recherche.[74,75,99] The two MUSTIC trials[74,75] and Krahn[101] received funds from independent sources. Four studies did not report a funding source.[96,98,100,104] Methodological quality of the trials in the safety review are summarized in Table 12 (end of chapter).

Quantitative Results

Efficacy Review

The nine trials included 2755 patients with NYHA Class III or IV CHF, and 461 patients with NYHA Class II symptoms.

All-cause mortality. Based on data pooled from all nine randomized controlled trials (311 deaths in patients with NYHA class III or IV symptoms at baseline, 14 deaths in those with NYHA class II symptoms), CRT significantly reduced all-cause mortality, with a relative risk of 0.75 (95% CI 0.60 to 0.93) (Figure 4 end of chapter). There was no significant statistical heterogeneity between trials (p=0.88, I-squared=0%). The results were identical when the analysis was restricted to patients with NYHA Class III or IV symptoms (RR 0.76, 95% CI 0.60 to 0.95). The all-cause mortality rate in the control patients with symptomatic heart failure (NYHA II-IV) was 14.9%, and the number needed to treat (NNT) to prevent one death was 27 in patients with symptomatic heart failure.

Time-to-death analysis. The time-to-death analysis (4 trials; n=2769 patients) demonstrated that length of followup affects results with the survival curves separating after 3 months (Figure 5). Trials with longer followup periods reported greater survival benefits. When data were used for trials with a followup of six months or more,[36,60,61] all-cause mortality remained significant with a relative risk of 0.70 (95% CI 0.56 to 0.89). The 12-month survival rate for the CRT group was 89% (95% CI 87% to 90%) and 83% (79% to 86%) for the non-CRT group; this difference was significant based on the log-rank test (p=0.005). To account for the separation of the curves at 3 months and since data were integrated from four studies, we used a Cox proportional hazards model (using study as a covariate) and only incorporated data from beyond the first three months. The hazard ratio was 0.59 (95% CI 0.43 to 0.81) for mortality after the first 3 months post-implantation.

Cardiac mortality. Seven trials reported progressive heart failure mortality in NYHA Class II to IV patients (n=60 deaths/1647 patients); the relative risk strongly favored CRT, although it just failed to reach statistical significance using the (methodologically correct, but statistically conservative) random effects model (RR 0.60, 95% CI 0.36 to 1.01; Figure 6). Restricting this

analysis to patients with NYHA Class III or IV symptoms gave similar results (RR 0.58, 95% CI 0.32 to 1.06).

Sudden cardiac death. Using data pooled from the eight trials that reported the cause of death, sudden cardiac death (n=28 deaths/1691 patients) was higher (although non-significantly) with CRT compared to controls (RR 1.99, 95% CI 0.95 to 4.16; Figure 7). This result was not statistically heterogeneous (p=0.98, I-squared=0%) and was similar if only trials of six months or longer were included or if only patients with NYHA Class III or IV were included (RR 1.89, 95% CI 0.76 to 4.70). Only one trial that included an implantable cardioverter defibrillator for all patients reported the cause of death; the risk for sudden cardiac death was non-significant (RR 1.89, 95% CI 0.35 to 10.21).[36]

Non-cardiac death. Pooled data from six trials (n= 17/1194 patients) did not demonstrate any significant differences in non-cardiac deaths between patients with CRT (RR 0.90, 95% CI 0.35 to 2.35; Figure 8). This result was not statistically heterogeneous (p=0.46, I-squared=0%). Restricting the analysis to patients in NYHA Class III or IV CHF did not alter this conclusion (RR 1.89, 95% CI 0.35 to 10.21).

Morbidity and functional outcomes.

Heart failure hospitalizations. Pooled results from the six trials that reported heart failure hospitalizations showed a relative risk of 0.68 (95% CI 0.41 to 1.12; Figure 9 end of chapter) in favor of CRT compared to control. This result was heterogeneous (p=0.01, I-squared=65%) and was also insignificant in the fixed effects analysis (RR 0.80, 95% CI 0.64 to 1.003). Restricting the analysis to patients with more advanced heart failure (those with NYHA Class III or IV symptoms) revealed significant reductions (RR 0.65, 95% CI 0.48 to 0.88; NNT=12) and was statistically homogeneous (p=0.31, I-squared=16%).

Six-minute walk test. CRT was associated with an improved six-minute walk test distance, with a weighted-mean-difference of 23 meters in favor of CRT (95% CI 9 m to 38 m, Figure 10 end of chapter). This improvement was similar in those patients with NYHA Class III or IV symptoms (WMD 26 m, 95% CI 11 m to 41 m). However, this result was heterogeneous (p=0.06, I-squared=50%) in part due to one trial[74] in which the control group worsened by 24 meters; the control groups in all other trials that reported baseline results showed an improvement. Although the data from the RD-CHF Trial were not available for pooling, the RD-CHF investigators reported statistically significant improvements in six-minute walk test distances with CRT (personal communication, Dr. Christophe Leclercq, November 2003).

New York Heart Association Functional Class. We were able to meta-analyze data for NYHA Class from three studies (although five studies reported baseline and endpoint NYHA Class). Combining these three studies showed improvements in NYHA Class in 57% of CRT patients and 34% of controls (CRT was associated with a 1.63 times increased chance of improving at least one NYHA Class (95% CI 1.05 to 2.52), Figure 11). This result was statistically heterogeneous (p=0.04, I-squared=70%). In patients with NYHA Class III or IV symptoms, the relative risk improved slightly to 1.68 (95% CI 1.25 to 2.27). The data from MIRACLE ICD[61] was not reported in a format that permitted pooling with the other 3 trials; however, the baseline

median NYHA Class for both groups was III and the endpoint median was II in the CRT group and III in the control group. This improvement in NYHA Class was significant (p=0.01) and favored CRT; the specific statistical test used was not reported. In contrast, PATH CHF[62] (which could also not be combined with the other trials due to the manner in which the data were reported) did not find a significant difference (p=0.36; Wilcox on matched-pairs test), although both groups showed significant improvement from baseline. Moreover, while the data from the RD-CHF Trial could not be pooled with the other trials, the RD-CHF investigators also reported statistically significant improvements in NYHA Class with CRT (personal communication, Dr. Christophe Leclercq, November 2003).

Quality of life. Quality of life was measured by the Minnesota Living With Heart Failure Instrument[109-111] for six of the eight trials; pooled results showed a significant improvement in favor of CRT (weighted mean difference –5.5 points (95% CI -9 to -2 points; Figure 12). This result was highly statistically heterogeneous (p=0.008, I-squared=68%); however results were consistent in direction. Restricting the analysis to only those patients with NYHA Class III or IV symptoms increased the difference between the CRT and control groups (WMD –6.4 points, 95% CI –9.4 to –3.4 points), but the results remained significantly heterogeneous (p=0.07, I-squared=50%). These differences are clinically significant since the minimal clinically important difference for the Minnesota Living with Heart Failure Questionnaire has been established to be 5 points.[109-111] 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 (personal communication, Dr. Christophe Leclercq, November 2003).

Other outcomes. Peak oxygen consumption significantly improved in the CRT patients compared to the control patients (1.05 ml/kg/min versus 0.39 ml/kg/min; WMD 0.65 ml/kg/min, 95% CI 0.27 to 1.04 ml/kg/min). Ejection fraction also significantly improved in the CRT arm compared to the control arm (4.17% versus 0.82%; WMD 3.35%, 95% CI 1.22 to 5.48%). The QRS interval also showed greater improvement in the CRT group (-30 msec versus -2 msec for controls; WMD –28, 95% CI –47 msec to –9 msec). Other echocardiographic indices including mitral regurgitation jet area were not significantly different between groups; there were insufficient data that could be pooled for left ventricular end-diastolic or end-systolic diameters.

Sensitivity analyses. Many *a priori* subgroup and sensitivity analyses (including examining any interactions between the effects of CRT in patients with different etiologies of heart failure, or by ethnic background, gender, age, comorbidities, and baseline medication use) could not be performed due to the paucity of subgroup data in the trial reports and our inability to obtain individual patient-level data from each of the trial lists despite our requests.

Post-hoc, we explored the impact of ICDs on the efficacy of CRT using meta-regression (a between-study non-randomized comparison). When the data were pooled for all-cause mortality from the two trials that included an ICD in both the experimental and control arms (i.e., CRT+ICD versus medical therapy +ICD),[36,73] the relative risk was 0.84 (95% CI 0.54 to 1.28). On the other hand, pooled data from the other five trials comparing CRT versus medical therapy demonstrated a relative risk of 0.78 (95% CI 0.56 to 1.08) with CRT (Figure 13).[61,62,74,75] This difference was not statistically significant (p=0.80), supporting the assertion that the benefits of CRT on all-cause mortality are not appreciably altered by addition of an ICD. Using the same meta-regression model, secondary outcomes (including heart failure hospitalizations, six-minute

walk test, quality of life, and NYHA improvements) were not significantly different in patients with, or without an ICD, in addition to their biventricular pacemaker. Of note, while the data from COMPANION[60] could not be used in the meta-regression for ICDs (since none of the arms in COMPANION[60] consisted of ICD alone), the COMPANION[60] data does provide the only direct comparison between CRT plus ICD versus CRT alone. This analysis did approach statistical significance (p=0.07) in favor of the CRT *plus* ICD group for all-cause mortality; however, the reductions in heart failure hospitalizations were similar in CRT-treated patients with/without ICDs. Until the detailed data from the COMPANION[60] sub-analyses are made available, the most conservative conclusion that can be made at this stage is that the benefits of CRT are similar with or without ICDs.

Post-hoc we also explored the relationship between the baseline use of beta-blockers and/or digoxin with the impact of CRT on all-cause mortality. Both meta-regressions were non-significant (p=0.37 and p=0.31, respectively), suggesting that the benefits of CRT are not modified by use of these medications. However, and as expected, the linear trends showed improved survival with greater use of beta-blockers.

Publication bias could not be quantitatively measured since all of the smaller studies had shorter followup times, hence confounding results. In a post-hoc subgroup analysis examining published versus unpublished studies, there was no appreciable difference between effect estimates for all-cause mortality (p=0.64).

Fixed effects estimates did not substantially alter the results of our meta-analysis (although the confidence intervals were naturally narrower and, as a result, the analysis for progressive heart failure mortality (RR 0.59, 95% CI 0.35 to 0.98) reached statistical significance).

Safety Review

As previously described, seventeen studies were used to examine the safety of CRT. Tables 13 and 14 report peri-implantation and post-implantation risks from individual studies as well as pooled results. In pooling data, we did not include studies that did not report any data for particular outcomes. However, where appropriate, we performed sensitivity analyses by assuming zero occurrences of that endpoint in that study.

Peri-implantation risks. Ten studies reported data on deaths while undergoing implantation of a biventricular pacemaker (Table 13, end of chapter). There were 13 deaths in 3113 patients (pooled risk 0.4%, 95% CI 0.2% to 0.7%); a sensitivity analysis assuming any studies that did not report mortality had zero occurrences yielded the same estimate. Immediate deterioration in heart function was noted after 1.3% (95% CI 0.7% to 2.2%) of implantation procedures. Implants of devices were successful in 89.9% (95% CI 88.8% to 90.9%) of attempts in 3475 patients from 17 studies; this rate did not vary, but trended toward improvement, by year of publication.

Problems with implantation of the left-ventricular lead were encountered in 6.0% (95% CI 4.7% to 7.2%) of cases. Assuming that any studies failing to report any implantation problems had zero occurrences in sensitivity analysis led to a reduced estimate of 3.9% (95% CI 3.1% to 4.8%). The device or battery was problematic in 0.9% (95% CI 0.6% to 1.6%) of cases (0.7%, 95% CI 0.4% to 1.2% with sensitivity analysis), and the procedure or equipment used for the procedure was reported to be a problem in 6.4% (95% CI 5.3% to 7.6%) of cases attempted (reduced to 5.6%, 95% CI 4.7% to 6.7% in sensitivity analysis). Further detailed information on

the type of equipment failure was not uniformly available, so pooling of results was not possible. Some of the specific problems in this category included lead fracture, loss of capture, inappropriate sensing, and extra-cardiac stimulation.

Post-implantation risks. Data from 13 studies were used to assess post-implantation risks with CRT (Table 14 end of chapter). Over a median 6 months of followup, mechanical malfunction of the CRT device was noted in 6.7% (95% CI 5.4% to 8.2%) of successful implants. On sensitivity analysis, assuming any studies that failed to report this outcome had zero occurrences, this rate fell to 4.4% (95% CI 3.6% to 5.4%). Lead dislodgment occurred in 8.5% (95% CI 7.4% to 9.9%) of patients, with no differences in those studies using specially designed left ventricular leads (this estimate was reduced to 8.3%, 95% CI 7.1% to 9.6% on sensitivity analysis). Post-implantation infection (most commonly in the device pocket) occurred in 1.4% (95% CI 0.8% to 2.3%) of patients (reduced to 0.9%, 95% CI 0.5% to 1.4%, with sensitivity analysis). Arrhythmias attributed to the CRT device occurred in 1.7% (0.8% to 3.4%) of patients during followup.

Decision Analysis

Effectiveness of Medical Therapy

Expanding on the results from our systematic review outlined above, annual event rates were calculated (median followup time was 22.8 weeks in these trials). The annual risk of death was mean 24.3% (95% CI 20.0% to 29.2%) and the annual risk of heart failure hospitalization was 56.0% (95% CI: 47.6% to 66.2%).

Effectiveness of Cardiac Resynchronization Therapy

Based on the results of the systematic review, annual event rates were calculated for patients with NYHA Class III heart failure randomized to CRT. The relative risks were: all-cause death 0.75 (95% CI: 0.60 to 0.93) and CHF hospitalizations 0.68 (95% CI: 0.41 to 1.12).

Cost-Effectiveness of Cardiac Resynchronization Therapy

In patients with NYHA Class III heart failure, medical therapy had median 2.68 (interquartile range, IQR=2.49, 2.85) discounted quality-adjusted life years and median $34,700 (IQR= $31,100 to $38,100) lifetime costs (Table 15). Cardiac resynchronization had median 3.03 (IQR= 2.82 to 3.27) discounted quality-adjusted life years and median $67,600 (IQR= $62,000 to $73,800) lifetime costs. Cardiac resynchronization was associated with an incremental cost of median $90,700 (IQR= $69,500 to $124,900) per additional quality-adjusted life year. Data points from Monte Carlo simulation illustrate that compared to medical therapy, CRT is consistently associated with a survival gain and an additional cost (Figure 14). The cost-effectiveness acceptability curve illustrates that the probability that CRT is cost-effective relative to medical therapy alone is less than 59%, given a maximum willingness-to-pay for a quality-adjusted life year of $100,00 (Figure 15).

Variability Analyses

The incremental cost-effectiveness of CRT was sensitive to reasonable changes in values for several variables including relative risk of either death or hospitalization with CRT, probability of death during either lead failure or battery replacement, and costs of either device insertion or battery replacement (Table 3). Also, if CRT were associated with greater health-related quality of life than medical therapy, then the incremental cost-effectiveness of CRT was reduced (details available from authors).

Chapter 4. Discussion

Systematic Review

Efficacy and Safety

When added to proven efficacious medical therapy, cardiac resynchronization therapy reduces risk of all-cause mortality by 25% in patients with symptomatic CHF who have prolonged QRS duration and reduced left ventricular ejection fraction. This relative survival benefit is similar to those reported for ACE inhibitors, beta-blockers, and aldosterone antagonists in recent trials.[30,31,109,138] When added to optimal medical therapy, 27 patients need to successfully undergo CRT implantation to prevent one death. This reduction in all-cause mortality occurs in both the sickest heart failure patients (those with NYHA Class III or IV symptoms) as well as those with milder disease (NYHA Class II symptoms), with identical relative benefits in both groups.

The survival benefits with cardiac resynchronization therapy become apparent by 3 months after implantation; after the first 3 months, those patients receiving a biventricular pacemaker had 41% lower mortality risk than those without cardiac resynchronization therapy. It is likely that the benefits do not appear for several months because long-term benefits of cardiac resynchronization therapy are mediated through morphometric remodeling of the left ventricle rather than neurohormonal changes.[136,139] Indeed, preliminary results have suggested that, while brain natriuretic peptide levels are reduced in patients by cardiac resynchronization,[94,140] levels of norepinephrine, big endothelin, and other markers of inflammation are all unchanged. Thus, while drug therapies that impact both the neurohormonal system and ventricular remodeling in heart failure patients (such as ACE inhibitors and beta blockers) reduce the incidence of sudden cardiac death within weeks of being prescribed (possibly due to their immediate impact on the renin-angiotensin and sympathetic systems), several months are required for the benefits of cardiac resynchronization to become apparent and these benefits are largely restricted to progressive heart failure deaths.

Most of the survival benefits with cardiac resynchronization therapy appear to be attributable to a substantial reduction in the rate of progressive heart failure deaths (a 40% relative reduction), which is similar to the 51% relative risk reduction in progressive heart failure deaths found in a previous meta-analysis that incorporated four of the eight trials in this analysis.[141] This is not surprising since the putative benefits of cardiac resynchronization therapy are via improved cardiac output, reduced mitral regurgitation, and reduced pulmonary capillary wedge pressure.[35,54,55] While we found a non-significant trend toward increased sudden cardiac death that was consistent across these trials, that trend was based on a very small number of events (28 in total) and thus is not interpretable without further trial data (particularly given the well recognized difficulties in sub-classifying cardiac deaths as sudden or non-sudden). In particular, the lack of a difference in the number of ventricular arrhythmia episodes between those patients with, versus without, CRT in the MIRACLE ICD Trial (22% vs. 26%, p=0.47) suggests that the trend toward excess sudden cardiac deaths may well be due to small numbers.[94]

Regardless, the benefits of cardiac resynchronization therapy are similar in patients with or without implantable cardioverter defibrillators, providing some reassurance that, in those patients who have indications for both an ICD and a biventricular pacemaker, the two may be administered together. An issue that remains to be resolved by ongoing studies (and is beyond the scope of this systematic review) is the role of ICDs for primary prevention in patients with heart failure,[47] which is particularly controversial in those patients with NYHA Class IV symptoms[142] or with non-ischemic dilated cardiomyopathy.[143,144] A large study, SCD-HeFT, which is due to report its findings in December 2003, should help clarify this isue.[84] (http://www.sicr.org/scdheft/index.html accessed August 18, 2003)

Cardiac resynchronization therapy also led to a 32% reduction in hospitalizations for heart failure. This benefit was more marked in those heart failure patients who were more symptomatic and thus at higher risk for hospitalization (i.e., those with NYHA Class III or IV symptoms): a 35% relative risk reduction. The magnitude of this benefit is similar to those reported for ACE inhibitors, beta-blockers, and aldosterone antagonists.[29-32,34-36]

Cardiac resynchronization therapy also conferred statistically and clinically significant benefits in quality of life, peak oxygen capacity, ejection fraction, left ventricular volumes, distance walked in six minutes, and NYHA Class in patients with advanced heart failure and prolonged QRS duration. Quality of life is an important endpoint for heart failure, and a pooled six-point improvement on the Minnesota Living With Heart Failure instrument is larger than that seen in other heart failure trials and is greater than the minimal clinically important difference of 5 reported by the developers of the scale.[109-111,145,146]

An important finding of this systematic review is the safety of cardiac resynchronization therapy and its tolerability in patients with advanced heart failure. Peri-implantation mortality rates were less than 1%, despite the increased peri-operative mortality risk many of these patients face secondary to their heart failure, age, and frequent comorbidities such as renal failure and diabetes mellitus.[147] Post-implantation infection rates were also low (approximately 1%). However, although there were few serious complications, implantation of a biventricular pacemaker (in particular the left ventricular [LV] lead) is technically challenging, even in experienced hands. Our systematic review identified a 10% failure rate for implantation of a biventricular pacemaker, largely due to problems positioning the LV lead. Furthermore, even if successfully implanted, these devices require close followup as 7% of devices malfunctioned over a median followup of six months, and 9% of LV leads dislodged. As such device failure complications will require another intervention and/or a new device to fix the problems, the failure rates have to be incorporated into any cost-effectiveness analyses for these devices. Further, the reductions in heart failure hospitalizations observed with CRT therapy may be offset to some degree by increased admissions for CRT revisions (although we were unable to obtain analyzable data on CRT revision admissions in these trials).

Location of the ventricular lead may be crucial to determining which patients respond best to therapy.[148,149] However, although individual trials reported the final location of the implanted LV lead, outcomes and other information regarding location were not useable for pooled analysis as data were not stratified by final location of the LV lead. It is plausible, though, that current implantation success rates may be higher than those documented in these trials, as the experience of CRT device implanters, the tools for implantation, and the sophistication of the devices has improved over the past few years; however, ongoing surveillance is necessary to substantiate this.

Potential Limitations of Systematic Review

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 in some pharmaceutical trials, does not affect the internal validity of the trials, but does impact the generalizability of the data because 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 cardiac resynchronization therapy.[150] Thus, costing exercises based on our systematic review must take into account the up-front failure rates and peri-implantation mortality rates demonstrated in Table 14.

It deserves emphasis that only selected patients and experienced providers participated in these trials; while this also does not affect the internal validity of the trials, it again impacts the generalizability of the results. In particular, the observed implant success rates and complication rates may not be achievable in other settings with clinicians less experienced with device implantation.

Our analysis incorporated publicly available information from the web site of the FDA; this information, although not in the peer-review literature, is valid information for use in a systematic review.[151] Indeed, a recent meta-analysis of non-steroidal anti-inflammatory agents has demonstrated that there is little difference in methodological quality between peer-reviewed published reports and the publicly available FDA reports.[151] We subjected this and other unpublished literature to the same rigorous assessment of quality as we used for the published literature. Two of the trials that we incorporated into this review were available directly from the FDA and represent over 1,000 patients; we supplemented this information with data from the primary investigators and other sources to ensure its validity. One of these trials (n=227) did not find any differences in survival or hospitalization (but did find "positive" effects on functional outcomes and quality of life scores) and remains unpublished more than two years since final data was presented. (CONTAK CD[73] was presented in May 2001 at the North American Society for Pacing and Electrophysiology 2001.) Exclusion of this trial exaggerates the benefit of cardiac resynchronization on all-cause mortality, a common finding amongst meta-analyses that exclude unpublished literature.[152]

Finally, very few patients in these trials had bradyarrhythmias, which would have necessitated conventional pacemakers, or atrial fibrillation. The role of cardiac resynchronization therapy 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 a conventional pacemaker).[97,153,154]

Decision Analysis

Our analysis shows that CRT plus medical therapy compared to medical therapy alone for patients with symptomatic heart failure is associated with a median incremental cost per quality-adjusted life year which is similar to that of other common medical interventions;[15] however, there is a large degree of uncertainty in these incremental costs per quality-adjusted life year. The results were sensitive to the value of several key variables, including the effectiveness of

CRT, the probability of cardiovascular death without pacing, and the incidence of device-related adverse effects.

The results of this analysis should be interpreted cautiously given the magnitude of the uncertainty in results. An intervention that is consistently more effective and less costly than its comparator is considered to be strongly dominant and always preferred to the alternative.[155] In the current example, cardiac resynchronization is likely more costly and more effective than medical therapy (i.e. in right upper quadrant of Figure 14). If CRT is as efficacious and inexpensive as demonstrated in this study, it may be good value for money. The challenge will be to ensure that CRT is used in patients who meet these trials' inclusion criteria, and that CRT devices are inserted by experienced providers who have low complication rates. However, the uncertainty about the benefits beyond one year needs to be acknowledged and there is insufficient long-term effectiveness and cost data to warrant broad implementation of CRT at this time.

This analysis has several strengths. It used currently recommended methods of economic evaluation.[78] The effectiveness estimates incorporated into the decision analysis were based on a high-quality systematic review. Long-term effects and costs were considered from a health care system perspective. Finally, the analysis was based on the framework of a previously published economic analysis[83] to facilitate comparison of the economics of different interventions in patients with cardiovascular disease.

Potential Limitations of Decision Analysis

This analysis has several limitations. First, CRT had a different pooled effect on all cause mortality versus cardiac mortality. These variable effects may reflect differences in the duration of followup since the former analysis was based on longer-term followup than the latter one. Conversely, the analysis of cardiac death is susceptible to bias since it is difficult to assign cause of death in cardiovascular trials. However, in a separate but related patient population, implantable defibrillator insertion was associated with increased early mortality.[157] Although the pooled effect of implantable defibrillators in patients at risk of sudden death is beneficial,[47,158] use of a combined implantable defibrillator and biventricular pacemaker will not necessarily decrease mortality.[159] Since patients with heart failure experience lethal bradyarrhythmia and tachyarrhythmias, a large randomized trial is evaluating the effect of devices with implantable defibrillator and biventricular pacemaking capability. (Personal communication, Dr. ASL Tang, August 25, 2003.)

Second, only selected implant physicians participated in the randomized trials assessing the effectiveness of CRT. It is plausible that the experience observed with the selected cases and experienced providers in these trials may not apply to other settings. If so, our analysis overestimates survival and underestimates the incremental cost of CRT in patients with heart failure. Conversely, if adverse effects are less frequent as providers gain experience, our analysis underestimates survival and overestimates the incremental cost of CRT in patients with heart failure. This is particularly important since the results of our analysis were sensitive to the rate of complications associated with CRT.

Third, the incidence of complications associated with CRT likely decreases over time while our analysis assumed that they were constant. If so, then our model underestimates survival and overestimates 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.

Fourth, it is likely that CRT may be associated with significant improvements in health-related quality of life relative to medical therapy. These trials demonstrated statistically significant differences in six-minute walk distance, functional class, and quality of life. Assuming that such short-term benefits persisted would have biased our results in favor of the intervention. Instead, the primary analysis assumed no difference in quality of life. Secondary analyses demonstrated that if resynchronization is associated with long-term improvements in quality of life, then it is even better value compared to medical therapy.

Fifth, it is unlikely that the relative benefit of CRT will be constant as the severity of heart failure increases. Therefore, as results from trials of CRT become available, our analysis should be revised to reflect better estimates of the true effectiveness and costs of the program.

Sixth, the model did not consider short- or long-term benefits and costs of selected surgical interventions for patients with heart failure. For example, cardiac transplantation is widely available but is infrequently used due to supply constraints and is associated with multiple long-term complications that were outside the scope of our analysis. Similarly, ventricular assist devices increase survival and quality of life, but are associated with frequent side effects and large costs.[44] Surgical remodeling is currently being evaluated in a large National Institutes of Health-sponsored trial. None of these interventions have been demonstrated to be effective in patients with moderate (NYHA Class II and III) heart failure similar to those composing the bulk of patients in the CRT trials.

Seventh, we assumed that heart failure costs were constant even though implementation of CRT will decrease heart failure costs if any associated 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. Until additional data are available on the long-term effectiveness and costs of CRT, device implantation should be limited to patients who meet the inclusion criteria of the trials in the absence of comorbid illness. Such device implantation should only be performed by experienced providers.

Conclusions

We have demonstrated a 24% relative reduction in all-cause mortality (largely driven by a 40% relative reduction in progressive heart failure deaths) and a 35% relative reduction in CHF hospitalizations with cardiac resynchronization therapy **in patients with reduced ejection fractions, NYHA class III or IV symptoms despite currently accepted medical management (ACE inhibitors, beta-blockers, and in many cases digoxin and/or spironolactone), and a prolonged QRS duration on electrocardiogram**. Successful implantation of a CRT device in 24 such patients would prevent one death and two heart failure hospitalizations.

We also found statistically and clinically significant improvements in quality of life and functional outcomes in patients receiving cardiac resynchronization therapy.

Up to 10% of CHF patients have reduced ejection fraction, NYHA Class III or IV symptoms, and a prolonged QRS duration; half of them would also have indications for an implantable

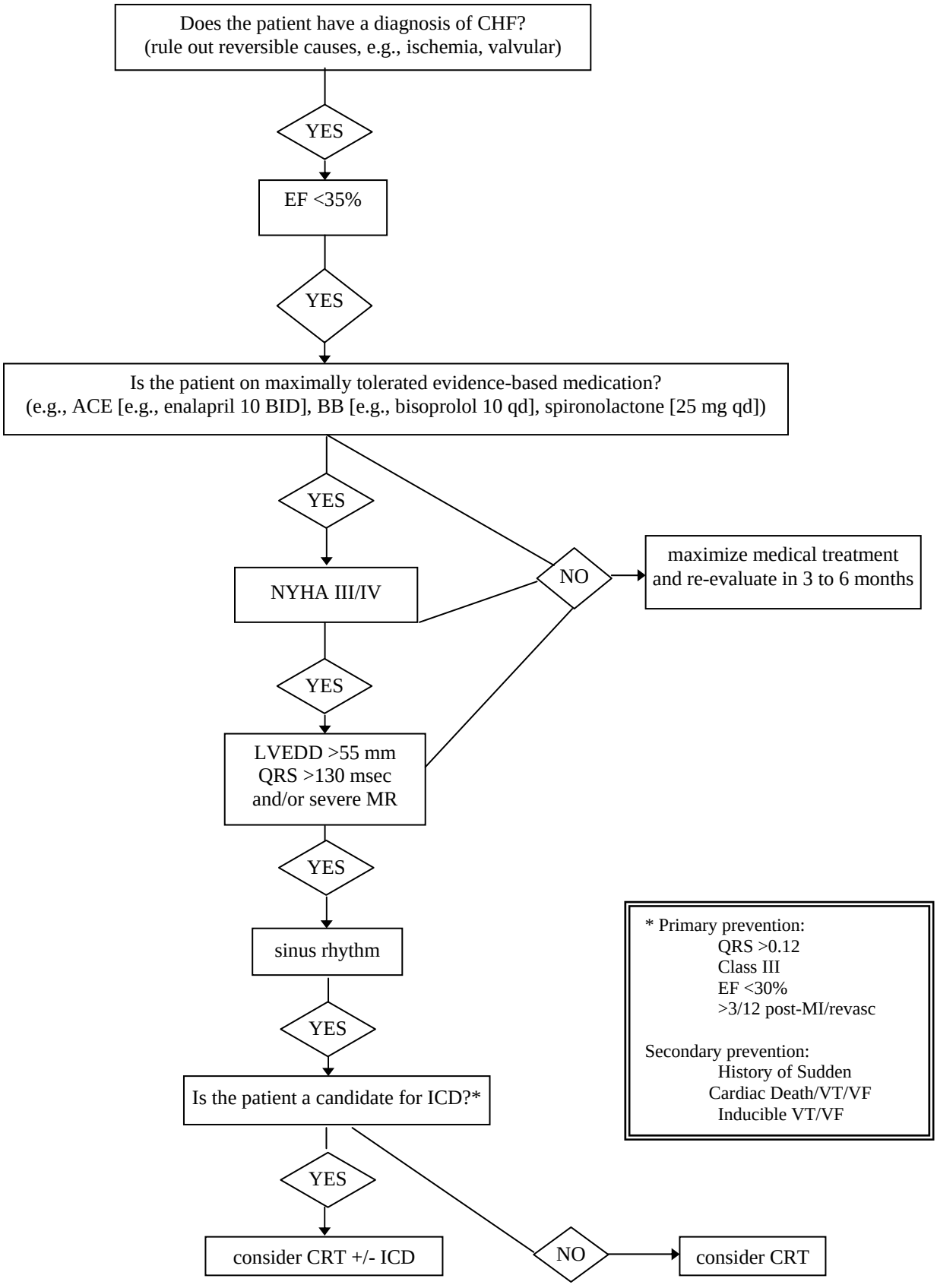
cardioverter defibrillator.[142,160-162] Thus, approximately 250,000 Americans may be eligible for a biventricular pacemaker and another 250,000 for a combined biventricular pacemaker/ICD.

While preliminary data suggest similar relative benefits (but lower absolute benefits) in patients with NYHA Class II symptoms, the role of cardiac resynchronization therapy in lower risk CHF patients with prolonged QRS duration is untested; further data are required before extending the device indications beyond those authorized by the FDA (i.e., patients with NYHA class III or IV symptoms). As very few such patients were enrolled in the trials, the role of cardiac resynchronization therapy in patients with either (1) indications for conventional pacemakers or (2) atrial fibrillation are unknown at this time and require further study.

However, some considerations need to be incorporated into any policy decisions about cardiac resynchronization therapy. First, although cardiac resynchronization appears to be relatively safe, there is a 10% failure rate for implantation; another 9% of patients may require the system to be partially or fully changed within six months due to malfunctions or lead displacements. As the technology develops, it is likely that the rates of implant failure and post-procedure complications will decrease (although close post-marketing surveillance is required to confirm this). Second, a marked paucity of data exists for the efficacy and complication rates with CRT devices beyond one year. Finally, none of these trials reported admission rates for CRT revisions; it is possible that much of the benefit in reduced heart failure hospitalization may well be offset by such admissions

Although the long-term cost-effectiveness of cardiac resynchronization therapy remains uncertain at this time (pending further data on longer term complication rates and benefits), our analyses do demonstrate that the incremental cost-effectiveness ratio is similar to other commonly used interventions, but has wide uncertainty and is sensitive to multiple inputs. There is insufficient long-term effectiveness and cost data to determine whether CRT is sufficient value for money to warrant its broad implementation at this time. We believe that, in light of the current evidence base, CRT should be reserved for selected heart failure patients with advanced disease (NYHA Class III or IV despite optimal medical therapy, reduced ejection fraction, and prolonged QRS duration—see Figure 16 for management algorithm), should only be implanted by clinicians competent in the technique, and should include close followup for complications.

Figure 16. Analytic framework for treatment options for patients with congestive heart failure



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Included Studies

Efficacy Review

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Excluded Studies

There were five main reasons for exclusion: the study was not a CRT trial; the article was a review, a protocol, an editorial, or it did not report required outcomes.

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34. Stellbrink C, Sinha AM, Diem B, et al. Implantable cardioverter-defibrillators with or without cardiac resynchronization therapy - multiple therapy in a single device: a review with special reference to the PACMAN study. Eur Heart J Suppl 2002; 4(D):D88-D94. Review article

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failure. Am J Cardiol 2000; 86(2):231-233. No required outcomes

42. Wilkoff B, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002; 288(24):3115-3123. Not a CRT trial

Figure 1. Decision model for medical therapy versus cardiac resynchronization therapy for heart failure

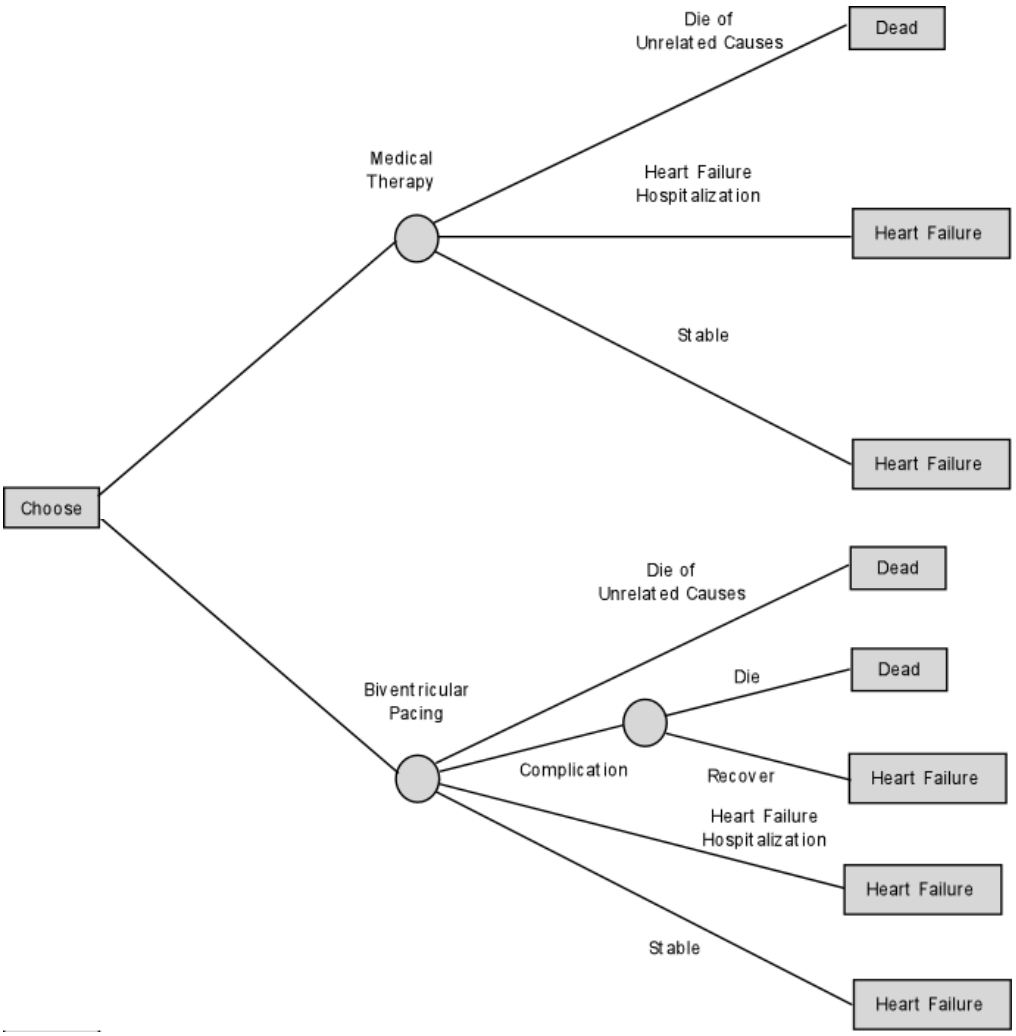
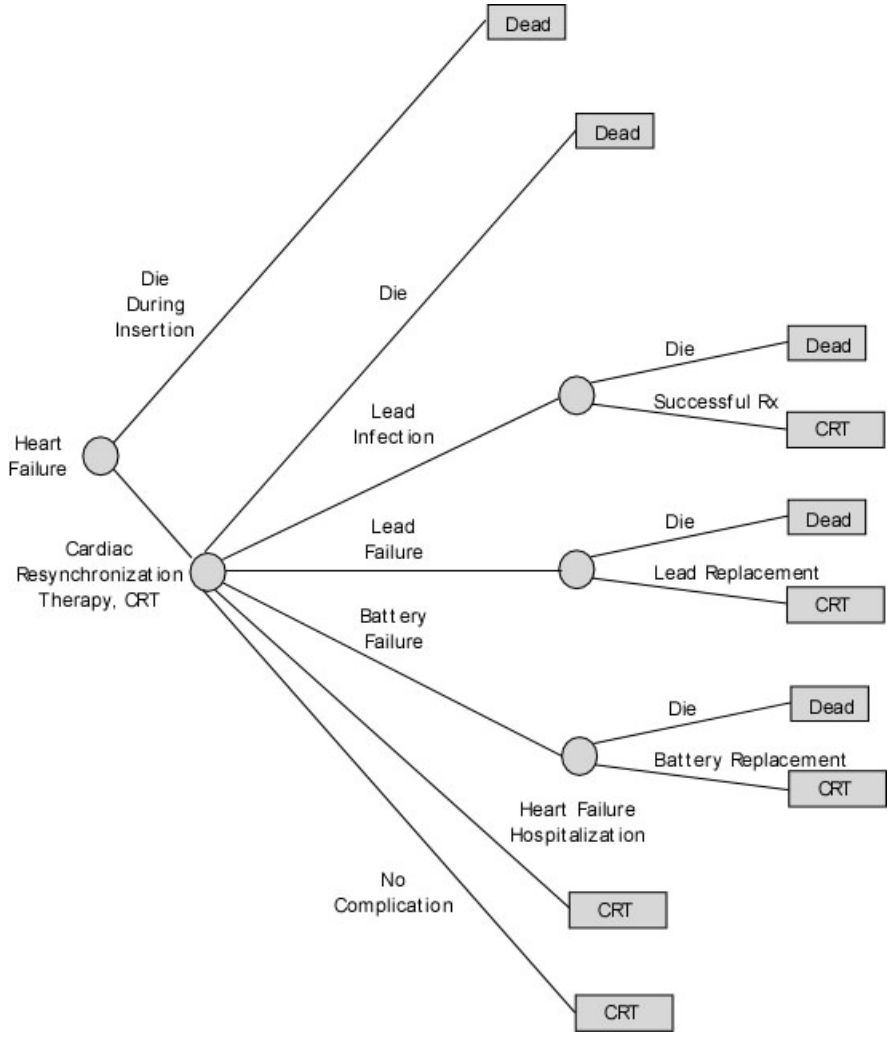


Figure 2. Markov Model of Resynchronization Therapy of Heart Failure



Rx= treatment

Chapter 3. Results

Literature Search

Of more than 3000 initial references, only nine and 17 studies were accepted for the efficacy and safety reviews, respectively (Figure 3). Two of these were unpublished manuscripts describing studies that met the inclusion criteria. Another was a report submitted to the FDA on the MIRACLE[35] trial to enhance data from the published trial results.[61] Also included were the FDA reports on the MIRACLE ICD[93] and CONTAK CD[73] trials found on the FDA web site. (We used the published report for data on patients with NYHA Class III or IV symptoms in the MIRACLE ICD[94] Trial, and the FDA report for NYHA Class II data since this was not included in the journal publication.) Bristow published the protocol for the COMPANION trial in 2000,[95] and the results were presented at the Annual Scientific Conference of the American College of Cardiology in Chicago, April 2003. Further unpublished data from this trial were made available to us and are included in the analysis.

Figure 3. Flow diagram of study retrieval and selection for cardiac resynchronization therapy

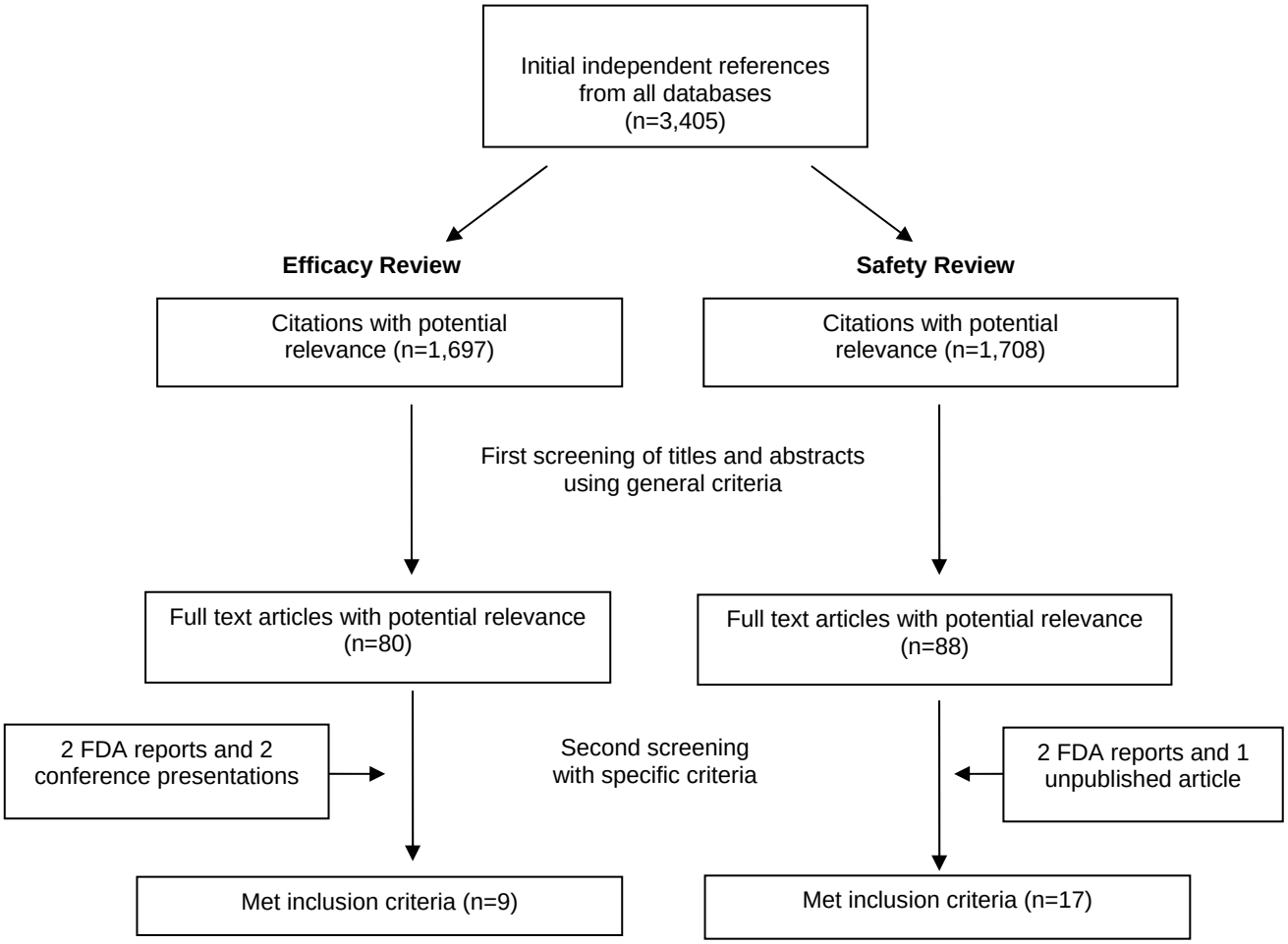


Figure 4. Meta-graph of all-cause mortality

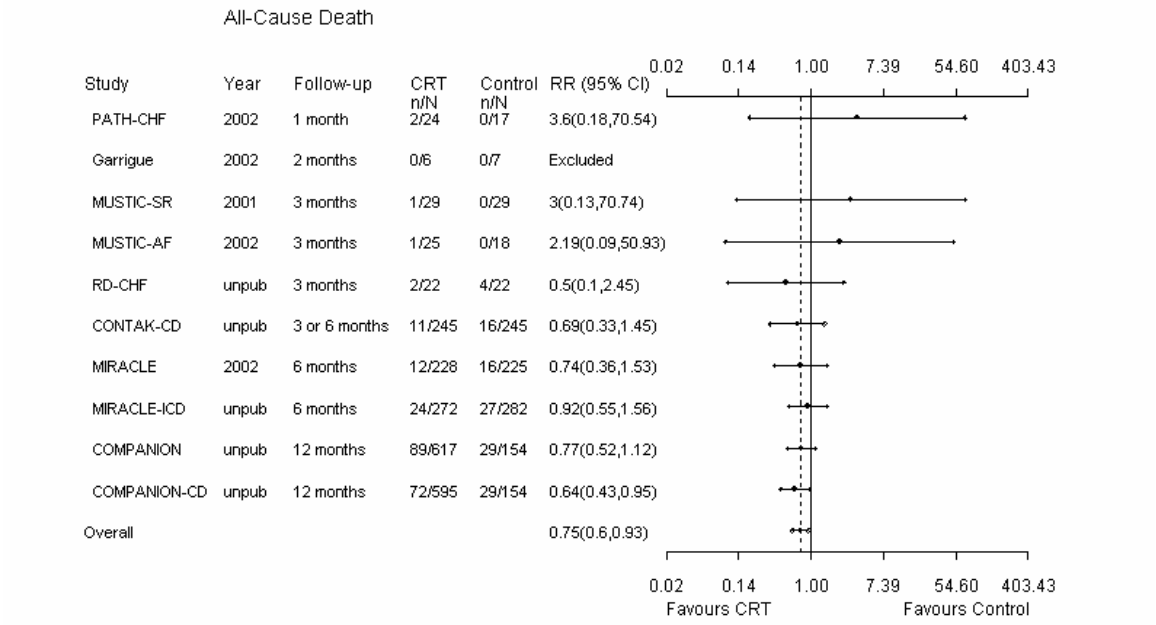
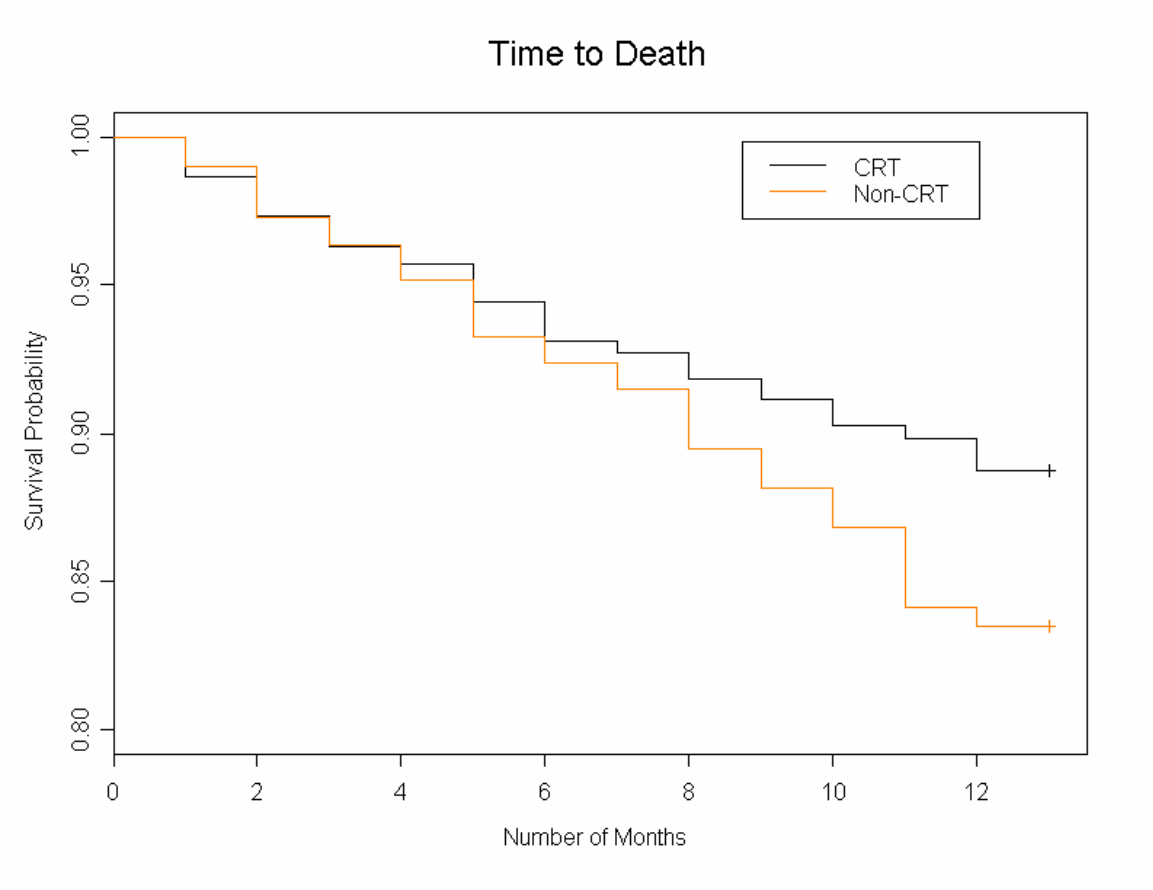


Figure 5. Time to all-cause death



Note: The COMPANION Trial consisted of three arms. To avoid "double counting" in calculating summary estimates of treatment effect, we divided the 58 deaths in 308 control patients into 29 deaths in 154 controls in each comparison.

Figure 6. Meta-graph of death due to congestive heart failure

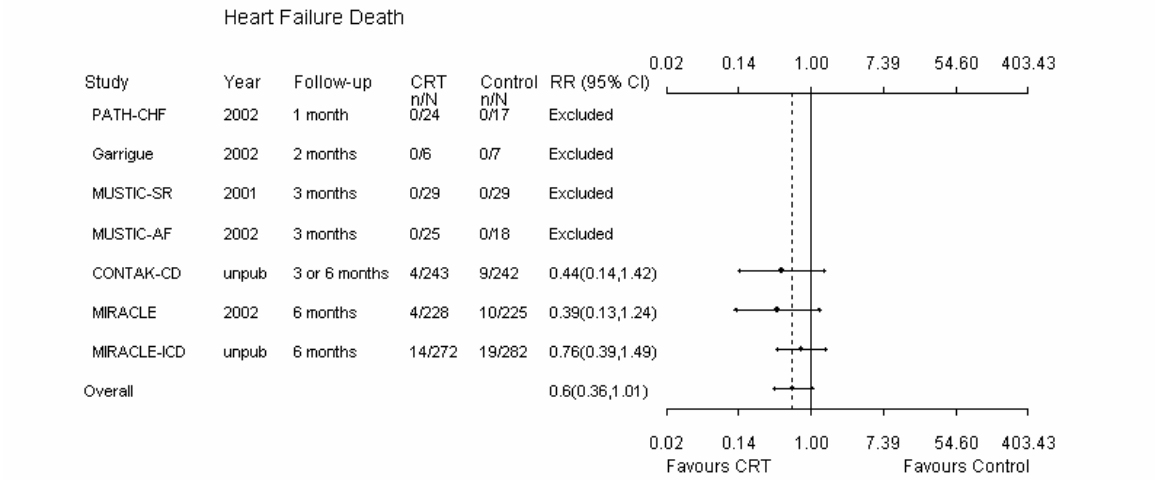


Figure 7. Meta-graph of sudden cardiac death

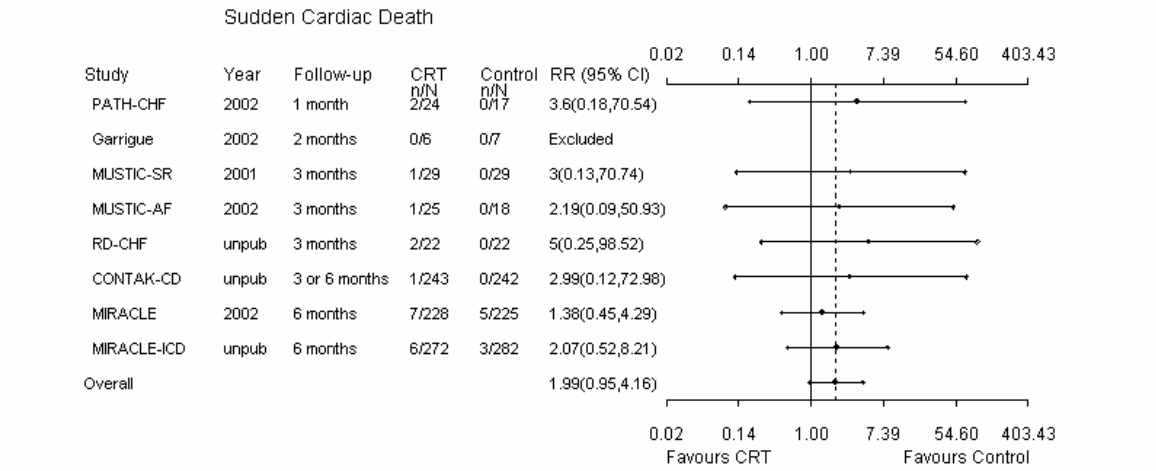


Figure 8. Meta-graph of non-cardiac death

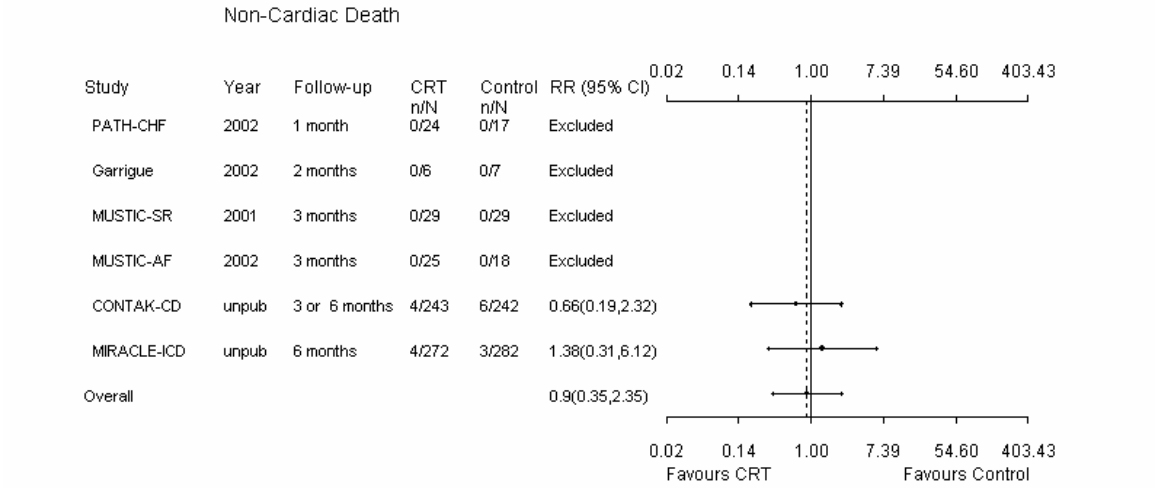


Figure 9. Meta-graph of hospitalizations due to congestive heart failure

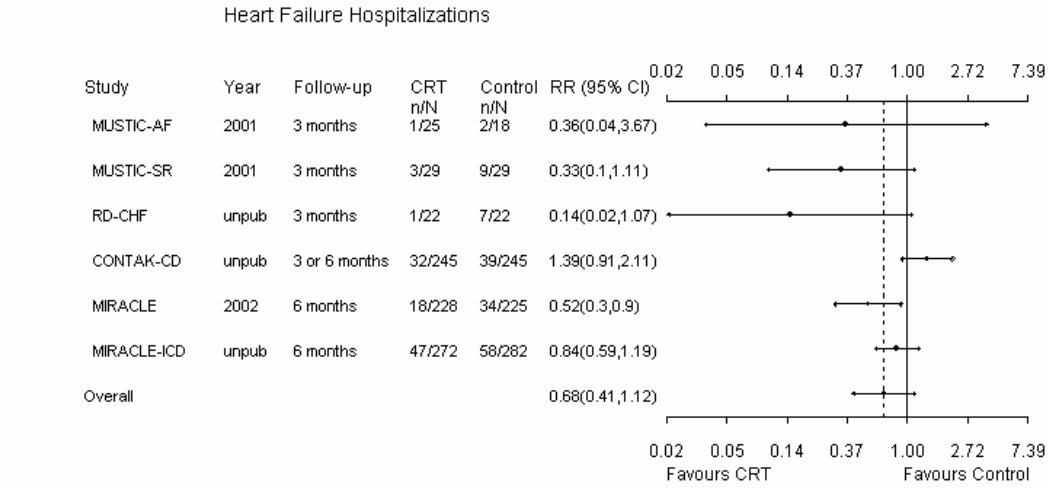


Figure 10. Meta-graph of six-minute walk test

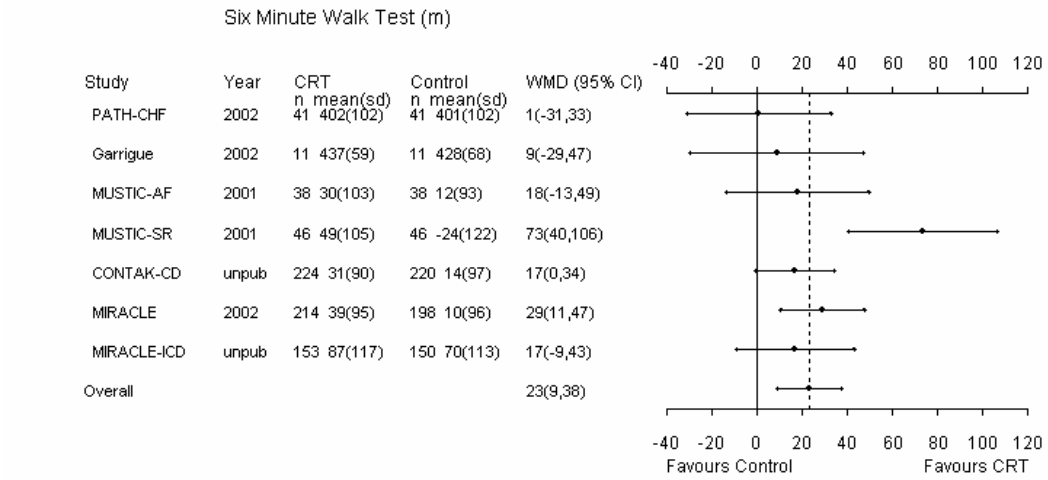


Figure 11. Meta-graph of changes in NYHA status

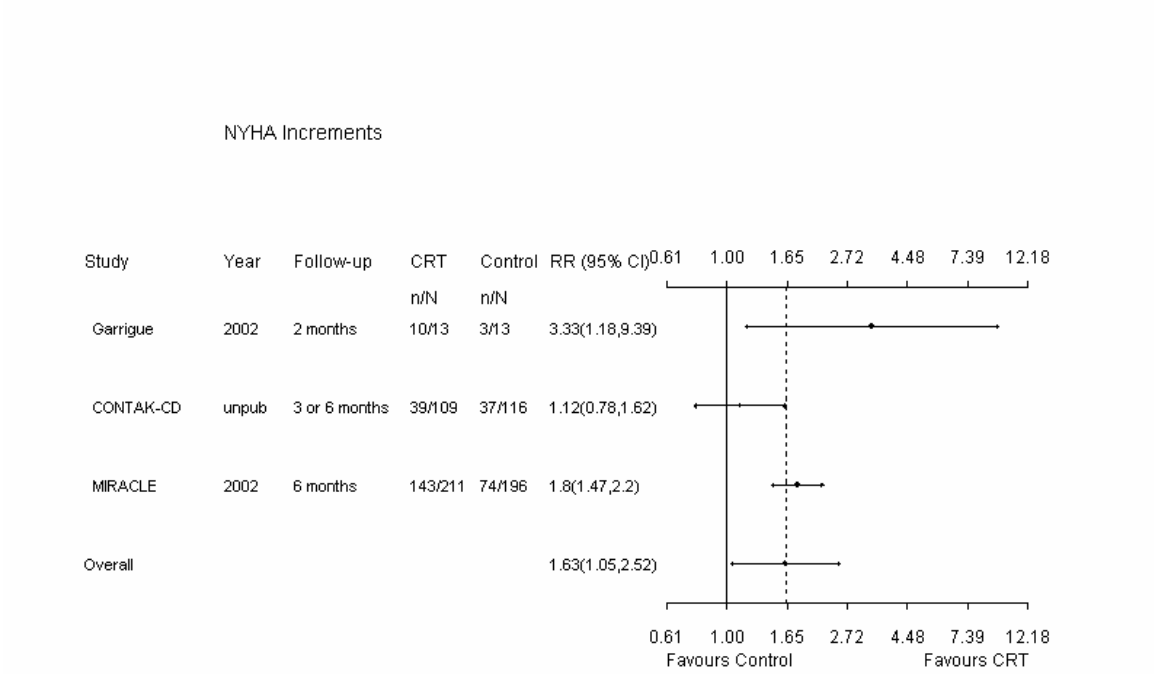


Figure 12. Meta-graph of quality of life (based on Minnesota Living with Heart Failure instrument)

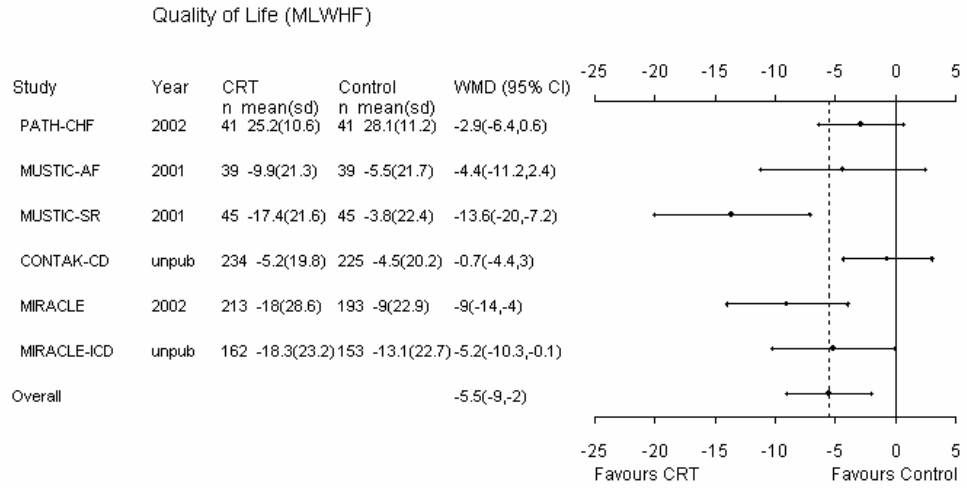


Figure 13. Meta-graph of all-cause mortality by cardioverter defibrillator vs non-cardioverter defibrillator

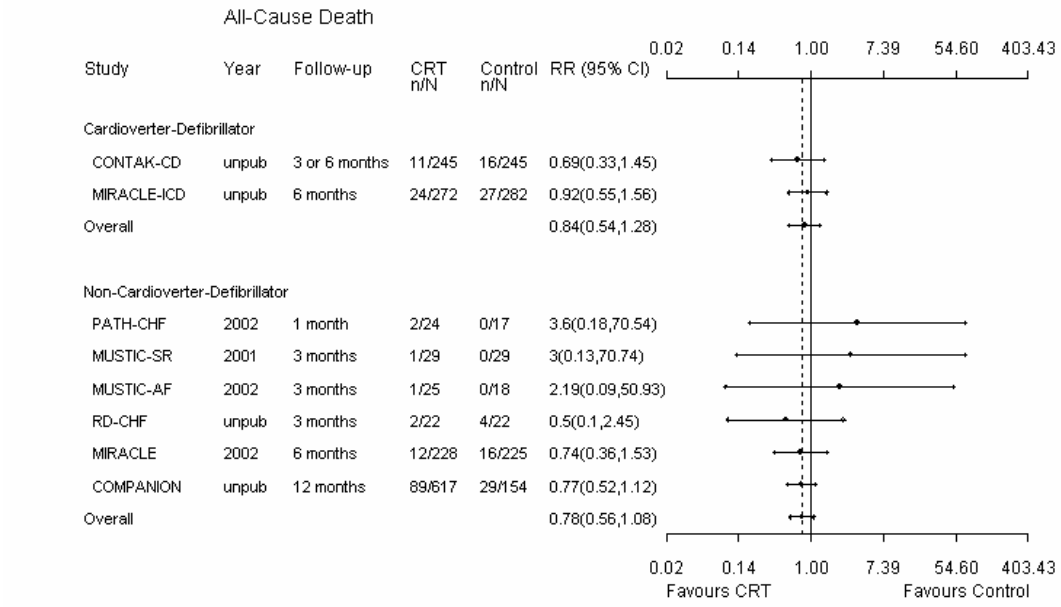


Figure 14. Distribution of Incremental Costs versus Incremental Effects for Cardiac Resynchronization versus Medical Therapy

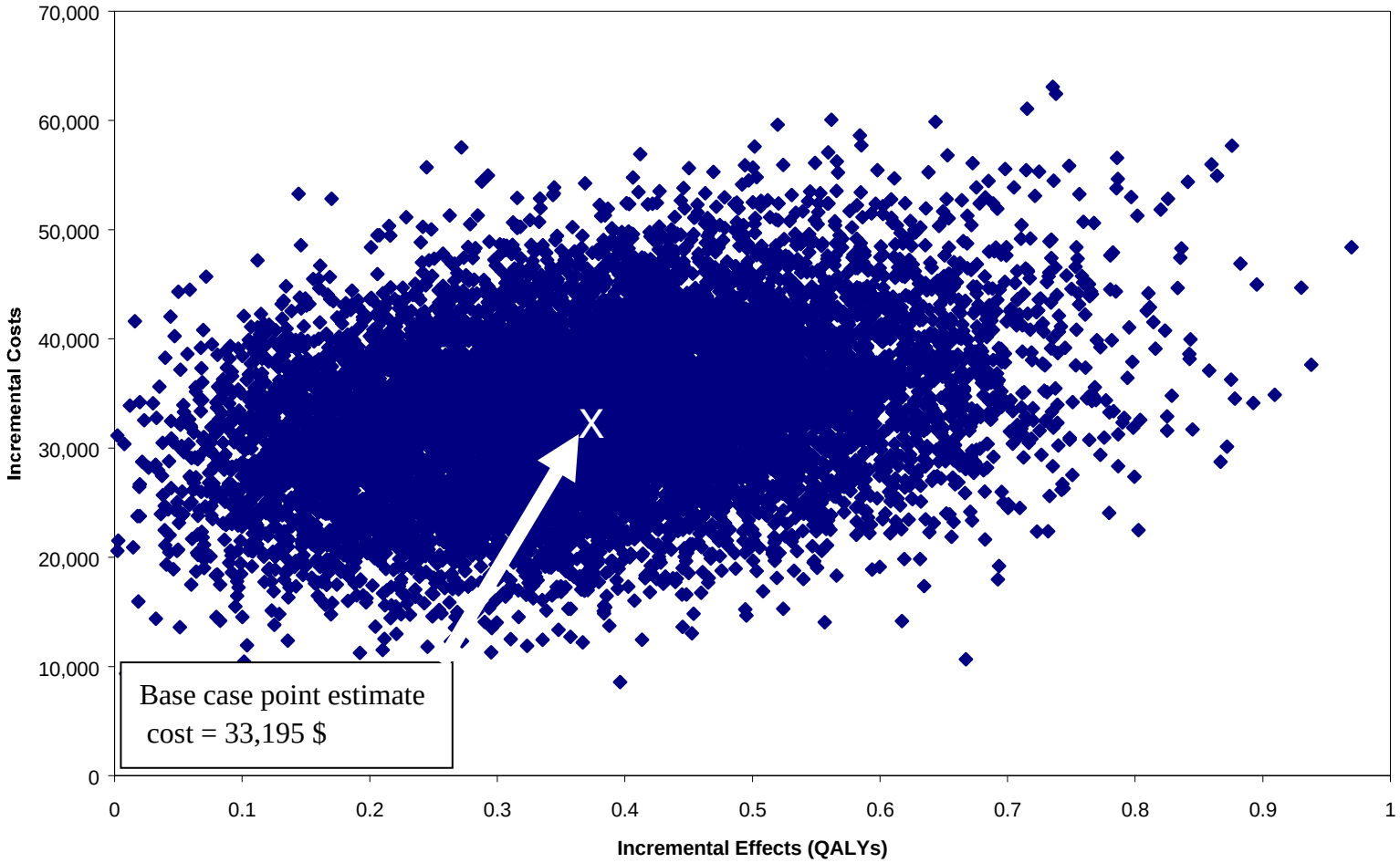
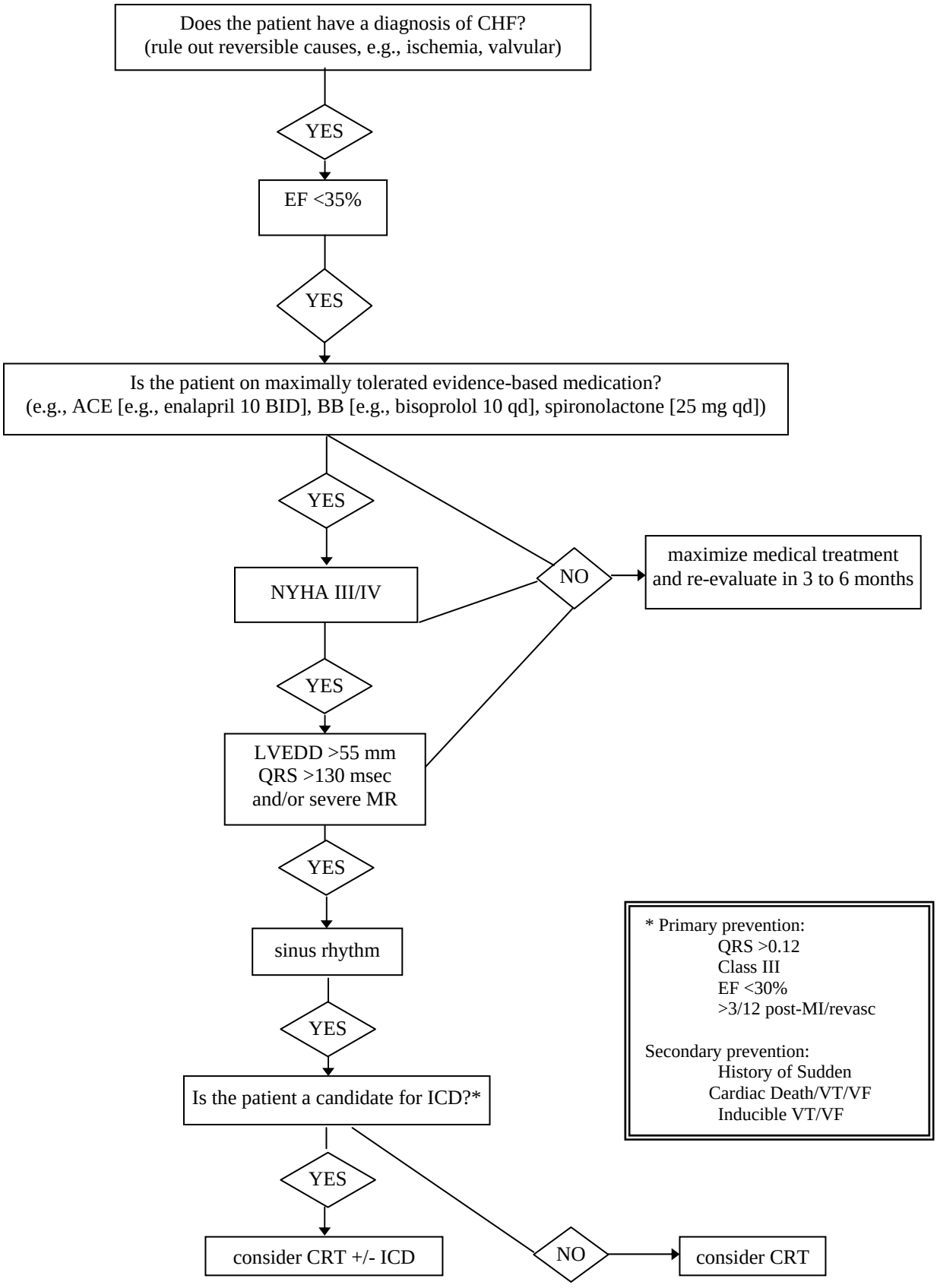


Figure 15. Cost-Effectiveness Acceptability Curve

Figure 16. Analytic framework for treatment options for patients with congestive heart failure



Current Risk Factors and Markers in Congestive Heart Failure

Many prognostic risk factors have been established in CHF (Table 1). Well-validated risk factors for short- and long-term mortality include demographic factors such as older age and male gender;[14] differing ethnic background (black patients have a higher mortality rate than white patients even after adjustment for important covariates);[15,16] co-morbidities such as diabetes mellitus,[17] anemia,[18] and poor renal function;[19] and physical examination findings such as a third heart sound and elevated jugular venous pressure.[20] Biochemical values that predict mortality include decreased serum sodium,[21] elevated aldosterone, angiotensin II, and arginine vasopressin,[22] elevated brain natriuretic peptide,[23] and elevated levels of other neurohormones.[24] Other prognostic risk factors have been explored (such as genetic and echocardiographic markers) and are reviewed elsewhere;[25] electrophysiologic prognostic factors are reviewed below.

Table 1. Prognostic risk factors in congestive heart failure

Demographics:	**Electrophysiologic findings:**
Older age	Ventricular arrhythmias
Male gender	Intraventricular conduction delay
Ethnic background (blacks have poorer outcomes than whites)	Atrial fibrillation T-wave alternans
Comorbidities:	
Diabetes	**Laboratory findings:**
Anemia	Elevated norepinephrine/epinephrine
Renal failure	Low sodium
	Elevated creatinine
Clinical Assessment:	Elevated aldosterone
Advanced symptoms (NYHA Class III or IV)	Elevated B-type natriuretic peptide
Elevated jugular venous pressure	Elevated Tumor Necrosis Factor-alpha
Edema	Elevated InterLeukin-6
Third heart sound	Elevated endothelin-1
	Elevated angiotensin II
Hemodynamics:	Elevated renin
Lower left ventricular ejection fraction	Elevated troponin I/T
Lower right ventricular ejection fraction	Elevated arginine vasopressin
Elevated pulmonary capillary wedge pressure	
Elevated pulmonary vascular resistance	

Source: adapted from Eichhorn EJ. Prognosis determination in heart failure. Am J Med 2001;110 (Suppl 7A);14S-36S[25]
NYHA=New York Heart Association

Current Therapeutic Strategies for Congestive Heart Failure

Current therapy for congestive heart failure incorporates a number of strategies to enhance the quality of life, improve exercise tolerance, and reduce morbidity and mortality. In the past two decades, advances in heart failure management have arisen from randomized clinical trials

Table 2. Inclusion/exclusion criteria for review on cardiac resynchronization therapy

Criterion	Efficacy review	Safety review
Study Design	Include: RCT (parallel or crossover) > 2 weeks duration. Exclude: non-RCTs, acute physiological studies, studies not involving human subjects	Include: RCT (parallel or crossover) or non-RCT (e.g., registry data, prospective cohort, FDA document, etc.) > 2 weeks duration. Exclude: acute physiological studies, studies not involving human subjects
Participants	Include: symptomatic CHF (NYHA Class ≥ II), decreased LVEF, prolonged QRS. Must be receiving stable optimal drug therapy	Include: symptomatic CHF (NYHA Class ≥ II), decreased LVEF, prolonged QRS. Must be receiving stable optimal drug therapy
Intervention	Treatment with active CRT (also called BVP, multi-site pacing, dual chamber pacer) compared to either placebo pacing or uni-ventricular pacing or optimal drug therapy	Treatment with active CRT (also called BVP, multi-site pacing, dual chamber pacer). Comparison group not necessary
Outcome measures	Mortality (all-cause, CHF, sudden cardiac death, non-cardiac), CHF hospitalizations, 6MWT, NYHA class, QOL	Peri-implant mortality, successful implant rate, risks of /during implantation, risks following implantation

BVP = biventricular pacing; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; QOL = quality of life; RCT = randomized controlled trial; 6MWT = six-minute walk test.

Quality Assessments

Efficacy review. The methodological quality of RCTs was assessed independently by two reviewers (JE, CS) using two quality assessment methods. First, allocation concealment was assessed as adequate, inadequate, or unclear. Second, a five-point scoring system validated by Jadad[58] was used to assess randomization, double blinding, and reporting of withdrawals and dropouts (Table B-3). In addition, the funding source and whether authors reported use of intention-to-treat analysis were noted. Discrepancies were resolved through discussion between the two reviewers.

Safety review. Studies included in the safety review were assessed for quality independently by two reviewers (CS, LH) using a partially validated checklist developed by Downs and Black.[59] The checklist includes 28 questions evaluating five criteria (Table B-4). These five criteria are: Reporting (10 questions, total score 11), External validity (three questions, total score 3), Internal validity – bias (seven questions, total score 7), Internal validity – confounding (six questions, total score 6) and Power (two questions, total score 2). Decision rules regarding application of the tool were developed *a priori* through discussions with a cardiologist and a methodologist. Discrepancies in quality assessment were resolved through discussion.

Data Extraction

Data were extracted using standard forms (Tables B-5 and B-6) designed for either RCTs (efficacy and safety reviews) or cohort studies (safety review) and entered into an Excel spreadsheet. Data were extracted by one reviewer (JE, CS, NW, or LH) and checked for accuracy and completeness by a second (JE, NW, or CS). Extracted data included study characteristics, inclusion/exclusion criteria, baseline drug use, characteristics of participants, procedural data, and outcomes. Efficacy outcomes included mortality (all cause as well as CHF death, sudden cardiac death, non-cardiac death) and time to death; CHF hospitalizations, six-

Table 3. Input data for decision analysis on cardiac resynchronization in patients with NYHA Class III heart failure

Variable	Best Estimate	Lowest	Highest	Distribution	Threshold Value	References
Age of patient (yr.)	60	50	70	Normal	n/a	Assumed
Annual probability of cardiac death without CRT (%)	24.3	20.0	29.2	Beta	n/a	This systematic review
Relative risk of death with CRT	0.75	0.60	0.93	Normal	0.78	This systematic review
Annual probability of heart failure hospitalization without CRT (%)	56.0	47.6	66.2	Beta	n/a	This systematic review
Relative risk of heart failure hospitalization with CRT	0.68	0.41	1.12	Normal	0.85	This systematic review
Annual rate of cardiac death without CRT (%)	20.3	15.1	27.0	Beta	n/a	This systematic review
Relative risk of cardiac death with CRT	0.60	0.36	1.01	Normal	n/a	This systematic review
Relative risk of death due to unrelated causes with CRT	1.0	0.9	1.1	Triangular	n/a	Assumed
Annual rate of lead infection (%)	2.0	1.1	3.2	Beta	n/a	This systematic review

Table 3. Input data for decision analysis on cardiac resynchronization in patients with NYHA Class III heart failure –continued

Variable	Best Estimate	Lowest	Highest	Distribution	Threshold Value	References
Annual rate of lead failure (%)	13.7	11.7	16.1	Beta	n/a	This systematic review
Annual rate of battery replacement (%)	10.8	8.7	13.4	Beta	n/a	This systematic review
Probability of death during insertion (%)	0.4	0.2	0.7	Beta	n/a	This systematic review
Probability of death during lead infection (%)	1.0	0	10	Beta	n/a	Assumed
Probability of death during lead failure (%)	1.0	0	10	Beta	7.3	Assumed
Probability of death during battery replacement (%)	1.0	0	10	Beta	8.6	Assumed
Utility of NYHA II heart failure	0.94	0.84	0.99	Triangular	n/a	Survey
Utility of NYHA III heart failure	0.84	0.71	0.98	Triangular	n/a	Survey

Table 3. Input data for decision analysis on cardiac resynchronization in patients with NYHA Class III heart failure–continued

Variable	Best Estimate	Lowest	Highest	Distribution	Threshold Value	References
Utility of NYHA IV heart failure	0.74	0.58	0.91	Triangular	n/a	Survey
Utility of hospitalization for heart failure	0.57	0.48	0.80	Triangular	n/a	Survey
Relative Utility of heart failure with CRT	1.0	0.9	1.1	Triangular	n/a	Assumed
Duration of hospitalization for CRT implantation	5 days	0	1 mos.	Triangular	n/a	Assumed
Duration of hospitalization for lead failure	5 days	0	1 mos.	Triangular	n/a	Assumed
Duration of hospitalization for lead infection	5 days	0	1 mos.	Triangular	n/a	Assumed
Duration of hospitalization for battery replacement	5 days	0	1 mos.	Triangular	n/a	Assumed
Discount rate for future costs and effects	3%	0%	10%	Triangular	n/a	Gold [78]

Table 3. Input data for decision analysis on cardiac resynchronization in patients with NYHA Class III heart failure –concluded

Variable	Best Estimate	Lowest	Highest	Distribution	Threshold Value	References
Cost of CRT insertion *	$33,495	$16,747	$50,242	Triangular	$41,000	Survey
Cost of CRT, per mo.	$771	$385	$1,216	Triangular	n/a	Owens[92]
Cost of hospitalization for lead infection	$30,997	$15,499	$46,496	Triangular	n/a	Owens[92]
Cost of hospitalization for lead failure	$30,997	$15,499	$46,496	Triangular	n/a	Owens[92]
Cost of battery replacement	$28,835	$14,417	$43,252	Triangular	$38,000	Owens[92]
Cost of heart failure hospitalization	$15,427	$10,660	$20,193	Normal	n/a	Kaul[82]

CRT= cardiac resynchronization therapy; NYHA= New York Heart Association
* Cost estimates in U.S. dollars

Table 4. Primary publications and associated publications of trials included in the reviews on cardiac resynchronization therapy in CHF

COMPANION Study
Primary report: [60] Bristow MR, et al. Comparison of medical therapy, pacing and defibrillation in heart failure. Presented at the 52nd Annual Scientific Conference, American College of Cardiology, Chicago, Illinois, USA, March 31st, 2003.

Other publications associated with COMPANION
[95]Bristow MR, Feldman AM, Saxon LA. Heart failure management using implantable devices for ventricular resynchronization: Comparison of medical therapy, pacing, and defibrillation in chronic heart failure (COMPANION) trial. J Card Fail 2000; 6(3):276-85

CONTAK CD Study
Primary report: [73]GUIDANT Corporation, Cardiac Rhythm Management. Summary of safety and effectiveness: Guidant CONTAK CD CRT-D system including the CONTACK CD CRT-D pulse generator model 1823, and software application model 2848. PMA: P010012. Food and Drug Administration July 10, 2002.

Other publications associated with CONTAK CD
[112]Boehmer JP, DeMarco T, Jaski BE, et al. Why ICD patients with heart failure (Class II-IV) are hospitalized: Do the reasons differ for patients who are treated with cardiac resynchronization therapy? [abst] J Am Coll Cardiol 2002;39(5):159A
[113]Higgins SL, Yong P, Sheck D, et al. Biventricular pacing diminishes the need for implantable cardioverter defibrillator therapy. Ventak CHF Investigators. J Am Coll Cardiol 2000;36(3):824-7
[163]Lozano I, Bocchiardo M, Achtelik M, et al. Impact of biventricular pacing on mortality in a randomized crossover study of patients with heart failure and ventricular arrhythmias. Pacing Clin Electrophysiol 2000;23(11Pt2):1711-12
[114]Saxon LA, Boehmer JP, Hummel J, et al. Biventricular pacing in patients with congestive heart failure: two prospective randomized trials. The VIGOR CHF and VENTAK CHF Investigators. Am J Cardiol 1999;83(5B):120-23D
[115]Saxon LA, De Marco T, Schafer J, et al. Effects of long-term biventricular stimulation for resynchronization on echocardiographic measures of remodeling. Circulation 2002;105(11):1304-10

INSYNC Study
Primary report: [100]Gras D, Leclercq C, Tang AS, et al. Cardiac resynchronization therapy in advanced heart failure the multicenter InSync clinical study. Eur J Heart Fail 2002;4(3):311-20.

Other publications associated with InSync
[116]Gras D, Mabo P, Tang T, et al. Multisite pacing as a supplemental treatment of congestive heart failure: preliminary results of the Medtronic Inc. InSync Study. Pacing Clin Electrophysiol 1998;21(11 pt2):2249-55
[117]Gras D, Cazeau S, Ritter P, et al. Long term results of cardiac resynchronization for heart failure patients: The InSync Clinical Trial [abst] Circulation 1999;100(18):2714
[118]Gras D, Cazeau S, Mabo P, et al. Long-term benefit of cardiac resynchronization in heart failure patients: The 12 month results of the InSync trial. [abst] J Am Coll Cardiol 2000;35(2):230A.
[119]Gras D, Mabo P, Bucknall C, et al. Responders and nonresponders to cardiac resynchronization therapy: Results from the InSync trial. J Am Coll Cardiol 2000;35(2):230A-230A
[120]Tang ASL, Gras D, Mabo P, et al. Mortality and outcome differences between survivors and nonsurvivors in the InSync cardiac resynchronization trial [abst] Circulation 1999;100(18):2715
[121]Zardini M, Tritto M, Bargiggia G, et al. The InSync-Italian Registry: analysis of clinical outcome and considerations on the selection of candidates to left ventricular resynchronization. Eur Heart J Supp 2002;2:J16-22

Table 4. Primary publications and associated publications—continued

Leclercq Studies
Primary report: [96]Leclercq C, Victor F, Alonso C, et al. Comparative effects of permanent biventricular pacing for refractory heart failure in patients with stable sinus rhythm or chronic atrial fibrillation. Am J Cardiol 2000;85(9):1154-56. Am J Cardiol 2000;85:1154-56

Other publications associated with Leclercq study
[107]Leclercq C, Cazeau S, Ritter P, et al. A pilot experience with permanent biventricular pacing to treat advanced heart failure. Am Heart J 2000;140(6): 862-70

MIRACLE Study
Primary report: [61]Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346(24):1845-1853

Other publications associated with the MIRACLE study
[122]Abraham WT. Rationale and design of a randomized clinical trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with advanced heart failure: The Multicenter InSync Randomized Clinical Evaluation (MIRACLE). J Card Fail 2000;6(4):369-80
[123]Abraham WT, Fisher W, Smith A, et al. Cardiac resynchronization therapy reduces morbidity in patients with moderate to severe systolic heart failure and intraventricular conduction delays [abst]. J Am Coll Cardiol 2002;39(5):171A
[124]Abraham WT, Fisher W, Smith A, et al. Long-term improvement in functional status, quality of life and exercise capacity with cardiac resynchronization therapy: The MIRACLE Trial experience [abst]. J Am Coll Cardiol 2002;39(5):171A
[125]Aranda JM, Curtis AB, Conti JB, et al. Rationale and design of a randomized clinical trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with advanced heart failure: The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) [abst]. J Am Coll Cardiol 2002;39(5):96A
[126]Packer M & Abraham WT. Effect of cardiac resynchronization on a composite clinical status endpoint in patients with chronic heart failure: Results of the MIRACLE trial [abst]. Circulation 2001;104(17):1995
[127]Sutton MGS, Plappert T, Abraham WT, et al. Cardiac resynchronization improves diastolic ventricular function in advanced heart failure: The MIRACLE trial [abst]. Circulation 2001;104(17):2920
[128]Wagoner LE, Zengel PW, Abraham WT, et al. Cardiac resynchronization therapy with the InSync stimulation system improves exercise performance in patients with heart failure: MIRACLE trial substudy results [abst]. Circulation 2001;104(17):2919

MIRACLE-ICD study
Primary report: [36]Medtronic, Inc. Summary of Safety and Effectiveness: InSync ICD Model 7272 dual chamber implantable cardioverter defibrillator with biventricular pacing for cardiac resynchronization, Attain Models 2187, 2188, 4189 leads. PMA: P010031. Food and Drug Administration, Dec 3, 2001

Other publications associated with MIRACLE ICD
[93]Medtronic, Inc. Summary of Safety and Effectiveness: InSync ICD Model 7272 dual chamber implantable cardioverter defibrillator with cardiac resynchronization therapy and the model 9969 Application Software. PMA: P010031. Food and Drug Administration, March 5, 2002
[94]Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure The MIRACLE ICD Trial. JAMA 2003;289(20):2685-94

Table 4. Primary publications and associated publications—concluded

MUSTIC AF study
Primary report: [75]Leclercq C, Walker S, Linde C, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J 2002;1780-87

MUSTIC SR study
Primary report: [74]Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344(12):873-80

Other publications associated with MUSTIC trials
[129]Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol 2002;40(1):111-18

PATH CHF study
Primary report: [62]Auricchio A, Stellbrink C, Sack S, et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol 2002;39(12):2026-33

Other publications associated with PATH-CHF
[53]Auricchio A, Stellbrink C, Sack S, et al. The Pacing Therapies for Congestive Heart Failure (PATH-CHF) study: rationale, design, and endpoints of a prospective randomized multicenter study. Am J Cardiol 1999;83(5B):130D
[130]Auricchio A, Klein H, Spinelli J. Pacing for heart failure: selection of patients, techniques and benefits. Eur J Heart Fail 1999;1(3);275-79
[53]Auricchio A, Stellbrink C, Block M, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. Circulation 1999;99(23):2993-3001
[131]Auricchio A, Ding J, Spinelli JC, et al. Cardiac resynchronization therapy restores optimal atrioventricular mechanical timing in heart failure patients with ventricular conduction delay. J Am Coll Cardil 2002;39(7):1163-69
[132]Baumann LS, Kadhiresan VA, Yu Y, et al. Optimization of cardiac resynchronization therapy in heart failure patients by measuring transient cycle length changes [abst]. Eur Heart J 2001;22:443
[148]Butter C, Auricchio A, Stellbrink C, et al. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. Circulation 2001;104(25):3026-29
[133]Cuesta F, Sack S, Auricchio A, et al. Long-term benefit of cardiac resynchronization therapy in heart failure patients: results of the PATH-CHF study. Eur Heart J 2001;22:130
[134]Cuesta F, Stellbrink C, Auricchio A, et al. Cardiac resynchronization therapy reduces heart failure hospitalization in the PATH-CHF study [abst]. Eur Heart J 2001;22:441
[135]Huth C, Friedl A, Klein H, Auricchio A. Pacing therapies for congestive heart failure considering the results of the PATH-CHF study] *Zeitschrift fur Kardiologie* 2001; 90 (Supp 1):10-15
[136]Stellbrink C, Auricchio A, Butter C, et al. Pacing therapies in congestive heart failure II study. Am J Cardiol 2000;86 (9 Supp 1):138K
[136]Stellbrink C, Breithardt OA, Franke A, et al. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. Am J Cardiol 2001;38(7):1957-65
[137]Vogt J, Krahnefeld O, Lamp B, et al. Electrocardiographic remodeling in patients paced for heart failure. Am J Cardiol 2000;86(Supp 1):152-56K

Table 5. Description of studies included in the efficacy review: CRT for CHF

				Number of Participants								
Study name	**Country**	**Design Duration**	**Control arm**	**Total enrolled**	**Exclusions**	**Total randomized**	**Treatment***	**Control***	**Withdrawals**	**Device Method of implant**	**Authors' primary outcome(s)**	**Other outcomes**
Abraham 2002 MIRACLE[61]	U.S. and Canada	RCT parallel 6 mo.	Pacer "Inactive"	571	4	453	228	225	Treatment 1 Control 8	InSync model 8040 Medtronic Transvenous	NYHA class; QOL, 6MWT	Peak O_2 consumption; time on a treadmill; LVEF; LVEDD; severity of mitral regurgitation; duration of QRS interval; clinical composite response (improved, worsened, unchanged); death; worsening heart failure; number of days spent in hospital
Auricchio 2002 PATH-CHF[62]	Germany, Netherlands	RCT X-over 1 mo.	Uni-ventricular pacing (4 right, 36 left)	42	1	41	24	17	Treatment 2 Control 5	Vigor / Discovery with LV lead Guidant Transthoracic	O_2 uptake at peak exercise; O_2 uptake at anaerobic threshold; 6MWT	NYHA; QOL
Bristow 2003 COMPANION[60]	U.S. multicenter	RCT parallel 3 arms 12 mo.	OPT	-	-	1520	CRT=617 CRT-D= 595	308	-	CONTAK TR Models 4510-4513, Model 1241 CONTAK CD Model 1823 Guidant. Transvenous	CRT: all-cause mortality & hospitalization. CRT-ICD: all-cause mortality & hospitalization	Cardiac morbidity; ADRs, implant success; peak O_2 uptake at exercise
Cazeau 2001[74] MUSTIC-SR	Europe (15 sites)	RCT X-over 3 mo.	Pacer "Inactive"	67	3	58	29	29	Treatment 4 Control 3	Chorum 7336 ELA Medical or InSync 8040 Medtronic Transvenous	6MWT	QOL (main secondary outcome); peak O_2 uptake; hospital admissions because of decompensated heart failure; patient's preference with regard to pacing (active vs. inactive) at the end of crossover; death

Table 5. Description of studies included in the efficacy review: CRT for CHF—continued

				Number of Participants								
Study name	**Country**	**Design** **Duration**	**Control arm**	**Total enrolled**	**Exclusions**	**Total randomized**	**Treatment***	**Control***	**Withdrawals**	**Device** **Method of implant**	**Authors' primary outcome(s)**	**Other outcomes**
Garrigue 2002[70]	France	RCT X-over 2 mo.	Left ventricular pacing	-	0	13	6	7	0	Model 2188 Medtronic Transvenous	Clinical and hemodynamic variables	Hemodynamic changes during exercise
Guidant 2002 CONTAK-CD[73] FDA Report	U.S. (47 sites)	RCT Phase I period 1 of X-over 3 mo. Phase II parallel 6 mo.	Pacer "Inactive"	581	15	490	245	245	Treatment 3 Control 1	CONTAK-CD Transvenous and Transthoracic	All-cause mortality; CHF hospitalizations; ventricular tachyarrhythmia requiring device intervention	Peak O_2 consumption; QOL; 6MWT, all adverse events
Leclercq 2002 MUSTIC-AF[75]	Europe (15 sites)	RCT X-over 3 mo.	Right ventricular pacing	64	10	43	25	18	Treatment 1 Control 2 Both 2	ELA medical, Medtronic Transvenous	6MWT	Peak O_2 consumption; QOL; hospital admissions for decompensated heart failure; mortality; patient's preferred period at end of crossover
Leclercq 2003 RD-CHF[**] Unpublished	France	RCT X-over 3 mo.	Right ventricular pacing	56	Un clear	44	22	22	Unclear	Transvenous	CHF hospitalization	N/a

Table 5. Description of studies included in the efficacy review: CRT for CHF—concluded

				Number of Participants								
Study name	**Country**	**Design** **Duration**	**Control arm**	**Total enrolled**	**Exclusions**	**Total randomized**	**Treatment***	**Control***	**Withdrawals**	**Device** **Method of implant**	**Authors' primary outcome(s)**	**Other outcomes**
Medtronic 2001 MIRACLE-ICD[36] FDA report	U.S. and Canada (53 sites)	RCT (post implant) parallel 6 mo.	Pacer "Inactive"	659	105	554	272	282	Treatment 7 Control 6	Model 7272 InSync ICD, Attain LV leads models 4189, 2187, 2188. Transvenous	NYHA; QOL; 6MWT;	ADRs; QRS; peak O_2 uptake; echocardiographic indices; LV lead electrical performance; VT/VF therapy; CHF composite response; implant ventricular defibrillation criterion; ATP therapy; healthcare utilization; death

ADR = adverse reaction; CRT = cardiac resynchronization therapy; CRT ICD = CRT with implanted cardioverter defibrillator; FDA = Food and Drug Administration; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; N/a = not available; NYHA = New York Heart Association class; QOL = quality of life; OPT = optimal pharmacological therapy; RCT = randomized control trial; 6MWT = 6-minute walk test; X-over = crossover study

* the intervention that crossover studies received in the first period

** detailed data not available for Leclercq 2003 (RD-CHF) at the time this report was prepared

[t] excludes deaths and implant failures, where applicable

Note: While the published report for MIRACLE-ICD was used for patients with NYHA Class III or IV symptoms, the FDA report was used for NYHA Class II patients as they were not included in the published MIRACLE-ICD manuscript

Table 6. Baseline characteristics of patients in trials included in the efficacy review: CRT for CHF

					NYHA class				ECG			Physical exam			Other co-morbidities	
					II	III	IV	Atrial fibril-lation	PR interval	QRS interval	LVEDD	Systolic BP	Diastolic BP	HR		
Trial name	**Study Group**	**Males n (%)**	**Age mean SD**	**Ischemic %**	**%**	**%**	**%**	**n (%)**	**mean SD (msec)**	**mean SD (msec)**	**mean SD (mm)**	**mean SD**	**mean SD**	**mean SD**	**LBBB %**	**LVEF %**
Abraham 2002[61] MIRACLE	CRT	155 (68)	64 +/- 11	50	-	90	110	0	-	167 +/- 21	70 +/- 10	114 +/- 18	69 +/- 10	73 +/- 13	-	22 +/- 6
	Control	153 (68)	65 +/- 11	58	-	91	9	0	-	165 +/- 20	69 +/- 10	115 +/- 18	68 +/- 10	75 +/- 13	-	22 +/- 6
Auricchio 2002 PATH-CHF[62]	CRT first	11 (46)	59 +/- 7	42	-	88	13	0	190 +/- 34	174 +/- 30	71 +/- 10	-	-	77 +/- 16	88	21 +/- 6
	Control first	10 (59)	60 +/- 5	6	-	82	18	0	207 +/- 30	178 +/- 34	75 +/- 13	-	-	80 +/- 13	100	20 +/- 7
	All	21 (50)	60 +/- 7	29	-	86	14	0	196 +/- 33	175 +/- 32	73 +/- 11	-	-	78 +/- 15	93	21 +/- 7
Bristow 2003[60] COMPANION	CRT	413 (67)	65	54	-	87	13	0	-	159	-	-	-	-	69	22
	Control	213 (69)	67	59	-	82	18	0	-	156	-	-	-	-	70	23
	CRT-ICD	399 (67)	66	55	-	86	14	0	-	159	-	-	-	-	73	23
Cazeau 2001[74] MUSTIC-SR	CRT first	19 (66)	64 +/- 11	-	-	100		0	-	172 +/- 22	-	-	-	-	-	-
	Control first	24 (83)	64 +/- 8	-	-	100		0	-	175 +/- 19	-	-	-	-	-	-
	All	43 (74)	64 +/- 9	37	-	100		0	215 +/- 43	174 +/- 20	73 +/- 10	-	-	-	-	23 +/- 7
Garrigue 2002[70]	All	13 (100)	64 +/- 12	46	-	77	33	100	-	208+/- 15	-	-	-	-	62	25 +/- 8

Table 6. Baseline characteristics of patients in trials included in the efficacy review: CRT for CHF—concluded

					NYHA class				ECG			Physical exam			Other co-morbidities	
					II	III	IV	Atrial fibril-lation	PR interval	QRS interval	LVEDD	Systolic BP	Diastolic BP	HR		
Trial name	**Study Group**	**Males n (%)**	**Age mean SD**	**Ischemic %**	**%**	**%**	**%**	**n (%)**	**Mean SD (msec)**	**Mean SD (msec)**	**Mean SD (mm)**	**Mean SD**	**Mean SD**	**Mean SD**	**LBBB %**	**LVEF %**
Guidant 2002[73] CONTAK-CD FDA report	CRT II-IV	210 (85)	66 +/- 11	67	32	60	8	0	205 +/- 42	160 +/- 27	-	118 +/- 21	67 +/- 12	73 +/- 12	54	21 +/- 7
	Control II-IV	211 (83)	66 +/- 11	70	33	57	10	0	202 +/- 49	156 +/- 26	-	118 +/- 21	69 +/- 12	75 +/- 14	55	22 +/- 7
	CRT III/IV	90 (77)	66 +/- 11	65	17*	73	10	0	204 +/- 41	164 +/- 27	-	116 +/- 20	68 +/- 12	75 +/- 13	50	21 +/-6
	Control III/IV	86 (78)	66 +/- 11	71	10*	71	19	0	200 +/- 54	152 +/- 24	-	117 +/- 23	67 +/- 14	74 +/- 15	54	21 +/- 6
Leclercq 2002[74] MUSTIC-AF	CRT first	21 (84)	65 +/- 9	-		100		25 (100)	-	209 +/- 21	70 +/- 9	-	-	75 +/- 6	-	23 +/- 7
	Control first	14 (78)	66 +/- 9	-		100		18 (100)	-	208 +/- 12	66 +/- 7	-	-	74 +/- 5	-	30 +/- 12
	All	35 (81)	65 +/- 8	43		100		43 (100)	-	209 +/- 18	68 +/- 8	-	-	74 +/- 5	-	26 +/- 10
Leclercq 2003 RD-CHF** Unpublished	N/a	N/a	73 +/- 8	N/a	0	N/a	N/a	23 (52)	N/a	N/a	N/a	N/a	N/a	N/a	N/a	25 +/-/9
Medtronic 2001[36] MIRACLE-ICD FDA report	CRT II-IV	231 (82)	66 +/- 12	38	32	60	8	16 (6)	-	166 +/- 23	71 +/- 9	113 +/- 19	67 +/- 11	73 +/- 13	0.7	21 +/- 7
	Control II-IV	217 (80)	66 +/- 11	32	38	55	7	12 (4)	-	163 +/- 22	70 +/- 9	113 +/- 17	68 +/- 12	73 +/- 13	0	21 +/- 7
	CRT III/IV	142 (76)	67 +/- 11	64		88	12	49 (26)	-	165 +/- 22	70 +/- 9	-	-	71 +/- 12	75	21 +/- 7
	Control III/IV	136 (77)	68 +/- 9	75		89	11	31 (18)	-	162 +/ - 22	71 +/- 9	-	-	72 +/- 13	71	20 +/- 6

CRT = cardiac resynchronization therapy; FDA = Food and Drug Administration; HR = heart rate; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; LBBB = left bundle branch block; N/a = not available; NYHA= New York Heart Association class

* pre-implant assessment

** detailed data not available for Leclercq 2003 (RD-CHF) at the time this report was prepared

Note: While the published report for MIRACLE-ICD was used for patients with NYHA Class III or IV symptoms, the FDA report was used for NYHA Class II patients as they were not included in the published MIRACLE-ICD manuscript

Table 7. Baseline drug therapy for trials included in the efficacy review: CRT for CHF

		Medications						
Trial name	**Study Groups**	**ACE %**	**ARB %**	**BB %**	**Spironolactone %**	**Digoxin %**	**Nitrates %**	**Others Name %**
Abraham 2002[61] MIRACLE	CRT	93*	-	62	-	78	-	Diuretics (94)
	Control	90*	-	55	-	79	-	Diuretics (93)
Auricchio 2002[62] PATH-CHF	CRT	96**	-	71	-	**	71	Amiodarone (29)
	Control	100**	-	65	-	**	71	Amiodarone (35)
	All	95**	-	67	-	**	69	Amiodarone (30)
Bristow 2003[60] COMPANION	CRT	89*	*	68	53	-	-	Diuretics (100); digoxin (100)
	Control	89*	*	66	55	-	-	
	CRT-ICD	90*	*	68	55	-	-	
Cazeau 2001[74] MUSTIC-SR	All	96*	*	28	22	48	-	Amiodarone (31), diuretics (100)
Garrigue 2002[70]	All	100	-	100	-		-	Diuretics (100); amiodarone (100) ; CCB (100)
Guidant 2002[73] CONTAK-CD FDA report	CRT, II-IV	86*	*	48	-	69	-	Diuretics (88)
	Control, II-IV	89*	*	46	-	68	-	Diuretics (83)
	CRT, III/IV	81*	*	45	-	72	-	Diuretics (92)
	Control, III/IV	89*	*	40	-	68	-	Diuretics (86)
Leclercq 2002[75] MUSTIC-AF	All	100*	*	23	16	58	-	-
Leclercq 2003 RD-CHF*** Unpublished	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
Medtronic 2001[36] MIRACLE-ICD FDA report	CRT, II-IV	93	-	63	-	71	31	Diuretics (91); anti-depressant (16); CCB (6); antiarrhythmic (40); positive ionotrope (71); anti-coagulant (77).
	Control, II-IV	90	-	59	-	72	30	Diuretics (90); anti-depressant (17); CCB (6); anti-coagulant (79); antiarrhythmic (33); positive ionotrope (72)
	CRT, III/IV	92	-	63	-	76	36	Diuretics (93); anti-depressant (19); CCB (7); anti-coagulant(77); antiarrhythmic (42); positive ionotrope (76)
	Control, III/IV	88	32	58	-	73	33	Diuretics (94); anti-depressant (20); CCB (6); anti-coagulant (81); antiarrhythmic (32); positive ionotrope (73)

ACE= angiotensin converting enzyme inhibitors; ARB= angiotension-receptor blocks; BB= beta blocker; CCB= calcium channel blocker
*receiving angiotensin-converting-enzyme inhibitors or angiotension-receptor blockers
**receiving angiotensin-converting-enzyme inhibitors or digoxin
*** detailed data not available for Leclercq 2003 (RD-CHF) at the time this report was prepared
N/a =not available

Table 8. Methodological quality of randomized trials included in the efficacy review

Study	Randomization		Double-blinding		Description of withdrawals/ drop-outs	Jadad Score	Allocation Concealment
	Stated	Method described	Stated	Method described			
Abraham 2002 MIRACLE[61]	Yes	Adequate	Yes	Adequate	Adequate	5	Clear
Auricchio 2000 PATH-CHF[62]	Yes	Unclear	Yes	Adequate	Adequate	4	Unclear
Bristow 2003 COMPANION[60]	Yes	Adequate	No	N/a	Unclear	3	Unclear
Cazeau 2001 MUSTIC-SR[74]	Yes	Adequate	No	N/a	Adequate	3	Unclear
Garrigue 2002[70]	Yes	Unclear	No	N/a	Unclear	1	Unclear
Guidant 2002 CONTAK-CD[73]	Yes	Unclear	Yes	Adequate	Adequate	4	Unclear
Leclercq 2002 MUSTIC-AF[75]	Yes	Adequate	No	N/a	Adequate	3	Unclear
Leclercq 2003 RD-CHF* (unpublished)	Yes	N/a	No	N/a	N/a	1	N/a
Medtronic 2001 MIRACLE-ICD[36]	Yes	Unclear	Yes	Adequate	Adequate	4	Unclear

N/a = not available
* detailed data not available for Leclercq 2003 (RD-CHF) at the time this report was prepared

Table 9. Description of studies included in the safety review: CRT for CHF

				Number of Participants								
Study name	**Country**	**Design** **Duration**	**Control arm**	**Total enrolled**	**Exclusions[t]**	**Total randomized**	**Treatment***	**Control***	**Withdrawals[t]**	**Device** **Method of implant**	**Authors' primary outcome(s)**	**Other outcomes**
Abraham 2002 MIRACLE[61]	US. & Canada	RCT parallel 6 mo.	Pacer "Inactive"	571	--	453	228	225	Treatment 1 Control 8	InSync model 8040 Medtronic Transvenous	NYHA class; QOL, 6MWT	Peak O_2 consumption; time on a treadmill; LVEF; LVEDD; severity of mitral regurgitation; duration of QRS interval; clinical composite response (improved, worsened, unchanged); death; worsening heart failure; number of days spent in hospital
Auricchio 2002 PATH-CHF[62]	Germany & Netherlands	RCT cross-over 1 mo.	Uni-ventricular pacing (4 Rt., 36 Lt.)	42	1	41	24	17	Treatment 2 Control 5	Vigor / Discovery with LV lead Guidant Transthoracic	O2 uptake at peak exercise; O2 uptake at anaerobic threshold; 6MWT	NYHA; QOL
Bristow 2003[60] COMPANION	US. multicentre	RCT parallel 3 arms 12 mo.	OPT	-	-	1520	CRT=617 CRT-D= 595	308	-	CONTAK TR Models 4510-4513, Model 1241 CONTAK CD Model 1823 Guidant. Transvenous	CRT: all-cause mortality & hospitalization. CRT-ICD: all-cause mortality & hospitalization	Cardiac morbidity; ADRs, implant success; peak O_2 uptake at exercise
Cazeau 2001[74] MUSTIC-SR	Europe (15 sites)	RCT cross-over 3 mo.	Pacer "Inactive"	67	3	58	29	29	Treatment 4 Control 3	Chorum 7336 ELA Medical or InSync 8040 Medtronic Transvenous	6MWT	QOL (main secondary outcome); peak O_2 uptake; hospital admissions because of decompensated heart failure; patient's preference with regard to pacing (active vs. inactive) at the end of crossover; death

Table 9. Description of studies included in the Safety review: CRT for CHF—continued

				Number of Participants								
Study name	**Country**	**Design** **Duration**	**Control arm**	**Total enrolled**	**Exclusions[t]**	**Total randomized**	**Treatment***	**Control***	**Withdrawals[t]**	**Device** **Method of implant**	**Authors' primary outcome(s)**	**Other outcomes**
Cazeau 1996[99]	France	Single-arm trial 2 mo.- 1 yr.	None	8	0	-	6	-	0	Chorus TM 6234 Ela Medical, Medtronic Thera 7940 DR Transthoracic (7) Transvenous (1)	Potential hemodynamic benefit of CRT	Not stated
Filho 2002[98]	Brazil	RCT cross-over 30, 90, 180 days	Rt. uni-ventricular pacing	24	0	-	-	-	0	Not reported Transthoracic	NYHA	QRS; mortality; LVEF; hospitalization
Gras 2002[100] INSYNC Italian Registry	Europe Canada	Single-arm trial up to 1 yr.	None	117	0	-	103	-	9	InSync Model 8040, Medtronic Transvenous	Feasibility, safety and long term effects	NYHA, QRS duration, 6MWT, QOL
Guidant 2002[73] CONTAK-CD FDA Report	US. (47 sites)	RCT Phase I period 1 of cross-over 3 mo Phase II parallel 6 mo	Pacer "Inactive"	581	15	490	245	245	Treatment 3 Control 1	CONTAK-CD Transvenous and Transthoracic	All-cause mortality; CHF hospitalizations; ventricular tachyarrhythmia requiring device intervention	Peak O_2 consumption; QOL; 6MWT, all adverse events

Table 9. Description of studies included in the safety review: CRT for CHF—continued

				Number of Participants								
Study name	**Country**	**Design** **Duration**	**Control arm**	**Total enrolled**	**Exclusions[t]**	**Total randomized**	**Treatment***	**Control***	**Withdrawals[t]**	**Device** **Method of implant**	**Authors' primary outcome(s)**	**Other outcomes**
Krahn 2002[101]	Canada	Single-arm trial 1, 3, 6 mo. then q 6 mo.	None	45	0	-	40	-	-	Medtronic InSync pacemaker or ICD or Guidant ContakTM or ICD Transvenous	QOL; NYHA	Mortality, electrocardiographic measures; transplants
Kuhlkamp 2002[102]	Germany	Single-arm trial 3 mo.	None	84	0	-	81	-	-	InSync Model 7272 Medtronic Transvenous	Not stated	6MWT; QOL; NYHA; complications; death
Leclercq 2000[96]	France	Single-arm trial 1, 3, 6 mo. then q 6 m	None	37	0	34	49	-	-	Various models Medtronic Transvenous Transthoracic	Mortality	NYHA;electrocardiographic measures; exercise tolerance.
Leclercq 2002[75] MUSTIC-AF	Europe (15 sites)	RCT cross-over 3 mo.	Rt. ventricular pacing	64	10	43	25	18	Treatment 1 Control 2 Both 2	ELA medical, Medtronic Transvenous	6MWT	Peak O_2 consumption; QOL; hospital admissions for decompensated heart failure; mortality; patient's preferred period at end of crossover

Table 9. Description of studies included in the safety review: CRT for CHF–continued

				Number of Participants								
Study name	**Country**	**Design** **Duration**	**Control arm**	**Total enrolled**	**Exclusions[t]**	**Total randomized**	**Treatment***	**Control***	**Withdrawals[t]**	**Device** **Method of implant**	**Authors' primary outcome(s)**	**Other outcomes**
Leclercq[104] Unpublished	France	Single-arm trial 1, 3, 6 mo. Then q 6 mo.	None	-	-	-	125	-	-	Not stated Transvenous	Not stated	Survival, QRS duration and axis; NYHA; LVEF; exercise tolerance
Leclercq 2003 RD-CHF** Unpublished	France	RCT cross-over 3 mo.	Rt. ventricular pacing	56	N/a	44	22	22	N/a	Transvenous	CHF hospitalization	N/a
Medtronic 2001[36] MIRACLE-ICD FDA Report,	US. & Canada (53 sites)	RCT parallel 6 mo.	Pacer "Inactive"	660	36	555	272	282	Treatment 7 Control 6	Model 7272 InSync ICD Transvenous	NYHA; QOL; 6MWT	Adverse events; QRS; peak O_2 uptake; echocardiographic indices; LV lead electrical performance; VT/VF therapy; CHF composite response; implant ventricular defibrillation criterion; ATP therapy; healthcare utilization; death
Leon 2002[106]	US.	Single-arm trial	None	20	0	-	20	-	0	Revised RV pacing system to CRT Medtronic leads Transvenous	Improved ventricular function	Success of procedure; NYHA; QOL; hospitalization

Table 9. Description of studies included in the safety review: CRT for CHF–concluded

				Number of Participants								
Study name	**Country**	**Design** **Duration**	**Control arm**	**Total enrolled**	**Exclusions[t]**	**Total randomized**	**Treatment***	**Control***	**Withdrawals[t]**	**Device** **Method of implant**	**Authors' primary outcome(s)**	**Other outcomes**
Molhoek 2002[103]	Netherlands	Single-arm trial 3, 6 mo.	None	40	0	-	40	-	0	Easytrack 4512-80, Contak TR or CD Guidant, or InSync III Transvenous	Clinical benefit, long-term prognosis	NYHA; QOL; 6MWT; electrocardiogram; hospitalization; mortality

CRT-ICD = CRT with implanted cardioverter defibrillator; LVEDD = Left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; N/a = not available; NYHA = New York Heart Association; OPT = optimal pharmacological therapy; QOL = quality of life; RCT = randomized control trial; 6MWT = 6-minute walk test

* the intervention that cross-over studies received in the first period

** detailed data not available for Leclercq 2003 (RD-CHF) at the time this report was prepared

[t] excludes deaths and implant failures, where applicable

Table 10. Baseline characteristics of patients in studies included in the safety review: CRT for CHF

					NYHA class				ECG			Physical exam			Other co-morbidities	
					II	III	IV	Atrial fibrillation	PR interval	QRS interval	LVEDD	Systolic BP	Diastolic BP	HR		
Trial name	Study Group	Males n (%)	Age mean SD	Ischemic %	%	%	%	n (%)	Mean SD (msec)	Mean SD (msec)	Mean SD (mm)	Mean SD	Mean SD	Mean SD	LBBB %	LVEF %
Abraham 2002[61] MIRACLE	CRT	155 (68)	64 +/- 11	50	-	90	10	0	-	167 +/- 21	70 +/- 10	114 +/- 18	69 +/- 10	73 +/- 13	-	22 +/- 6
	Control	153 (68)	65 +/- 11	58	-	91	9	0	-	165 +/- 20	69 +/- 10	115 +/- 18	68 +/- 10	75 +/- 13	-	22 +/- 6
Auricchio 2002[62] PATH-CHF	CRT first	11 (46)	59 +/- 7	42	-	88	13	0	190 +/- 34	174 +/- 30	71 +/- 10	-	-	77 +/- 16	88	21 +/- 6
	Control first	10 (59)	60 +/- 5	6	-	82	18	0	207 +/- 30	178 +/- 34	75 +/- 13	-	-	80 +/- 13	100	20 +/- 7
	All	21 (50)	60 +/- 7	29	-	86	14	0	196 +/- 33	175 +/- 32	73 +/- 11	-	-	78 +/- 15	93	21 +/- 7
Bristow 2003[60] COMPANION	CRT	413 (67)	65	54	-	87	13	0	-	159	-	-	-	-	69	22
	Control	213 (69)	67	59	-	82	18	0	-	156	-	-	-	-	70	23
	CRT-ICD	399 (67)	66	55	-	86	14	0	-	159	-	-	-	-	73	23
Cazeau 2001[74] MUSTIC-SR	CRT first	19 (66)	64 +/- 11	-	-	100	-	0	-	172 +/- 22	-	-	-	-	-	-
	Control first	24 (83)	64 +/- 8	-	-	100	-	0	-	175 +/- 19	-	-	-	-	-	-
	All	43 (74)	64 +/- 9	37	-	100	-	0	215 +/- 43	174 +/- 20	73 +/- 10	-	-	-	-	23 +/- 7
Cazeau 1996[99]	All	7 (88)	66 +/- 5	50	-		100	3 (38)	200 +/- 20	200 +/- 35	-	-	-	-	25	22 +/- 8
Filho 2002[98]	All	23 (96)	55 +/- 13	38	33	67	4	-	225 +/- 80	181 +/- 31	-	-	-	-	100	19 +/- 5.2
Gras 2002[100] INSYNC Italian Registry	All	81 (77)	67 +/- 10	48	0	68	32	0	-	178 +/- 28	72 +/- 10	-	-	-	-	22 +/- 6
Guidant 2002[73] CONTAK-CD FDA report	CRT II-IV	210 (85)	66 +/- 11	67	32	60	8	0	205 +/- 42	160 +/- 27	-	118 +/- 21	67 +/- 12	73 +/- 12	54	21 +/- 7
	Control II-IV	211 (83)	66 +/- 11	70	33	57	10	0	202 +/- 49	156 +/- 26	-	118 +/- 21	69 +/- 12	75 +/- 14	55	22 +/- 7
	CRT III/IV	90 (77)	66 +/- 11	65	17 *	73	10	0	204 +/- 41	164 +/- 27	-	116 +/- 20	68 +/- 12	75 +/- 13	50	21 +/-6
	Control III/IV	86 (78)	66 +/- 11	71	10 *	71	19	0	200 +/- 54	152 +/- 24	-	117 +/- 23	67 +/- 14	74 +/- 15	54	21 +/- 6

Table 10. Baseline characteristics of patients in studies included in the safety review: CRT for CHF–concluded

					NYHA class				ECG			Physical exam			Other co-morbidities	
					II	III	IV	Atrial fibrillation	PR interval	QRS interval	LVEDD	Systolic BP	Diastolic BP	HR		
Trial name	**Study Group**	**Males n (%)**	**Age mean SD**	**Ischemic %**	**%**	**%**	**%**	**n (%)**	**Mean SD (msec)**	**mean SD (msec)**	**Mean SD (mm)**	**Mean SD**	**Mean SD**	**Mean SD**	**LBBB (%)**	**LVEF (%)**
Krahn 2002[101]	All	37 (82)	65 +/- 10	69	6	76	18	15 (33)	240 +/- 63	166 +/- 20	-	-	-	-	98	19 +/- 5
Kuhlkamp 2002[102]	All	74 (91)	64 +/- 9	-	32	59	9	19 (23) PAFr 10 (12 AF	-	170 +/- 30	71 +/- 11	-	-	-	-	25 +/-7
Leclercq 2002[75] MUSTIC-AF	CRT first	21 (84)	65 +/- 9	-	-	100	-	25 (100)	-	209 +/- 21	70 +/- 9	-	-	75 +/- 6	-	23 +/- 7
	Control first	14 (78)	66 +/- 9	-	-	100	-	18 (100)	-	208 +/- 12	66 +/- 7	-	-	74 +/- 5	-	30 +/- 12
	All	35 (81)	65 +/- 8	43	-	100	-	43 (100)	-	209 +/- 18	68 +/- 8	-	-	74 +/- 5	-	26 +/- 10
Leclercq 2000[107]	All	34(92)	68 +/- 8	38	0	70	30	14 (28)	260 +/- 30	181 +/- 23	87 +/- 8	-	-	-	-	23 +/-5
Leclercq[104] unpublished	All	110 (88)	68 +/- 9	38	-	68	32	36 (29)	248 +/- 56	183 +/- 29	74 +/- 8.5	-	-	-	-	21 +/- 6
Leclercq 2003 RD-CHF** Unpublished	-	N/a	73 +/- 8	N/a	0	N/a	N/a	23	N/a	N/a	N/a	N/a	N/a	N/a	N/a	25 +/- 9
Leon 2002[106]	All	17 (85)	70 +/- 11	55	0	60	40	20 (100)	-	213 +/- 40	68 +/- 8	-	-	-	-	22 +/- 7
Medtronic 2001[36] MIRACLE-ICD FDA report 2001	CRT II-IV	217 (80)	66 +/- 12	38	32	60	8	16 (6)	-	166 +/- 23	71 +/- 9	113 +/- 19	67 +/- 11	73 +/- 13	10	21 +/- 7
	Control II-IV	231 (82)	66 +/- 11	32	38	55	7	12 (4)	-	163 +/- 22	70 +/- 9	113 +/- 17	68 +/- 12	73 +/- 13	0	21 +/- 7
	CRT III/IV	142 (76)	67 +/- 11	64	-	88	12	49 (26)	-	165 +/- 22	70 +/- 9	-	-	71 +/- 12	75	21 +/- 7
	Control III/IV	136 (77)	68 +/- 9	75	-	89	11	31 (18)	-	162 +/ - 22	71 +/- 9	-	-	72 +/- 13	71	20 +/- 6
Molhoek 2002[103]	All	31 (78)	64 +/- 10	48	mean = 3.3 +/- 0.5			4 (10)	-	range 120-240	-	-	-	-	100	24+/- 9

CRT = cardiac resynchronization therapy; FDA = Food and Drug administration; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter; N/a = not available; NYHA = New York Heart association; SD = standard deviation

*pre-implant assessment

** detailed data not available for Leclercq 2003 (RD-CHF) at the time this report was prepared

Table 11. Baseline drug therapy in included patients in the safety review: CRT for CHF

		Medications						
Trial name	**Study Groups**	**ACE %**	**ARB %**	**BB %**	**Spironolactone %**	**Digoxin %**	**Nitrates %**	**Others Name %**
Abraham 2002[61] MIRACLE	CRT	93*	-	62	-	78	-	Diuretics (94)
	Control	90*	-	55	-	79	-	Diuretics (93)
Auricchio 2002[62] PATH-CHF	CRT	96**	-	71	-	**	71	Amiodarone (29)
	Control	100**	-	65	-	**	71	Amiodarone (35)
	All	95**	-	67	-	**	69	Amiodarone (30)
Bristow 2003[60] COMPANION	CRT	89*	*	68	53	-	-	Diuretics (100); digoxin (100)
	Control	89*	*	66	55	-	-	
	CRT-D	90*	*	68	55	-	-	
Cazeau 2001[74] MUSTIC-SR	All	96*	*	28	22	48	-	Amiodarone (31), diuretics (100)
Cazeau 1996[99]	All	100	-	-	-	-	-	All on maximal medical therapy; 4 on IV dobutamine &/or dopamine
Filho 2002[98]	All	92	-	-	42	100	13**	Diuretics (100); carvedilol (29); amiodarone (50);
Gras 2002[100] INSYNC Italian Registry	All	70	16	17	-	58	-	Amiodarone (50); diuretic (93); vasodilators (17); CCB (15) anticoagulants (34); IV inotropic support (2)
Guidant 2002[73] CONTAK-CD FDA report	CRT, II-IV	86*	*	48	-	69	-	Diuretics (88)
	Control, II-IV	89*	*	46	-	68	-	Diuretics (83)
	CRT, III/IV	81*	*	45	-	72	-	Diuretics (92)
	Control, III/IV	89*	*	40	-	68	-	Diuretics (86)
Krahn 2002[101]	All	84	-	56	-	-	-	Antiarrhythmic agents (47); diuretic (100)
Kuhlkamp 2002[102]	All	85	-	54	-	32	31	Diuretics (54); anticoagulants (56); antiarrhythmics (58)
Leclercq 2002[75] MUSTIC-AF	All	100*	*	23	16	58	-	-

Table 11. Baseline drug therapy in included patients in the safety review: CRT for CHF—concluded

		Medications						
Trial name	**Study Groups**	**ACE %**	**ARB %**	**BB %**	**Spironolactone %**	**Digoxin %**	**Nitrates %**	**Others Name %**
Leclercq 2000[96]	All	100	-	-	-	60	-	Diuretics (100), captopril (95 +/- 30mg/d)
Leclercq[104] unpublished	All	98	-	34	-	60	-	Diuretics (100),
Leclercq 2003 RD-CHF*** Unpublished	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
Leon 2002[106]	All	90	-	25	-	60	-	Diuretics (95)
Medtronic 2001[36] MIRACLE-ICD FDA report	CRT, II-IV	93	-	63	-	71	31	Diuretics (91); anti-depressant (16); CCB (6); antiarrhythmic (40); positive ionotrope (71); anti-coagulant (77).
	Control, II-IV	90	-	59	-	72	30	Diuretics (90); anti-depressant (17); CCB (6); anti-coagulant (79); antiarrhythmic (33); positive ionotrope (72)
	CRT, III/IV	92	-	63	-	76	36	Diuretics (93); anti-depressant (19); CCB (7); anti-coagulant (77); antiarrhythmic (42); positive ionotrope (76)
	Control, III/IV	88	32	58	-	73	33	Diuretics (94); anti-depressant (20); CCB (6); anti-coagulant (81); antiarrhythmic (32); positive ionotrope (73)
Molhoek 2002[103]	All	Not stated	-	-	-	-	-	-

ACE= angiotensin-converting-enzyme inhibitors; ARB= angiotension-receptor blocker; BB= beta blocker; CCB= calcium channel blocker
*ACE or ARB
** receiving nitrates or hydralazine
*** detailed data not available for Leclercq 2003 (RD-CHF) at the time this report was prepared

Table 12. Methodological quality assessments of included studies: safety review

Study name	Sponsor	Downs and Black Quality Score[59]					
		Reporting Maximum 11	External validity Maximum 3	Internal validity [bias] maximum 7	Internal validity [confounding] Maximum 6	Power Maximum 2	Overall Maximum 29
Abraham 2002 MIRACLE[61]	Medtronic Inc.	11	2	7	6	2	28
Auricchio 2002[62] PATH-CHF	Guidant Corporation	11	2	7	5	1	26
Bristow 2003[60] COMPANION	Guidant Corporation	8	1	5	4	2	20
Cazeau 2001[74] MUSTIC-SR	ELA Recherche, Medtronic, Swedish Heart and Lung Association; Swedish Medical Research Council	11	1	6	5	2	25
Cazeau 1996[99]	technical support from ELA Recherche	9	1	5	4	0	19
Filho 2002[98]	None indicated	7	1	5	4	1	18
Gras 2002[100] INSYNC Italian Registry	None indicated	9	1	5	1	1	17
Guidant 200[173] CONTAK-CD FDA report	Guidant Corporation	11	2	7	4	1	25
Krahn 2002[101]	Heart and Stroke Foundation of Ontario	10	3	5	4	0	22
Kuhlkamp 2002[102]	Medtronic Inc.	11	1	5	3	0	20
Leclercq 2002[75] MUSTIC-AF	ELA Recherche, Medtronic, European Society of Cardiology, Centre Hospitalier Universitaire de Rennes; Swedish Heart and Lung Association, Swedish Medical Research Council	11	2	6	5	2	26
Leclercq 2000[96]	None indicated	10	2	5	2	0	19
Leclercq Unpublished[104]	None indicated	10	2	5	3	1	21
Leclercq 2003 RD-CHF* Unpublished	N/a	N/a	N/a	N/a	N/a	N/a	N/a
Leon 2002[106]	Medtronic provided fellowship support	11	3	5	3	0	22

Table 12. Methodological quality assessments of included studies: safety review–concluded

Study name	Sponsor	Downs and Black Quality Score[59]					
		Reporting Maximum 11	External validity Maximum 3	Internal validity [bias] maximum 7	Internal validity [confounding] Maximum 6	Power Maximum 2	Overall Maximum 29
Medtronic 2001[36] MIRACLE-ICD FDA report	Medtronic Inc	11	1	7	3	1	23
Molhoek 2002[103]	Medtronic Inc.	10	2	5	3	0	20

N/a = not available
* detailed data not available for Leclercq 2003 (RD-CHF) at the time report prepared

Table 13. Peri-implant risks for cardiac resynchronization therapy

Study	n/N	Simple Pool Risk % [95% CI]
Peri-implant deaths		
MUSTIC-SR 2001[74]	0/64	0
MUSTIC-AF 2002[75]	0/59	0
PATH-CHF 2002[62]	0/41	0
MIRACLE 2002[61]	2/571	0.4 [0.1,1.4]
MIRACLE-ICD 2003[94]	0/429	0
COMPANION unpub[60]	5/617	0.8 [0.3,2.0]
COMPANION-ICD unpub[60]	3/595	0.5 [0.1,1.6]
Cazeau 1996[99]	1/7	14.3 [8.4,54.0]
Filho 2002[98]	0/24	0
Leclercq unpub[104]	0/139	0
Total [N=10]	**13/3113**	**0.4 [0.2,0.7]**
Sensitivity Total [N=16]	**13/3456**	**0.4 [0.2,0.7]**
Implant successes		
MUSTIC-SR 2001[74]	59/64	92.2 [82.0,97.1]
MUSTIC-AF 2002[75]	54/59	91.5 [80.6,96.8]
MIRACLE 2002[61]	528/571	92.5 [89.9,96.8]
PATH-CHF 2002[62]	41/41	100
MIRACLE-ICD 2003[94]	379/429	88.3 [84.8,91.1]
COMPANION unpub[60]	538/617	87.2 [84.2,89.7]
COMPANION-ICD unpub[60]	540/595	90.8 [88.1,92.9]
CONTAK-CD unpub[73]	501/567	88.4 [85.4,90.8]
RD-CHF unpub[#]	45/56	80.4 [67.2,89.3]
Cazeau 1996[99]	6/7	85.7 [42.0,99.2]
Gras 2002[100]	125/139	89.9 [83.4,94.2]
Krahn 2002[101]	40/45	88.9 [75.2,95.8]
Kuhlkamp 2002[102]	81/84	96.4 [89.2,99.1]
Leon 2002[106]	20/20	100
Filho 2002[98]	24/24	100
Molhoek 2002[103]	40/40	100
Leclercq unpub[104]	125/139	89.9 [83.4,94.2]
Total [N=16]*	**3124/3475**	**89.9 [88.8,90.9]**
Related to left ventricular lead		
MUSTIC-SR 2001[74]	5/64	7.8 [2.9,18.0]
MUSTIC-AF 2002[75]	5/59	8.5 [3.2,19.4]
MIRACLE-ICD 2003[36]	31/429	7.2 [5.0,10.2]
CONTAK-CD unpub[73]	17/517	3.3 [2.0,5.3]
Gras 2002[100]	12/117	10.3 [5.6,17.6]
Krahn 2002[101]	6/45	13.3 [5.5,27.5]
Kuhlkamp 2002[102]	4/84	4.8 [1.5,12.4]
Filho 2002[98]	0/24	0
Total [N=8]	**80/1339**	**6.0 [4.7,7.2]**
Sensitivity Total [N=14]**	**80/2055**	**3.9 [3.1,4.8]**
Related to the device and battery		
PATH-CHF 2002[62]	3/41	7.3 [1.9,21.0]
MIRACLE 2002[61]	2/571	0.4 [0.06,1.4]
MIRACLE-ICD 2003[94]	3/429	0.7 [0.2,2.2]
CONTAK-CD unpub[73]	7/517	1.4 [0.6,2.9]
Filho 2002[98]	0/24	0
Total [N=5]	**15/1582**	**0.9 [0.6,1.6]**
Sensitivity Total [N=14]**	**15/2055**	**0.7 [0.4,1.2]**

Table 13. Peri-Implant risks for cardiac resynchronization therapy—concluded

Study	n/N	Simple Pool Risk % [95% CI]
Related to implant procedure and/or tools		
MIRACLE 2002[61]	35/571	6.1 [4.4,8.5]
MIRACLE-ICD 2003[94]	19/429	4.4 [2.8,7.0]
CONTAK-CD unpub[73]	50/517	9.7 [7.3,12.6]
Gras 2002[100]	3/117	2.6 [0.7,7.9]
Krahn 2002[101]	4/45	8.9 [2.9,22.1]
Kuhlkamp 2002[102]	4/84	4.8 [1.5,12.4]
Leon 2002[106]	0/20	0
Filho 2002[98]	0/24	0
Total [N=8]	**115/1807**	**6.4 [5.3,7.6]**
Sensitivity Total [N=14]**	**115/2055**	**5.6 [4.7,6.7]**
Related to heart function		
MIRACLE 2002[61]	1/571	0.2 [0.009,1.1]
MIRACLE-ICD 2003[94]	11/429	2.6 [1.4,4.7]
Cazeau 1996[99]	1/7	14.3 [8.4,54.0]
Filho 2002[98]	0/24	0
Total [N=4]	**13/1031**	**1.3 [0.7,2.2]**
Sensitivity Total [N=14]**	**13/2055**	**0.6 [0.4,1.1]**

* only safety outcome that includes data from RD-CHF

** COMPANION omitted – full report not available; Leclercq 2002 omitted, - there was 10% or 14/139 failed implants but they did not specify the event

Table 14. Post-implantation risks of cardiac resynchronization therapy

Study	n/N	Simple Pool Risk % [95% CI]
Mechanical malfunction		
MUSTIC-SR 2001[74]	2/58	3.4 [0.6,13.0]
MUSTIC-AF 2002[75]	2/54	3.7 [0.6,13.8]
CONTAK-CD unpub[73]	22/448	4.9 [3.2,7.5]
MIRACLE-ICD unpub[36]	25/364	6.9 [4.6,10.1]
Leclercq 2000[96]	3/37	8.1 [2.1,23.0]
Gras 2002[100]	4/103	3.9 [1.3, 10.2]
Kuhlkamp 2002[102]	1/84	1.2 [0.1,7.4]
Filho 2002[98]	3/24	12.5 [3.3,33.5]
Leclercq unpub[104]	25/125	20.0 [13.6,28.3]
Total [N=9]	**87/1297**	**6.7 [5.4,8.2]**
Sensitivity Total [N=15]*	**87/1968**	**4.4 [3.6,5.4]**
Lead dislodgement		
MUSTIC-SR 2001[74]	8/58	13.8 [6.6,25.9]
MUSTIC-AF 2002[75]	5/54	9.3 [3.5,21.1]
MIRACLE 2002[61]	30/524	5.7 [4.0,8.2]
CONTAK-CD unpub[73]	31/448	6.9 [4.8,9.8]
MIRACLE-ICD unpub[36]	46/364	12.6 [9.5,16.6]
Cazeau 1996[99]	2/6	33.3 [6.0,75.9]
Leclercq 2000[96]	2/37	5.4 [0.9,19.5]
Gras 2002[100]	10/103	9.7 [5.0,17.5]
Krahn 2002[101]	4/40	10.0 [3.3,24.6]
Kuhlkamp 2002[102]	7/84	8.3 [3.7,17.0]
Filho 2002[98]	0/24	0
Molhoek 2002 [103]	3/40	7.5 [2.0,21.5]
Leclercq unpub[104]	15/125	12.0 [7.1,19.3]
Total [N=13]	**163/1907**	**8.5 [7.4,9.9]**
Sensitivity Total [N=15]*	**163/1968**	**8.3 [7.1,9.6]**
Infection		
MIRACLE 2002[61]	7/524	1.3 [0.6,2.9]
MIRACLE-ICD unpub[36]	2/364	0.5 [0.1,2.2]
Gras 2002[100]	2/103	1.9 [0.3,7.5]
Kuhlkamp 2002[102]	2/84	2.4 [0.4,9.1]
Filho 2002[98]	1/24	4.2 [0.2,23.1]
Leclercq unpub[104]	3/125	2.4 [0.6,7.4]
Total [N=6]	**17/1224**	**1.4 [0.8,2.3]**
Sensitivity Total [N=15]*	**17/1968**	**0.9 [0.5,1.4]**
Arrhythmias associated with CRT		
MUSTIC-AF 2002[75]	1/54	1.9 [0.1,11.2]
PATH-CHF 2002[62]	4/41	9.8 [3.2,24.1]
MIRACLE-ICD unpub[36]	3/364	0.8 [0.2,2.6]
Filho 2002[98]	0/24	0
Molhoek 2002[103]	1/40	2.5 [0.1,14.7]
Total [N=5]	**9/523**	**1.7 [0.8,3.4]**
Sensitivity Total [N=15]*	**9/1968**	**0.5 [0.2,0.9]**

Table 14. Post-implantation risks of cardiac resynchronization therapy–concluded

Study	n/N	Simple Pool Risk % [95% CI]
Pain		
Krahn 2002[101]	1/40	2.5 [0.1,14.7]
Filho 2002[98]	3/24	12.5 [3.3,33.5]
Total [N=2]	**4/64**	**6.3 [2.0,16.0]**
Sensitivity Total [N=15]*	**4/1968**	**0.2 [0.07,0.6]**

* COMPANION omitted – full report not available

Table 15. Potential cost-effectiveness of cardiac resynchronization therapy

	Discounted Quality-Adjusted Life Years (QALYs), Median (Interquartile Range)	Discounted Lifetime Cost ($)*, Median (Interquartile Range)	Incremental Cost-Effectiveness ($/QALYs), Median (Interquartile Range)
Medical Therapy	2.68 (2.49, 2.85)	$34,700 ($31,400, $38,100)	
Cardiac Resychronization Therapy	3.03 (2.82, 3.27)	$67,600 ($62,000, $73,800)	$90,700 ($69,500, $124,900)

* 2003 U.S. $ rounded to nearest hundred

Appendixes

to

Cardiac Resynchronization Therapy for Congestive Heart Failure

(Contract No. 290-02-0023)

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services

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Exact Search Strings

Search Strategies

Search Strategies

Electronic Databases

The search was designed by a medical librarian in consultation with a cardiologist (EC, JE), then performed systematically by the librarian (EC). The following electronic resources were searched:

- The Cochrane Central Register of Controlled Trials (22)
- DARE (2)
- Cochrane Database of Systematic Reviews (2)
- EMBASE (basic=4619, safety=1040, efficacy=1415)
- International Pharmaceutical Abstracts (1)
- MEDLINE (basic=9817, safety=2168, efficacy=444)
- PubMed (basic=1558, safety=828, efficacy=449)
- Web of Science (basic=313, safety=17, efficacy=27)

The total number of references with duplicates removed were 1697 (for the efficacy part of the review) and 1708 (safety).

Trial Registries

Several trial registries were also searched using keywords from the searches below. These included:

- http://www2.umdnj.edu/~shindler/trials/trials_a.html
- http://www.nhlbi.nih.gov/index.htm
- http://www.controlled-trials.com/
- clinicaltrials.gov
- http://www.update-software.com/National/
- http://www.centerwatch.com/search.asp
- http://www.cardiosource.com

Each trial retrieved from the registries was reviewed independently by two investigators.

Companies

The companies that manufacture biventricular devices were contacted:

- Medtronic
- Guidant
- ELA Medical (Montrouge, France)

Keywords and Subject Headings

The search strategies included the following keywords and appropriate subject headings, specifically tailored for each resource: Biventricular pacing, biventricular pacer, biventricular stimulation, Biv, congestive heart failure, Chf, chronic heart failure, artificial cardiac pacing, heart diseases, chronic cardiac failure resynchronization therapy, dual-chamber pacing, cardiac resynchronization, Medtronic, Insync, ELA medical; randomized controlled trial, controlled clinical trial, meta-analysis, multi-center trial; safety, risk, adverse effects, side effects, harm, etiology, aetiology, contraindications, causation, causality, predict.
The search process also involved: citation searches; contacting the primary author of key, ongoing or unpublished studies, and reviewing the reference lists of all selected articles.

The search was not limited by language or publication status.

The detailed search strings appear on the following pages. They cover the years 1988 to the present (June 2003).

Basic Searches

Table A-1 Medline –CRT for CHF: (basic search)

Set	Search
1	(biventricular adj (pacing or pacer$ or stimulat$)).mp.
2	resynchronization therapy.mp.
3	biv.mp.
4	(dual-chamber adj (pacing or pacer$ or stimulat$)).mp.
5	((cardiac or heart) adj resynchronization).mp.
6	medtronic.mp.
7	Insync.mp.
8	"ela medical".mp.
9	exp cardiac pacing, artificial/
10	or/1-8
11	or/1-9
12	exp heart failure, congestive/
13	"congestive heart failure$".mp.
14	chf.mp.
15	exp heart diseases/
16	"congestive cardiac failure$".mp.
17	"chronic cardiac failure$".mp.
18	"chronic heart failure$".mp.
19	or/12-18
20	10 and 19
21	11 and 19

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Table A-2 EMBASE: CRT for CHF - (basic search)

Set	Search
1	(biventricular adj (pacing or pacer$ or stimulat$)).mp.
2	exp heart pacing/
3	resynchronization therapy.mp.
4	biv.mp.
5	(dual-chamber adj (pacing or pacer$ or stimulat$)).mp.
6	((cardiac or heart) adj resynchronization).mp.
7	medtronic.mp.
8	insync.mp.
9	"ela medical".mp.
10	or/1-9
11	exp Congestive heart failure/
12	"congestive heart failure$".mp.
13	chf.mp.
14	exp Heart disease/
15	"congestive cardiac failure$".mp.
16	"chronic cardiac failure$".mp.
17	"chronic heart failure$".mp.
18	or/11-17
19	10 and 18

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Table A-3 nternational Pharmaceutical Abstracts CRT for CHF (basic search)

Set	Search
1	(biventricular adj (pacing or pacer$ or stimulat$)).mp.
2	resynchronization therapy.mp.
3	biv.mp.
4	(dual-chamber adj (pacing or pacer$ or stimulat$)).mp.
5	((cardiac or heart) adj resynchronization).mp.
6	"cardiac pacing".mp.
7	medtronic.mp.
8	insync.mp.
9	"ela medical".mp.
10	or/1-9
11	"congestive cardiac failure$".mp.
12	"congestive heart failure$".mp.
13	chf.mp.
14	heart disease$.mp.
15	"chronic cardiac failure$".mp.
16	"chronic heart failure$".mp.
17	or/11-16
18	10 and 17

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Table A-4 PubMed: CRT for CHF (basic search)

#19	Search **#10 AND #18**
#18	Search **#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17**
#17	Search **"CHRONIC HEART FAILURE*"**
#16	Search **"CHRONIC CARDIAC FAILURE*"**
#15	Search **"CONGESTIVE CARDIAC FAILURE*"**
#14	Search **HEART DISEASES[MESH]**
#13	Search **CHF**
#12	Search **"CONGESTIVE HEART FAILURE"**
#11	Search **HEART FAILURE, CONGESTIVE[MESH]**
#10	Search **#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8**
#8	Search **"ELA MEDICAL"**
#7	Search **INSYNC**
#6	Search **MEDTRONIC**
#5	Search **(CARDIAC OR HEART) AND RESYNCHRONIZATION**
#4	Search **DUAL-CHAMBER AND (PACING OR PACER* OR STIMULAT*)**
#3	Search **BIV**
#2	Search **RESYNCHRONIZATION THERAPY**
#1	Search **biventricular AND (PACING OR PACER* OR STIMULAT*)**

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Table A-5 Web of Science: CRT for CHF (basic search)

#3	**316**	#1 AND #2
#2	**84,712**	TS=(congestive heart failure* or chf or heart disease or congestive cardiac failure* or chronic cardiac failure* or chronic heart failure*)
#1	**3,268**	TS=(biventricular pacing OR biventricular pacer* OR resynchronization therapy OR biv OR dual chamber pacing OR dual chamber pacer* OR dual chamber stimulat* OR cardiac resynchronization OR heart resynchronization OR cardiac pacing OR medtronic OR insync OR ela medical)

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Safety Searches

Table A-6 Medline: CRT for CHF - (safety search)

Set	Search
1	(biventricular adj (pacing or pacer$ or stimulat$)).mp.
2	resynchronization therapy.mp.
3	biv.mp.
4	(dual-chamber adj (pacing or pacer$ or stimulat$)).mp.
5	((cardiac or heart) adj resynchronization).mp.
6	medtronic.mp.
7	insync.mp.
8	"ela medical".mp.
9	exp cardiac pacing, artificial/
10	or/1-8
11	or/1-9
12	exp heart failure, congestive/
13	exp heart diseases/
14	"congestive cardiac failure$".mp.
15	"congestive heart failure$".mp.
16	"chronic cardiac failure$".mp.
17	"chronic heart failure$".mp.
18	chf.mp.
19	or/12-18
20	10 and 19
21	11 and 19
22	(safe or safety).mp.
23	risk$.mp.
24	exp risk/
25	adverse effect$.mp.
26	side effect$.mp.
27	harm.mp.
28	etiology.mp.
29	aetiology.mp.
30	contraindicat$.mp.
31	(cause or causation or causing or causal$).mp.
32	exp causality/
33	predict$.mp.
34	or/22-33
35	20 and 34
36	21 and 34

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Table A-7 EMBASE: CRT for CHF- (safety search)

Set	Search
1	(biventricular adj (pacing or pacer$ or stimulat$)).mp.
2	exp heart pacing/
3	resynchronization therapy.mp.
4	biv.mp.
5	(dual-chamber adj (pacing or pacer$ or stimulat$)).mp.
6	((cardiac or heart) adj resynchronization).mp.
7	medtronic.mp.
8	insync.mp.
9	"ela medical".mp.
10	or/1-9
11	exp Congestive heart failure/
12	"congestive heart failure$".mp.
13	chf.mp.
14	exp Heart disease/
15	"congestive cardiac failure$".mp.
16	"chronic cardiac failure$".mp.
17	"chronic heart failure$".mp.
18	or/11-17
19	10 and 18
20	(safe or safety).mp.
21	exp risk/
22	risk$.mp.
23	exp Side effect/
24	"side effect$".mp.
25	"HARM".mp.
26	exp etiology/
27	aetiology.mp.
28	Treatment contraindication/
29	contraindicat$.mp.
30	(cause or causation or causing or causal$).mp.
31	*Epidemiology/
32	exp prediction/
33	or/20-32
34	19 and 33

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Table A-8 PubMed: CRT for CHF (safety search)

#30	Search **#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29**
#29	Search **predict***
#28	Search **CAUSALITY[MESH]**
#27	Search **cause OR CAUSATION OR CAUSING OR CAUSAL***
#26	Search **contraindicat***
#25	Search **aetiology**
#24	Search **etiology**
#23	Search **HARM**
#22	Search **side effect***
#21	Search **adverse effect***
#20	Search **RISK[MESH]**
#19	Search **RISK***
#18	Search **SAFE OR SAFETY**
#17	Search **#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16**
#16	Search **CHF**
#15	Search **"CHRONIC HEART FAILURE*"**
#14	Search **"CHRONIC CARDIAC FAILURE*"**
#13	Search **"CONGESTIVE HEART FAILURE*"**
#12	Search **"CONGESTIVE CARDIAC FAILURE*"**
#11	Search **HEART DISEASES[MESH]**
#10	Search **HEART FAILURE, CONGESTIVE[MESH]**
#9	Search **#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8**
#8	Search **ELA MEDICAL**
#6	Search **MEDTRONIC**
#7	Search **INSYNC**
#5	Search **(CARDIAC OR HEART) AND RESYNCHRONIZATION**
#4	Search **DUAL-CHAMBER AND (PACING OR PACER* OR STIMULAT*)**
#1	Search **biventricular AND (PACING OR PACER* OR STIMULAT*)**
#3	Search **BIV**
#2	Search **RESYNCHRONIZATION THERAPY**

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Table A-9 Web of Science: CRT for CHF (safety search)

#4	#1 AND #2 AND #3
#3	TS=(safe or safety or risk* or adverse effect* or side effect* or harm or etiology or aetiology or contraindicat* or cause or causation or causing or causal* or predict*)
#2	TS=(congestive heart failure* or chf or heart disease or congestive cardiac failure* or chronic cardiac failure* or chronic heart failure*)
#1	TS=(biventricular pacing or biventricular pacer* or resynchronization therapy or biv or dual-chamber pacing or dual-chamber pacer* or dual-chamber stimulat* or cardiac resynchronization or heart resynchronization or cardiac pacing or medtronic or insync or ela medical)

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Efficacy Searches

Table A-10 Medline: CRT for CHF (efficacy search)

Set	Search
1	(biventricular adj (pacing or pacer$ or stimulat$)).mp.
2	resynchronization therapy.mp.
3	biv.mp.
4	(dual-chamber adj (pacing or pacer$ or stimulat$)).mp.
5	((cardiac or heart) adj resynchronization).mp.
6	medtronic.mp.
7	insync.mp.
8	"ela medical".mp.
9	exp cardiac pacing, artificial/
10	or/1-8
11	or/1-9
12	exp heart failure, congestive/
13	"congestive heart failure$".mp.
14	chf.mp.
15	exp heart diseases/
16	"congestive cardiac failure$".mp.
17	"chronic cardiac failure$".mp.
18	"chronic heart failure$".mp.
19	or/12-18
20	10 and 19
21	11 and 19
22	limit 20 to (controlled clinical trial or meta analysis or multicenter study or randomized controlled trial)
23	limit 21 to (controlled clinical trial or meta analysis or multicenter study or randomized controlled trial)

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Table A-11 EMBASE: CRT for CHF -(efficacy search)

Set	Search
1	(biventricular adj (pacing or pacer$ or stimulat$)).mp.
2	exp heart pacing/
3	resynchronization therapy.mp.
4	biv.mp.
5	(dual-chamber adj (pacing or pacer$ or stimulat$)).mp.
6	((cardiac or heart) adj resynchronization).mp.
7	medtronic.mp.
8	insync.mp.
9	"ela medical".mp.
10	or/1-9
11	exp Congestive heart failure/
12	"congestive heart failure$".mp.
13	chf.mp.
14	exp Heart disease/
15	"congestive cardiac failure$".mp.
16	"chronic cardiac failure$".mp.
17	"chronic heart failure$".mp.
18	or/11-17
19	10 and 18
20	"randomized controlled trial"/
21	random$.mp.
22	exp controlled study/
23	"meta analysis"/
24	multi center trial$.mp.
25	"systematic review$".mp.
26	or/20-25
27	19 and 26

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Table A-12 Cochrane Controlled Trials Register (CENTRAL): CRT for CHF -(efficacy search)

Set	Search
1	(biventricular adj (pacing or pacer$ or stimulat$)).mp.
2	resynchronization therapy.mp.
3	biv.mp.
4	(dual-chamber adj (pacing or pacer$ or stimulat$)).mp.
5	((cardiac or heart) adj resynchronization).mp.
6	medtronic.mp.
7	insync.mp.
8	"ela medical".mp.
9	or/1-8
10	"congestive heart failure$".mp.
11	chf.mp.
12	heart disease$.mp.
13	"congestive cardiac failure$".mp.
14	"chronic cardiac failure$".mp.
15	"chronic heart failure$".mp.
16	or/10-15
17	9 and 16

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Table A-13 Database of Abstracts of Reviews of Effectiveness (DARE): CRT for CHF - (efficacy search)

Set	Search
1	(biventricular adj (pacing or pacer$ or stimulat$)).mp.
2	resynchronization therapy.mp.
3	biv.mp.
4	(dual-chamber adj (pacing or pacer$ or stimulat$)).mp.
5	((cardiac or heart) adj resynchronization).mp.
6	medtronic.mp.
7	insync.mp.
8	"ela medical".mp.
9	or/1-8
10	"congestive heart failure$".mp.
11	chf.mp.
12	heart disease$.mp.
13	"congestive cardiac failure$".mp.
14	"chronic cardiac failure$".mp.
15	"chronic heart failure$".mp.
16	or/10-15
17	9 and 16

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Table A-14 Cochrane Database of Systematic Reviews: CRT for CHF - (efficacy search)

Set	Search
1	(biventricular adj (pacing or pacer$ or stimulat$)).mp.
2	resynchronization therapy.mp.
3	biv.mp.
4	(dual-chamber adj (pacing or pacer$ or stimulat$)).mp.
5	((cardiac or heart) adj resynchronization).mp.
6	medtronic.mp.
7	insync.mp.
8	"ela medical".mp.
9	or/1-8
10	"congestive heart failure$".mp.
11	chf.mp.
12	heart disease$.mp.
13	"congestive cardiac failure$".mp.
14	"chronic cardiac failure$".mp.
15	"chronic heart failure$".mp.
16	or/10-15
17	9 and 16

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Table A-15 PubMed: CRT for CHF (efficacy search)

#25 Search **#19 AND #24**
#23 Search **MULTICENTER STUDY**
#24 Search **#20 OR #21 OR #22 OR #23**
#22 Search **meta analysis**
#21 Search **controlled clinical trial***
#20 Search **RANDOMIZED CONTROLLED TRIAL[PT]**
#19 Search **#10 AND #18**
#18 Search **#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17**
#17 Search **"CHRONIC HEART FAILURE*"**
#16 Search **"CHRONIC CARDIAC FAILURE*"**
#15 Search **"CONGESTIVE CARDIAC FAILURE*"**
#14 Search **HEART DISEASES[MESH]**
#13 Search **CHF**
#12 Search **"CONGESTIVE HEART FAILURE*"**
#11 Search **HEART FAILURE, CONGESTIVE[MESH]**
#10 Search **#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8**
#8 Search **ELA MEDICAL**
#7 Search **INSYNC**
#6 Search **MEDTRONIC**
#5 Search **(CARDIAC OR HEART) AND RESYNCHRONIZATION**
#4 Search **DUAL-CHAMBER AND (PACING OR PACER* OR STIMULAT*)**
#3 Search **BIV**
#2 Search **RESYNCHRONIZATION THERAPY**
#1 Search **biventricular AND (PACING OR PACER* OR STIMULAT*)**

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Table A-16 Web of Science: CRT for CHF (efficacy search)

#4	**31**	#1 AND #2 AND #3
#3	**>100,000**	TS=(random* or controlled trial* or clinical trial* or multi-center or meta-analys* or systematic review*)
#2	**84,712**	TS=(congestive heart failure* or chf or heart disease or congestive cardiac failure* or chronic cardiac failure* or chronic heart failure*)
#1	**3,268**	TS=(biventricular pacing or biventricular pacer* or resynchronization therapy or biv or dual-chamber pacing or dual-chamber pacer* or dual-chamber stimulat* or cardiac resynchronization or heart resynchronization or cardiac pacing or medtronic or insync or ela medical)

CRT= cardiac resynchronization therapy; CHF= congestive heart failure

Sample Data Forms

Inclusion/Exclusion Criteria

- Form B-1 Inclusion Form: CRT for CHF: Efficacy Review
- Form B-2 Inclusion Form: CRT for CHF Safety Review

Quality Assessment

- Form B-3 Assessment of methodology for randomized controlled trials (RCT): Efficacy review
- Form B-4 Assessment of methodology for RCTs and non-RCTs: Safety Review

Data Extraction

- Form B-5 Data extraction - CRT for CHF: Efficacy review
- Form B-6 Data extraction – CRT for CHF: Safety review

Form B-1 Inclusion Form: CRT for CHF: Efficacy Review

Please assess each study according to the criteria below.

1. **Study Design**:
   Were patients randomly assigned to parallel treatment groups?
   or
   Was the study a randomized cross-over trial? **Yes** ☐ **No** ☐

1a. Was the study ≥ 2 weeks in duration? **Yes** ☐ **No** ☐

2. **Population**:
   Did the population have class III or IV congestive heart failure as measured by decreased left ventricular ejection fraction while receiving stable optimal drug therapy? **Yes** ☐ **No** ☐

3. **Intervention**:
   Did one group or period include treatment with an active CRT?
   Yes ☐ **No** ☐

4. **Control**:
   Did one group or period include treatment with a placebo pacing or optimized medical therapy?
   (in a crossover trial CRT off/on in randomized order)
   Yes ☐ **No** ☐

(other names for cardiac resynchronization therapy (CRT), Bi ventricular pacing (CRT); multi-site pacing; dual chamber pacer)

5. **Outcome**:
   Is any one of the following an outcome in the study:
   quality of life, functional class (NYHA), ability to perform a six-minute walk test, CHF hospitalization, emergency department visits, morbidity measures, or mortality (all-cause, cardiac, CHF, sudden cardiac death
   Yes ☐ **No** ☐

6. **Final decision**:

Should this study be included in the next stage? **Yes** **No** ☐

Unsure ☐

Put into Unsure group for consensus

7. Consensus decision:

Yes ☐ **No** ☐ **3rd Party** ☐

Form B-2 Inclusion Form: CRT for CHF Safety Review

Please assess each study according to the criteria below.

1. Study Design:

INCLUDE: -an RCT (parallel or crossover) **Yes** ☐ **No** ☐
-registry data
-a prospective cohort study
-an FDA document

EXCLUDE: acute physiological studies, non-human studies.

1a. Was the study ≥ 2 weeks in duration? **Yes** ☐ **No** ☐

2. Population:

Did the population have class ≥ II congestive heart failure as measured by decreased left ventricular ejection fraction while receiving stable optimal drug therapy? **Yes** ☐ **No** ☐

3. Intervention:

Did one group or period include treatment with an active CRT? Yes ☐ No ☐

4. Control: (If part of the design)

Did one group or period include treatment with placebo pacing, or other pacing mode or accepted standard treatment? **Yes** ☐ **No** ☐

(other names for cardiac resynchronization therapy (CRT), Biventricular pacing (CRT): multi-site pacing, dual chamber pacer)

5. Outcome: (Please highlight which ones were reported)

Are there any reported outcomes that in any way indicate CRT is either safe or unsafe? E.g.
Unsafe indicators: **A. Risks of/during implantation** - Related to the device with battery; left ventricular lead, right ventricular lead, or to right atrial lead; to system function; to implant tools. Procedure related – patient complaints, heart function, or mortality.

B. Risks post implantation -Worsening heart failure; unwanted post surgical sequalae – e.g. keloids, pocket infection, pain; mechanical malfunction; lead dislodgment, replacement; -arrhythmia's caused by CRT; emergency department/clinic/outpatient visits; hospitalization (all cause and CHF related); mortality (all cause and cardiac related).

Yes ☐ **No** ☐

Other unsafe indicators not listed above (describe)

e.g.
Successful implants rate **Yes** ☐ **No** ☐

6. Final decision: Should this study be included? **Yes** ☐ **No** ☐

Unsure ☐

Put into Unsure group for consensus

Consensus decision:

Yes ☐ No ☐ 3rd party ☐

Form B-3 Assessment of methodology for randomized controlled trials (RCT)

CRT Systematic Review 2002	**Quality Form**	Reviewer:
UAEPC	RCT	Reference No.:

Please assess each study according to the criteria below.

A. ***JADAD CRITERIA*** **SCORE**

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)? Yes = 1 No = 0 ☐
2. Was the study described as double-blind? Yes = 1 No = 0 ☐
3. Was there a description of withdrawals and dropouts? Yes = 1 No = 0 ☐
4. Additional points: *Add* 1 point if:
   a. Method to generate the sequence of randomization was described and was appropriate (e.g. IVRS, table of random numbers, etc.) ☐
   b. Method of double blinding described and appropriate (identical placebo, active placebo) ☐
5. Deduction of points: *Subtract* 1 point if:
   a. Method of randomization described and inappropriate (e.g., alternatively, hospital #, etc.) ☐
   b. Method of double blinding described and inappropriate (IV vs. PO w/ no blind) ☐

OVERALL SCORE (maximum 5) ☐

B. ***SCHULZ CRITERIA***

Concealment of treatment allocation:

- ☐ Adequate
- ☐ Inadequate
- ☐ Unclear

Adequate: central randomization; numbered/coded containers; drugs prepared from pharmacy; serially numbered; opaque sealed envelopes
Inadequate: alternation; use of case record numbers, DOB or weeks, open lists
Unclear: Allocation concealment approach not reported or doesn't fit above categories

Form B-4 Assessment of methodology for RCTs and non-RCTs: Safety Review

Quality Form (nonRCTs)

CRT Systematic Review 2002 Reviewer:
UAEPC Reference No.:

(from Downs and Black, J Epidemiol Community Health 1998;52:377-384)

REPORTING

1. Is the hypothesis/aim/objective of the study clearly described? This question refers to a clear statement of the objective, i.e. to measure the effectiveness of x in population y with respect to z, even if x, y and z are not clearly described (see questions 2, 3 and 4)

Yes	1	
No	0	

2. Are the main outcomes to be measured clearly described in the Introduction or Methods section? If the main outcomes are first mentioned in the Results section, the question should be answered no. In case-control studies the case definition should be considered the outcome.

Yes	1	
No	0	

3. Are the characteristics of the patients included in the study clearly described in the Introduction or Methods section? In cohort studies and trials, inclusion and or exclusion criteria should be given. In case-control studies, a case definition and the source for controls should be given.

Yes	1	
No	0	

4. Are the interventions of interest clearly described in the Introduction or Methods section? Treatments and placebo (where relevant) that are to be compared should be clearly described.

Yes	1	
No	0	

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided.

Yes	2	
Partially	1	
No	0	

6. Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. This question does not cover statistical tests, which are considered below.

Yes	1	
No	0	

7. Does the study provide estimates of the random variability in the data for the main outcomes? In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	1	
No	0	

8. Have all important adverse events that may be a consequence of the intervention been reported? This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).

Yes	1	
No	0	

9. Have the characteristics of patients lost to follow-up been described? This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.

Yes	1	
No	0	

10. Have 95% CIs and/or actual probability values been reported (e.g. p=0.035 rather than p <0.05) for the main outcomes except where the probability value is less than 0.001? (both CI and p value, either CI or p value, neither)

Yes	1	
No	0	

EXTERNAL VALIDITY

Form B-4 Assessment of methodology for RCTs and non-RCTs: Safety Review—continued

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

Yes	1	
No	0	
Unable to determine	0	

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited? The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

Yes	1	
No	0	
Unable to determine	0	

13. Were the staff, places, and facilities where study patients were treated, representative of the treatment the majority of patients receive? For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

Yes	1	
No	0	
Unable to determine	0	

INTERNAL VALIDITY - BIAS

14. Was an attempt made to blind study subjects to the intervention they have received? For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

Yes	1	
No	0	
Unable to determine	0	

15. Was an attempt made to blind those measuring the main outcomes of the intervention?

Yes	1	
No	0	
Unable to determine	0	

16. If any of the results of the study were based on "data dredging", was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

Yes	1	
No	0	
Unable to determine	0	

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? Where follow-up was the same for all study patients that answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

Yes	1	
No	0	
Unable to determine	0	

18. Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data. For example non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	1	
No	0	
Unable to determine	0	

Form B-4 Assessment of methodology for RCTs and non-RCTs: Safety Review—continued

19. Was compliance with the interventions reliable? Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

Yes	1	
No	0	
Unable to determine	0	

20. Were the main outcome measures used accurate (valid and reliable)? For studies where the outcomes measured are clearly described, the question should be answered yes. For studies that refer to other work or that demonstrate the outcome measures are accurate, the question should be answered as yes.

Yes	1	
No	0	
Unable to determine	0	

INTERNAL VALIDITY – CONFOUNDING (SELECTION BIAS)

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.

Yes	1	
No	0	
Unable to determine	0	

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

Yes	1	
No	0	
Unable to determine	0	

23. Were the subjects randomized to intervention groups? Studies which state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example alternate allocation would score no because it is predictable.

Yes	1	
No	0	
Unable to determine	0	

24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? All non-randomized studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

Yes	1	
No	0	
Unable to determine	0	

25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders different between the treatment groups but was not taken into account in the analyses. In non-randomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.

Yes	1	
No	0	
Unable to determine	0	

26. Were losses to patients to follow-up take into account? (yes, no, unable to determine) If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.

Yes	1	
No	0	
Unable to determine	0	

Form B-4 Assessment of methodology for RCTs and non-RCTs: Safety Review—concluded

POWER

27. Was a power calculation reported for the primary outcome?

Yes	1	
No	0	
Unable to determine	0	

28. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance in less than 5%?

Yes	1	
No	0	
Unable to determine	0	

Form B-5 Data extraction - CRT for CHF: Efficacy review

CRT SR 2002 UAEPC Efficacy RCT	**Data Extraction Form**	Reviewer: Checker: Reference No.:

Study Characteristics

Authors:		
Title:		
Journal citation:		
Year of publication:	Language:	Country(ies) where study conducted:
Funding: ❑ Private industry ❑ Foundation ❑ Government ❑ Internal ❑ Other		
Author's primary outcome:		
Author's inclusion criteria:	Author's exclusion criteria:	
Comments:		

Form B-5 Data extraction Efficacy review—continued

Design Characteristics

Study design:	Parallel	Crossover Carryover effect?	Other
Subject-blinded:	Yes	No	Unclear
Outcome assessor-blinded:	Yes	No	Unclear
Intent to treat design:	Yes	No	
Intent to treat analysis:	Yes	No	N/A

Participants

Number of eligible participants:		Number enrolled in study:	
Exclusions:	Yes	No	Unclear
If yes, reasons:			
Withdrawals/dropouts	Yes	No	Unclear
If yes, reasons:	CRT group:		
	Placebo group:		
	All participants:		

Form B-5 Data extraction Efficacy review—continued

Baseline Characteristics Please indicate the statistic, e.g., %, mean, SD, range, etc AND the units

	CRT group	Placebo group	All participants
Males/females:			
Age:			
Race:			
Ischemic/non-ischemic:			
NYHA class:			
I			
II			
III			
IV			
Diabetes Mellitus:			
Hypertension:			
Coronary artery disease:			
previous MI			
previous PTCA			
CABG			
Strokes:			
History of SCD:			
Atrial fibrillation:			
Renal failure:			
ECG:			
PR interval			
QRS interval			

Form B-5 Data extraction Efficacy review—continued

More Baseline Characteristics: Indicate the statistic, e.g., %, mean, SD, etc AND the units

ECHO:			
LVEDD			
LVESD			
dp/dt			
MR grade			
Area of MR jet			
Physical exam:			
Systolic Blood Pressure			
Diastolic Blood Pressure			
Heart rate			
Weight			
Other Co-morbidities:			

Procedural Characteristics: Indicate the statistic, e.g., %, mean, SD, range, IQ, etc AND the units

	CRT group	Placebo group	All participants
Drug therapy:			
ARB			
ACE			
BB			
spironolactone			
digoxin			
nitrates			
lipid lowering agent			
warfarin			
Device:			
Method of implantation:			
Other co-interventions:			

Form B-5 Data extraction Efficacy review—continued

Outcomes: Timepoints indicate time since RANDOMIZATION in DAYS.

Indicate which period if it's a crossover study or which subgroup where necessary:

	Biventricular Pacemakers			Control		
Time to death: ❑ All-cause mortality	Number at risk	Number of events	Number censored	Number at risk	Number of events	Number censored
Timepoint 0						
Timepoint 15						
Timepoint 30						
Timepoint 45						
Timepoint 60						
Timepoint 90						
Timepoint 120						
Timepoint 150						
Timepoint 180						
Timepoint 210						
Timepoint						
Timepoint						
Timepoint						
Timepoint						
Timepoint						

	Biventricular Pacemakers			Control		
Time to death: ❑ Sudden cardiac death	Number at risk	Number of events	Number censored	Number at risk	Number of events	Number censored
Timepoint 0						
Timepoint 15						
Timepoint 30						
Timepoint 45						
Timepoint 60						
Timepoint 90						
Timepoint 120						
Timepoint 150						
Timepoint 180						
Timepoint 210						
Timepoint						
Timepoint						
Timepoint						
Timepoint						
Timepoint						

Form B-5 Data extraction Efficacy review—continued

Outcomes: Timepoints indicate time since RANDOMIZATION in DAYS.

Indicate which period if it's a crossover study or which subgroup where necessary:

	Biventricular Pacemakers			Control		
Time to death: ❑ CHF	Number at risk	Number of events	Number censored	Number at risk	Number of events	Number censored
Timepoint 0						
Timepoint 15						
Timepoint 30						
Timepoint 45						
Timepoint 60						
Timepoint 90						
Timepoint 120						
Timepoint 150						
Timepoint 180						
Timepoint 210						
Timepoint						
Timepoint						
Timepoint						
Timepoint						
Timepoint						

	Biventricular Pacemakers			Control		
Time to death: ❑ Cardiac mortality	Number at risk	Number of events	Number censored	Number at risk	Number of events	Number censored
Timepoint 0						
Timepoint 15						
Timepoint 30						
Timepoint 45						
Timepoint 60						
Timepoint 90						
Timepoint 120						
Timepoint 150						
Timepoint 180						
Timepoint 210						
Timepoint						
Timepoint						
Timepoint						
Timepoint						
Timepoint						

Form B-5 Data extraction Efficacy review—continued

Outcomes: Timepoints indicate time since RANDOMIZATION in DAYS.

Indicate which period if it's a crossover study or which subgroup where necessary:

	Biventricular Pacemakers				Control			
Dichotomous outcomes: **n/N**	Baseline	Time-point	Time-point	Time-point	Baseline	Time-point	Time-point	Time-point
Death								
CHF hospitalizations								
ED visits								
Other								

	Biventricular Pacemakers				Control			
Continuous outcomes: **mean(sd)**	Baseline	Time-point	Time-point	Time-point	Baseline	Time-point	Time-point	Time-point
Ejection Fraction								
VO_2 Max								
6 minute walk test								
Other								

Form B-5 Data extraction Efficacy review—concluded

Outcomes: Timepoints indicate time since RANDOMIZATION in DAYS.

Indicate which period if it's a crossover study or which subgroup where necessary:

	Biventricular Pacemakers				Control			
Other outcomes: **[indicate summary measures]**	Baseline	Time-point	Time-point	Time-point	Baseline	Time-point	Time-point	Time-point
NYHA functional class								
Quality of life Name of measure?								
Global Assessment Name of measure?								
ECG								
PR interval								
QRS interval								
ECHO								
LVEDD								
LVESD								
dp/dt								
MR grade								
Area of MR jet								
Other								

Form B-6 Data extraction – CRT for CHF: Safety review

CRT SR 2002 UAEPC Safety CCT	**Data Extraction Form**	Reviewer: Checker: Reference No.:

Study Characteristics

Authors:		
Title:		
Journal citation:		
Year of publication:	Language:	Country(ies) where study conducted:
Funding: ❑ Private industry ❑ Foundation ❑ Government ❑ Internal ❑ Other		
Author's primary outcome:		
Authors's inclusion criteria:	Authors's exclusion criteria:	
Comments:		

Form B-6 Data extraction Safety review—continued

Design Characteristics

Allocation:			
Subject-blinded:	Yes	No	Unclear
Outcome assessor-blinded:	Yes	No	Unclear
Intent to treat design:	Yes	No	N/A
Intent to treat analysis:	Yes	No	N/A

Participants

Number of eligible participants:		Number enrolled in study:	
Exclusions:	Yes	No	Unclear
If yes, reasons:			
Withdrawals/dropouts	Yes	No	Unclear
If yes, reasons: ❑ Didn't specify which group:	CRT group:		
	Placebo group:		

Form B-6 Data extraction Safety review—continued

Baseline Characteristics: Please indicate the statistic, e.g., %, mean, SD, range, etc AND the units

	CRT group	Placebo group	All participants
Males/females:			
Age:			
Race:			
Ischemic/non-ischemic:			
NYHA class:			
I			
II			
III			
IV			
Diabetes Mellitus:			
Hypertension:			
Coronary artery disease:			
previous MI			
previous PTCA			
CABG			
Strokes:			
History of SCD:			
Atrial fibrillation:			
Renal failure:			
ECG:			
PR interval			
QRS interval			

Form B-6 Data extraction Safety review—continued

More Baseline Characteristics: Indicate the statistic, e.g., %, mean, SD, etc. AND the units

ECHO:			
LVEDD			
LVESD			
dp/dt			
MR grade			
Area of MR jet			
Physical exam:			
Blood pressure			
Heart rate			
Weight			
Other Co-morbidities:			

Procedural Characteristics: Indicate the statistic, e.g., %, mean, SD, range, IQ, etc. AND the units

	CRT group	Placebo group	All participants
Drug therapy:			
ARB			
ACE			
BB			
spironolactone			
digoxin			
nitrates			
lipid lowering agent			
warfarin			
Device:			
Method of implantation:			
Other co-interventions:			

Form B-6 Data extraction Safety review—continued

Outcomes: These tables are by treatment group and by subgroup (if provided)

Treatment group (e.g., CRT, Placebo, etc):
Subgroup (e.g., NYHA Class, Ischemic, etc.):

Risks of/during Implantation

Time to death: ❑ All-cause ❑ Cardiac ❑ CHF ❑ Sudden cardiac death	Number at risk	Number of events	Number censored
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			

If other than n/N, e.g., events per person-months, indicate units

Dichotomous outcomes: **n/N**	Baseline	Timepoint	Timepoint	Timepoint
Death				
Related to the device with battery				
Related to the left ventricular lead				
Related to the right ventricular lead				
Related to the right atrial lead				
Related to the system function				
Related to implant tools				
Procedure related – patient complaints				
Related to heart function				
Other				

Form B-6 Data extraction Safety review—continued

Outcomes: These tables are by treatment group and by subgroup (if provided)

Treatment group (e.g., CRT, placebo, etc. AND which period if it's a crossover study):
Subgroup (e.g., NYHA Class, ischemic, etc.):

Risks Post-Implantation

Time to death: ❑ All-cause ❑ Cardiac ❑ CHF ❑ Sudden cardiac death	Number at risk	Number of events	Number censored
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			
Timepoint			

If other than n/N, e.g., events per person-months, indicate units

Dichotomous outcomes: **n/N**	Baseline	Timepoint	Timepoint	Timepoint
Death				
CHF hospitalizations				
ED visits				
Worsening heart failure				
Unwanted post surgical sequalae (e.g., keloids, pocker infection, pain)				
Mechanical malfunction				
Lead dislodgement				
Arrhythmia's caused by CRT				
Other				

Form B-6 Data extraction Safety review—concluded

Outcomes: These tables are by treatment group and by subgroup (if provided)

Treatment group (e.g., CRT, Placebo, etc. AND which period if it's a crossover study):
Subgroup (e.g., NYHA Class, Ischemic, etc.):

Safe Indicators: If other than n/N, e.g., events per person-months, indicate units

Dichotomous outcomes: **n/N**	Baseline	Timepoint	Timepoint	Timepoint
Successful implants				
Other				

Appendix C: Evidence Tables

Appendix C: Evidence Tables

Table C-1. Inclusion criteria of randomized trials on CRT for CHF: Efficacy review

	Inclusion Criteria								Exclusion Criteria
Trial name	**NYHA class**	**LVEF**	**QRS**	**LVEDD**	**Meds required**		**Sinus rhythm (%)**	**Other**	
					ACEi	**BB**			
Abraham 2002[1] MIRACLE	III or IV	<=35%	>=130 ms	>=55 mm	yes	yes	yes	6MWT <=450 m; expected to remain stable	Had a pacemaker or defibrillator; had an indication for or contraindication against cardiac pacing; unstable angina; acute MI; cardiac ischemic event, or revascularization in past 3 mo.; atrial arrhythmia in past 1 mo.
Auricchio 2002[2] PATH-CHF	III or IV	-	>=120 ms	-	no	no	yes	PR interval >=150 ms	Primary operable valvular heart disease (other than mitral or tricuspid regurgitation with clinical symptoms due to LV systolic HF); indication for conventional pacemaker or implantable cardioverter-defibrillator or other noncardiac conditions that could limit exercise capacity and life expectancy
Bristow 2003[3] COMPANION Scientific Presentation 2003	III or IV	<=25%	>=120 ms	>=60 mm	yes	yes	yes	> 18 yr.; PR > 150ms; diuretic; spironolactone; digoxin; Hx hospitalization <12 mo. > 1 mo. prior to enrollment; OPT for CHF	Meet indications for general ICD or antibradycardia pacing; chronic atrial tachyarrhythmias; MI or PTCA < 60 days; uncontrolled BP; unstable angina; have a tricuspid prothesis; expected to have transplant or life expectancy < 6 mo.
Cazeau 2001[4] MUSTIC-SR	III	<35%	>150 ms	>60 mm	yes	no	yes	diuretics	Hypertrophic or restrictive cardiomyopathy; correctable valvulopathy; acute coronary syndrome or coronary revascularization in past 3 mo.; scheduled revascularization; severe obstructive lung disease; indication for an ICD

Appendix C: Evidence Tables

	Inclusion Criteria								Exclusion Criteria
Trial name	**NYHA class**	**LVEF**	**QRS**	**LVEDD**	**Meds required**		**Sinus rhythm (%)**	**Other**	
					ACEi	**BB**			
Garrique 2002[5]	III or IV	< 40%	> 140 ms	>=60 mm	yes	yes	no	OPT for CHF; diuretics; chronic AF; HIS bundle ablation	< 18 or > 80 yr.; unstable angina < 2 mo. of start; acute MI < 6 mo.; angioplasty or CABG < 1 yr.
Guidant 2002[6] CONTAK-CD FDA report	II, III or IV	<=35%	>=120 ms	-	yes	no	yes	Meet indications for ICD; diuretics and/or digoxin; >=18 yr.	Meet indications for antibradycardia pacing; refractory atrial tachycardia; require concomitant cardiac surgery; not suitable for the procedure
Leclercq 2002[7] MUSTIC-AF	III	<35%	>200 ms	>60 mm	yes	no	no	diuretics; AF >3 mo.; requiring pacing (AV ablation or spontaneously); 6MWT <450 m	Hypertrophic or restrictive cardiomyopathy; correctable valvulopathy; acute coronary syndrome or coronary revascularization in past 3 mo.; scheduled revascularization; severe obstructive lung disease; indication for an ICD
Leclercq 2003 RD-CHF[*] Unpublished	III or IV	<=35%	>180 ms	N/a	N/a	N/a	N/a	N/a	N/a
Medtronic 2001[9] MIRACLE-ICD FDA report	II, III or IV	<=35%	>=130 ms	>=55 mm	yes	no	no	ICD indication; =>18 yr.; previous MI; recurrent or sustained VT	Unstable angina; MI, CABG, PTCA, TIA or CVA in past 3 mo., indications for or contraindications against standard cardiac pacing; systolic BP <80 or >170mm; HR >140bpm; hepatic function >3 times upper limit of normal; primary valvular disease/rt heart valve, COPD; life expectancy <6 mo.

Appendix C: Evidence Tables

	Inclusion Criteria								Exclusion Criteria
Trial name	**NYHA class**	**LVEF**	**QRS**	**LVEDD**	**Meds required**		**Sinus rhythm (%)**	**Other**	
					ACEi	**BB**			

ACEi = angiotensin converting enzyme inhibitors; AF = atrial fibrillation; BB = beta blockers; BP = blood pressure; CABG = coronary artery bypass grafting; CHF = congestive heart failure; COPD = chronic obstructive lung disease; CVA = coronary vascular accident; FDA = Food and Drug Administration; HR = heart rate; HX = history; ICD = implantable cardioverter-defibrillator; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA= New York Heart Association class; OPT= optimal pharmacological therapy; PTCA= percutaneous trans cardiac angioplasty; 6MWT= 6 min. walk test; n/a = not available; TIA = transient ischemic attack; VT = ventricular tachycardia.

* detailed data not available for Leclercq 2003 (RD-CHF) at the time this report was prepared; information included in this report was obtained through personal communication with the author

Reference List for Table C-1

1. Abraham WT. Cardiac resynchronization therapy for heart failure: Biventricular pacing and beyond. Curr Opin Cardiol 2002; 17(4):346-352.

2. Auricchio A, Stellbrink C, Sack S, et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay (PATH CHF Trial). J Am Coll Cardiol 2002; 39(12):2026-2033.

3. Bristow M, et al. Comparison of medical therapy, pacing and defibrillation in heart failure (COMPANION Trial). Presented at the 52nd Annual Scientific Conference, American College of Cardiology, Chicago, Illinois, USA, March 31st: 2003.

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Table C-2. Inclusion criteria of studies included in the safety review on CRT for CHF

	Inclusion Criteria								Exclusion Criteria
Trial name	**NYHA class**	**LVEF**	**QRS**	**LVEDD**	**Meds required**		**Sinus rhythm (%)**	**Other**	
					ACEi	**BB**			
Abraham 2002[1] MIRACLE	III or IV	<=35%	>=130 ms	>=55 mm	yes	yes	yes	6MWT <=450 m; expected to remain stable	Had a pacemaker or defibrillator; had an indication for or contraindication against cardiac pacing; unstable angina; acute MI; cardiac ischemic event, or revascularization in past 3 mo.; atrial arrhythmia in past 1 mo.
Auricchio 2002[2] PATH-CHF	III or IV		>=120 ms		no	no	yes	PR interval >=150 ms	Primary operable valvular heart disease (other than mitral or tricuspid regurgitation with clinical symptoms due to LV systolic HF); indication for conventional pacemaker or implantable cardioverter-defibrillator or other noncardiac conditions that could limit exercise capacity and life expectancy
Bristow 2003[3] COMPANION Scientific Presentation 2003	III or IV	<=25%	>=120 ms	>=60 mm	yes	yes	yes	> 18 yr.; PR > 150ms; diuretic; spironolactone; digoxin; Hx hospitalization <12 mo. > 1 mo. prior to enrollment; OPT for CHF	Meet indications for general ICD or antibradycardia pacing; chronic atrial tachyarrhythmias; MI or PTCA < 60 days; uncontrolled BP; unstable angina; have a tricuspid prothesis; expected to have transplant or life expectancy < 6 mo.
Cazeau 1996[4]	-	-	-	-	-	-	-	End stage CHF who refused or not eligible for transplant all had Hx of HD >=10 yr. and >=1 episode of pulmonary edema	No specific inclusion/exclusion criteria stated

Table C-2. Inclusion criteria of studies included in the safety review on CRT for CHF – continued

Trial name	Inclusion Criteria								Exclusion Criteria
	NYHA class	LVEF	QRS	LVEDD	Meds required		Sinus rhythm (%)	Other	
					ACEi	BB			
Cazeau 2001[5] MUSTIC-SR	III	<35%	>150 ms	>60 mm	yes	no	yes	diuretics	Hypertrophic or restrictive cardiomyopathy; correctable valvulopathy; acute coronary syndrome or coronary revascularization in past 3 mo.; scheduled revascularization; severe obstructive lung disease; indication for an ICD
Filho 2002[6]	III or IV	< 30%	-	-	-	-	-	> 18 yr.; irreversible cause of cardiomyopathy; maximum medical therapy; clinically stable x 2 weeks; LBBB.	2nd or 3rd degree heart block; acute myocarditis; unstable angina; referred for surgery
Gras 2002[7] INSYNC Italian Registry	III or IV	<=35	>150ms	>60mm	no	no	-	Refractory to medical therapy X 1 month	] 18 yr.; had a contraindication to DDD pacing; unstable angina; acute MI < 3mo; permanent AF; presence of ICD; other life-limiting disease
Guidant[8] CONTAK-CD FDA report 2002	II, III or IV	<=35%	>=120 ms	-	yes	no	yes	Meet indications for ICD; diuretics and/or digoxin; >=18 yr.	Meet indications for antibradycardia pacing; refractory atrial tachycardia; require concomitant cardiac surgery; not suitable for the procedure
Krahn 2002[9]	>=II	-	>=130 ms	-	yes	yes	-	HF stable x 1 mo. on best medical therapy unless intolerant, diuretics	HF caused by diastolic dysfunction; unable to provide f/u; life expectance <1 yr.
Kuhlkamp 2002[10]	-	<=35	>130 ms	>55 mm	no	no	-	Symptomatic sustained ventricular tachycardia and/or survival of cardiac arrest; symptomatic HF despite appropriate therapy	None stated

Table C-2. Inclusion criteria of studies included in the safety review on CRT for CHF – continued

Trial name	Inclusion Criteria								Exclusion Criteria
	NYHA class	LVEF	QRS	LVEDD	Meds required		Sinus rhythm (%)	Other	
					ACEi	BB			
Leclercq 2002[11] MUSTIC-AF	III	<35%	>200 ms	>60 mm	yes	no	no	Diuretics; AF >3 mo.; requiring pacing (AV ablation or spontaneously); 6MWT <450 m	Hypertrophic or restrictive cardiomyopathy; correctable valvulopathy; acute coronary syndrome or coronary revascularization in past 3 mo.; scheduled revascularization; severe obstructive lung disease; indication for an ICD
Leclercq 2000[12]	III or IV	<=35	>=120 ms	>=60 mm	yes	no	-	Drug refractory CHF; optimal medical therapy; diuretics	Suspected acute myocarditis; correctable valvular disease; acute coronary syndrome <3 mo.; CA revascularization within preceding 12 mo.
Leclercq[13] unpublished	III or IV	<=35%	>120 ms (first 16 pts), then changed to 150 ms	>=60mm	-	-	-	-	Suspicion of acute myocarditis; patients who benefited from coronary revascularization procedure within the past 12 months; acute coronary "accident" in past 3 months; patients who could benefit from valvular surgery
Leclercq 2003* RD-CHF Unpublished	III or IV	<=35%	>180 ms	N/a	N/a	N/a	48	N/a	N/a
Leon 2002[14]	III or IV	<=35	-	-	-	-	-	Chronic AF; AV ablation and RV pacing >=6 mo.; symptoms refractory to standard medical care	None stated

Table C-2. Inclusion criteria of studies included in the safety review on CRT for CHF – concluded

Trial name	Inclusion Criteria								Exclusion Criteria
	NYHA class	LVEF	QRS	LVEDD	Meds required		Sinus rhythm (%)	Other	
					ACEi	BB			
Medtronic 2001[15] MIRACLE-ICD FDA report	II, III or IV	<=35%	>=130 ms	>=55 mm	yes	no	no	ICD indication; =>18 yr.; previous MI; recurrent or sustained VT	Unstable angina; MI, CABG, PTCA, TIA or CVA in past 3 mo., indications for or contraindications against standard cardiac pacing; systolic BP <80 or >170mm; HR >140bpm; hepatic function >3 times upper limit of normal; primary valvular disease right heart valve; COPD; life expectancy <6 mo.
Molhoek 2002[6]	III or IV	<=35	>=120 ms or > 200	-	-	-	-	LBBB	Not stated

ACEi = angiotensin converting enzyme inhibitors; AF = atrial fibrillation; BB =- beta blockers; BP= blood pressure; CABG = coronary artery bypass grafting; CHF = congestive heart failure; COPD = chronic obstructive lung disease; CVA = coronary vascular accident; FDA = Food and Drug Administration; f/u = followup; HD= heart disease; HR = heart rate; HX = history; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; MI = myocardial infarction; N/a = not available; NYHA = New York Heart Association class; OPT = optimal pharmacological therapy; PTCA = percutaneous trans cardiac angioplasty; 6MWT = 6 min. walk test; TIA = transient ischemic attack; VT = ventricular tachycardia.

* detailed data not available for Leclercq 2003 (RD-CHF) at the time this report was prepared; information included in this report was obtained through personal communication with the author

Reference List for Table C-2

1. Abraham WT. Cardiac resynchronization therapy for heart failure: Biventricular pacing and beyond. Curr Opin Cardiol 2002; 17(4):346-352.

2. Auricchio A, Stellbrink C, Sack S et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay (PATH CHF Trial). J Am Coll Cardiol 2002; 39(12):2026-2033.

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