

Systematic Review: Cardiac Resynchronization in Patients with Symptomatic Heart Failure

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Background: Even with optimal pharmacotherapy, symptomatic heart failure is associated with substantial morbidity and mortality.

Purpose: To determine the efficacy and safety of cardiac resynchronization therapy in adults with advanced systolic heart failure.

Data Sources: The Cochrane Central Register of Controlled Trials (2002, volume 4), MEDLINE (1980–2003), EMBASE (1980–2003), other electronic databases, and U.S. Food and Drug Administration reports. We contacted primary study authors and device manufacturers, and we hand searched bibliographies of relevant papers and conference proceedings.

Study Selection: Randomized, controlled clinical trials for efficacy and controlled trials plus prospective cohort studies for safety.

Data Extraction: Two reviewers chose studies and extracted data independently; random-effects models were used for analyses.

Data Synthesis: Nine trials were included in the efficacy review (3216 patients). All trial participants had reduced ejection fraction and prolonged QRS duration, and 85% had New York Heart Association (NYHA) class III or IV symptoms. Cardiac resynchronization therapy improved ejection fraction (weighted mean difference, 0.035 [95% CI, 0.015 to 0.055]), quality of life (weighted mean reduction in score on the Minnesota Living with Heart Failure Questionnaire, 7.6 points [CI, 3.8 to 11.5 points]), and function (58% vs. 37% of patients improved by at least 1 NYHA class). Heart failure hospitalizations were reduced by 32% (relative risk [RR], 0.68 [CI, 0.41 to 1.12]), with benefits most marked

in patients with NYHA class III or IV symptoms at baseline (RR, 0.65 [CI, 0.48 to 0.88]; number needed to treat for benefit [NNT_B], 12). All-cause mortality was reduced by 21% (RR, 0.79 [CI, 0.66 to 0.96]; NNT_B, 24), driven largely by reductions in death from progressive heart failure (RR, 0.60 [CI, 0.36 to 1.01]). Eighteen studies (total of 3701 patients with cardiac resynchronization devices) were included in the safety review. Implant success rate was 90% (CI, 89% to 91%), and 0.4% of patients died during implantation (CI, 0.2% to 0.7%). Over a median 6-month follow-up, leads dislodged in 9% of patients (CI, 7% to 10%) and mechanical malfunctions occurred in 7% (CI, 5% to 8%).

Limitations: These trials enrolled only patients with heart failure with NYHA class III or IV symptoms despite medical therapy, a prolonged QRS duration, and reduced ejection fraction; in addition, experienced providers implanted the devices. Because all but one of these trials randomly assigned patients after device implantation, their results may overestimate the potential benefits of cardiac resynchronization. Finally, since few patients in these trials had bradyarrhythmias or atrial fibrillation, the role of cardiac resynchronization in such patients is uncertain.

Conclusions: In selected patients with heart failure, cardiac resynchronization therapy improves functional and hemodynamic status, reduces heart failure hospitalizations, and reduces all-cause mortality.

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Heat failure is the fastest-growing cardiovascular diagnosis in North America, and the lifetime risk is now estimated at nearly 20% (1, 2). Despite many diagnostic and pharmacotherapeutic advances over the past 2 decades, symptomatic heart failure still carries a poor prognosis (1, 3). Thus, novel therapies for heart failure are still needed. To improve survival, these therapies must 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) (4, 5).

Intraventricular conduction disturbances are common in heart failure and are associated with increased mortality (6–8). As such, electrophysiologic therapies may help improve outcomes in heart failure. Indeed, studies have recently evaluated atrial-synchronized biventricular pacing (cardiac resynchronization therapy) and implantable cardioverter-defibrillators (ICDs) for their effects in heart fail-

ure. While ICDs do not improve functional outcomes, they do provide substantial mortality benefits by preventing sudden cardiac death in patients with heart failure who have an ischemic substrate, poor ejection fraction, and history of ventricular arrhythmias (9). On the other hand, cardiac resynchronization therapy improves many of the pathophysiologic changes seen in patients with wide QRS complexes: less mechanical dyssynchrony leading to increased left ventricular filling time, reduced mitral regurgitation, and reduced septal dyskinesis (10). Several trials have shown that cardiac resynchronization therapy improves quality of life, NYHA class, and 6-minute walk distances in patients with advanced heart failure; however, they have not yet shown this therapy to confer a conclusive mortality benefit because of the small number of deaths in each trial. This distinction is important, since not all therapies that improve functional outcomes in patients with heart failure reduce mortality (11).

A meta-analysis of the efficacy of cardiac resynchroni-

Context

A biventricular pacemaker to resynchronize ventricular contraction is a new therapy for heart failure. A 2003 meta-analysis included only 2 published and 2 unpublished trials, but 5 additional studies have since become available.

Contribution

Data from 3216 patients who participated in 9 trials demonstrate that cardiac resynchronization improves many outcomes, including mortality. Data from 3701 patients participating in 18 studies showed that leads dislodged in 9% of patients during 6 months of follow-up and that the device malfunctioned in 7%.

Implications

In select patients, cardiac resynchronization is an effective therapy for heart failure.

—The Editors

zation therapy has been published (10); however, it combined data from only 2 published trials and 2 U.S. Food and Drug Administration (FDA) reports (both of which have subsequently been published) (12–15). We conducted this systematic review as an update: Five additional trials have now been reported, and we obtained further details on 3 of the 4 studies included in the earlier meta-analysis through contact with the trial investigators (12–14). Moreover, while the earlier meta-analysis focused on efficacy data, we systematically examined the success rate and safety of biventricular pacemaker implantation as well as the efficacy data.

METHODS**Search Strategy**

We developed detailed search strategies (see the Appendix and **Appendix Tables 1 to 16**, available at www.annals.org) for the following electronic resources: Cochrane Central Register of Controlled Trials, Cochrane Database of Abstracts of Reviews of Effectiveness (DARE), Cochrane Database of Systematic Reviews, EMBASE, International Pharmaceutical Abstracts, MEDLINE, PubMed, Web of Science, and several trial registries (www2.umdj.edu/~shindler/trials/trials_a.html, www.nhlbi.nih.gov/index.htm, www.controlled-trials.com/, <http://clinicaltrials.gov>, www.update-software.com/National/, www.centerwatch.com/search.asp, and www.cardiosource.com). In addition, we contacted the primary authors of included studies, sought FDA reports, and reviewed the reference lists of all included articles. We also sought additional data from the companies that produce biventricular devices: Medtronic Inc. (Minneapolis, Minnesota), Guidant Corporation (Indianapolis, Indiana), and ELA Medical (Le Plessis-Robinson, France). The search was not limited by language or publication status and is considered up to date as of 4 May 2004.

Study Selection

Two investigators independently screened all titles and abstracts to determine whether an article met the general inclusion criteria (that is, a study that investigated cardiac resynchronization therapy; was done in humans; and included patients with symptomatic heart failure). For the efficacy substudy, we selected only randomized, controlled trials; for the safety substudy, we selected controlled trials or prospective cohort studies. Then, another 2 investigators independently assessed the full text of potentially relevant studies using specific inclusion criteria (study duration \geq 2 weeks, primary outcomes of interest [all-cause mortality or heart failure hospitalization or both] reported according to randomized treatment, confirmation that general inclusion criteria were met) for final inclusion. Two of the investigators independently abstracted data. Discrepancies were resolved through third-party adjudication and consensus.

Statistical Analysis

We did intention-to-treat analyses by using the same standardized end point definitions as in the primary studies. We used Stata 7.0 (Stata Corp., version 7.0, 2003) to pool data and calculate summary relative risks (RRs) for dichotomous results and weighted mean differences for continuous variables. Because of the differences expected between studies (particularly in control group therapies), a priori we decided to combine results primarily by using a random-effects model; fixed-effects models were considered in sensitivity analyses. Statistical heterogeneity was assessed by using the chi-square test and was quantified using the I^2 statistic (16). Time-to-event data were summarized by the log hazards ratio. An individual-patient data set for this analysis was constructed by using summary monthly mortality tables in the trial manuscripts. A priori sensitivity analyses included the effects of cardiac resynchronization therapy on patients with NYHA class III or IV symptoms. We planned to examine the effect of ICDs, β -blockers, and digoxin in indirect subgroup comparisons using meta-regression. Estimates of carryover effect were extracted from crossover designs. Only period 1 data were used for irreversible outcomes (that is, death and heart failure hospitalizations). Standard errors for crossover weighted mean differences were calculated (17). Simple pooling and exact 95% CIs were used for the safety analyses.

Role of the Funding Source

The Agency for Healthcare Research and Quality had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

DATA SYNTHESIS

Figure 1 shows the results of the search and study selection. Nine randomized trials (**Table**) met the inclusion

criteria for the efficacy review (12–15, 18–22). Eight of these and an additional 10 studies—9 of which were published (23–31) and 1 of which remains unpublished (Leclercq C, Alonso F, d'Allones FR, et al. Effets à moyen terme de la stimulation multisite biventriculaire dans l'insuffisance cardiaque sévère. Personal communication. May 2003)—met the inclusion criteria for the safety review. Data in addition to those reported in the journal publications or conference presentations were provided by the investigators from 6 trials and are included in these analyses (12–14, 20–22). Although most of the trials reported secondary outcomes in multiple publications, we include only the reference to the primary publication for each trial in this manuscript (for a listing of all publications from each trial, please see the full Agency for Healthcare Research and Quality (AHRQ) report at www.ahrq.gov/clinic/epc/index.html#Reports).

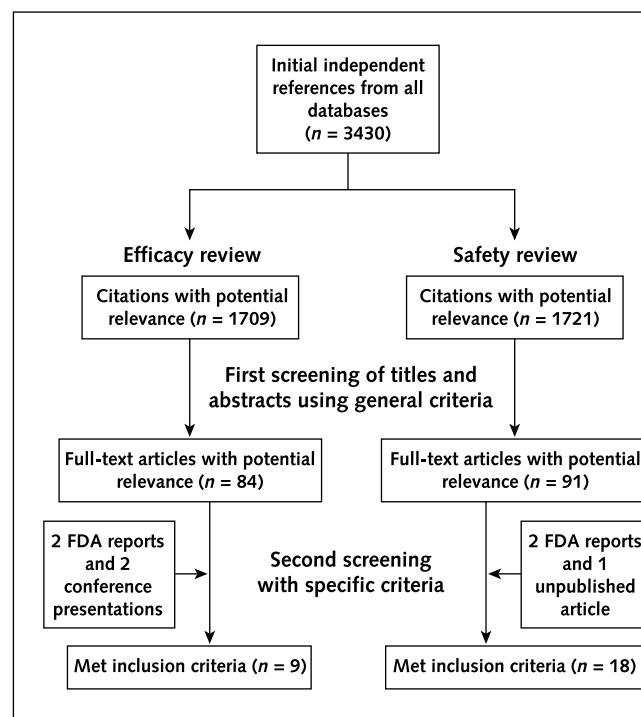
Three trials evaluated the effects of cardiac resynchronization therapy with ICDs (14, 15, 21). Of the 9 randomized trials, 2 were open-label (20, 21), 3 were single-blind (the patient was blinded to treatment) (12, 18, 22), and 4 were double-blind (the patient and outcome assessor were blinded to treatment) (13–15, 19).

All trials enrolled only patients with prolonged QRS duration: 120 milliseconds or longer in 3 trials (15, 19, 21), 130 milliseconds or longer in 2 trials (13, 14), longer than 140 milliseconds in 1 trial (20), longer than 150 milliseconds in 1 trial (12), longer than 180 milliseconds in 1 trial (22), and longer than 200 milliseconds in 1 trial (18). Left bundle-branch block was present in 64% of patients, and most patients were in sinus rhythm. All 9 trials were restricted to patients with reduced left ventricular ejection fractions (≤ 0.35 in 7 trials, ≤ 0.25 in 1 trial, and ≤ 0.40 in 1 trial), with mean ejection fractions similar across trials (Table). Eight of the trials used a transvenous approach to place the epicardial lead; 1 small trial (19) used a transthoracic approach exclusively, and 53 patients in the Guidant CONTAK-CD CRT-D System Trial (15) required a transthoracic approach.

In total, 3574 patients were enrolled in these 9 trials and 3216 were randomly assigned to receive cardiac resynchronization therapy ($n = 2063$) or control treatment (most commonly, a pacemaker turned off [$n = 1153$]). The mean patient age was 64 years; 74% of patients were male, 58% had an ischemic cause of heart failure, 75% had NYHA class III symptoms, 10% had NYHA class IV symptoms, and 5% had atrial fibrillation (Table).

Of the 10 prospective cohort studies included in the safety analyses, 7 described experiences with transvenous pacemakers and 3 reported results with either transvenous or transthoracic approaches. The demographic characteristics of these study patients were similar to those in the 9 randomized trials (Appendix Table 17, available at www.annals.org).

Figure 1. Flow diagram of study selection.



FDA = U.S. Food and Drug Administration.

Quantitative Results

All-Cause Mortality

Figure 2 shows data on all-cause mortality. Cardiac resynchronization therapy significantly reduced all-cause mortality (RR, 0.79 [95% CI, 0.66 to 0.96]) in the 9 randomized trials. The results were identical when we limited analyses to patients with NYHA class III or IV symptoms (407 deaths in 2763 patients; RR, 0.80 [CI, 0.66 to 0.97]). There was no statistically significant heterogeneity between trials ($I^2 = 0\%$; $P > 0.2$). The number needed to treat for benefit (NNT_B) to prevent 1 death was 24. The time-to-death analysis demonstrated that the benefits of cardiac resynchronization therapy became apparent by 3 months after implantation.

Cardiac Mortality

Although pooled data from the 7 trials that reported mortality from progressive heart failure (60 deaths in 1647 patients) favored cardiac resynchronization therapy, this finding just failed to reach statistical significance according to a random-effects model (RR, 0.60 [CI, 0.36 to 1.01]) (12–15, 18–20). There was no appreciable statistical heterogeneity ($I^2 = 0\%$; $P > 0.2$), and the fixed-effects analysis did achieve significance (RR, 0.59 [CI, 0.35 to 0.98]). In contrast, cardiac resynchronization therapy did not significantly reduce overall cardiac deaths ($n = 91$ in 1628 patients from 6 trials; RR, 0.84 [CI, 0.56 to 1.25]) (12–15, 18, 19) because of a nonsignificant excess number of sudden cardiac deaths ($n = 28$ in 1691 patients from 8 trials;

RR, 1.99 [CI, 0.95 to 4.16]) (12–15, 18–20, 22). Of note, data on causes of death in the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure) trial (21) were not available at the time we conducted this meta-analysis.

Noncardiac Mortality

Cardiac resynchronization therapy did not significantly change rates of noncardiac deaths (17 in 1194 patients from 6 trials; RR, 0.90 [CI, 0.35 to 2.35]) (12, 14, 15, 18–20). This result was not statistically heterogeneous.

Heart Failure Hospitalizations

Figure 3 shows data on hospitalizations for heart failure. The pooled data revealed an RR of 0.68 (CI, 0.41 to 1.12) in favor of cardiac resynchronization therapy compared to control (316 events in 1642 patients from 6 trials) (12–15, 18, 22). This result was heterogeneous ($I^2 = 65\%$; $P = 0.01$). However, restricting this analysis to patients with NYHA class III or IV symptoms revealed homogeneous ($I^2 = 16\%$; $P > 0.2$) and statistically significant reductions in heart failure hospitalizations (RR, 0.65 [CI, 0.48 to 0.88]; NNT_B, 12).

Six-Minute Walk Test

In the 8 trials measuring this end point, cardiac resynchronization therapy was associated with improvements in 6-minute walk distances, with a weighted mean difference of 28 meters (CI, 16 to 40 meters) in all symptomatic patients and 30 meters (CI, 18 to 42 meters) in patients with NYHA class III or IV failure (12–15, 18–21). Although the data from the RD-CHF trial (22) were not available for pooling, the RD-CHF investigators reported statistically significant improvements in 6-minute walk test distances with cardiac resynchronization therapy (Leclercq C. Personal communication. November 2003).

NYHA Functional Class

Combining the data on change in NYHA class from the 4 trials that reported this end point revealed that 58% of patients receiving cardiac resynchronization therapy improved by at least 1 NYHA class compared with 37% of controls (thus, cardiac resynchronization therapy was associated with an RR for improving by 1 NYHA class of 1.6 [CI, 1.3 to 1.9]) (13, 15, 20, 21). Although the data from MIRACLE-ICD (Multicenter InSync Randomized Clinical Evaluation ICD) (14) were not available in a format that permitted pooling with the other trials, the results of this study were consistent with these findings (the median NYHA class improved from III at baseline to II after cardiac resynchronization therapy but did not change in the control group; $P = 0.01$). Moreover, although 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 cardiac resynchronization therapy (Leclercq C. Personal communication. November 2003).

Quality of Life

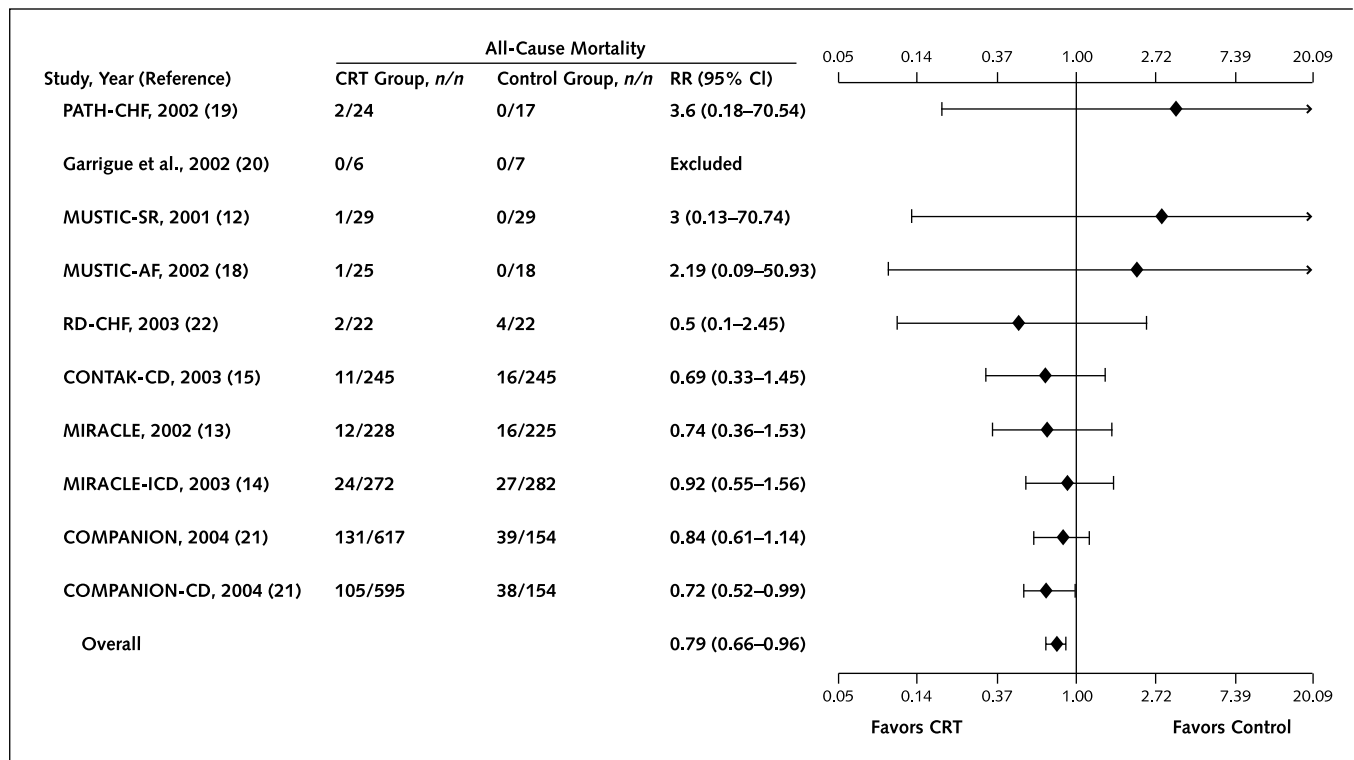
Figure 4 shows data on quality of life. Pooled results from the 7 trials that used the Minnesota Living with Heart Failure Questionnaire showed a statistically and clinically significant 7.6-point improvement with cardiac resynchronization therapy (CI, 3.8- to 11.5-point improvement) (12–15, 18, 19, 21). This result was statistically heterogeneous ($I^2 = 80\%$; $P < 0.001$), but results were consistent in direction in all 7 trials. Restricting the analysis to only those patients with NYHA class III or IV symptoms increased the weighted mean improvement to 8.4 points (CI, 5.0 to 11.7 points), and the results were less heterogeneous ($I^2 = 70\%$; $P = 0.002$). Furthermore, although the use of a different scale in RD-CHF prevented pooling with the other trials, the RD-CHF investigators

Table. Description of Randomized Trials Included in the Efficacy Review and Baseline Characteristics of Patients*

Study (Reference)	Duration of Treatment, mo	Sample Size, n	Mean Age ± SD, y	Ischemic Cause, %	Men, %	NYHA Class III or IV Symptoms, %	Atrial Fibrillation, %	Mean LVEF ± SD	ACE Inhibitors or ARBs, %
Crossover trials									
MUSTIC-SR (12)	3	58	64 ± 9	37	74	100	0	0.23 ± 0.07	96
MUSTIC-AF (18)	3	43	65 ± 8	43	81	100	100	0.26 ± 0.10	100
Garrigue et al. (20)	2	13	64 ± 12	46	100	100	100	0.25 ± 0.8	NR
PATH-CHF (19)	1	41	60 ± 7	29	50	100	0	0.21 ± 0.07	NR
CONTAK-CD (15)	3	490	66 ± 11	69	84	68	0	0.22 ± 0.07	88
RD-CHF (22)	3	44	73 ± 8	NR	NR	100	52	0.25 ± 0.09	NR
Parallel-arm trials									
MIRACLE (13)	6	453	65 ± 11	54	68	100	0	0.22 ± 0.06	92
MIRACLE-ICD (14)	6	555	66 ± 12	35	81	65	14	0.21 ± 0.07	92
COMPANION (21)	12	1520	67	55	68	100	0	0.23	89

* ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CHF = congestive heart failure; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure; CONTAK CD = Guidant CONTAK CD CRT-D System Trial; LVEF = left ventricular ejection fraction; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD = Multicenter InSync Randomized Clinical Evaluation ICD [implantable cardioverter-defibrillator]; MUSTIC AF = Multisite Stimulation in Cardiomyopathies Atrial Fibrillation; MUSTIC SR = Multisite Stimulation in Cardiomyopathies Sinus Rhythm; NR = not reported; NYHA = New York Heart Association Class; PATH-CHF = Pacing Therapies for Congestive Heart Failure.

Figure 2. All-cause mortality with cardiac resynchronization therapy (CRT) versus controls.



CHF = congestive heart failure; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure; CONTAK CD = Guidant CONTAK CD CRT-D System Trial; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD = Multicenter InSync Randomized Clinical Evaluation ICD [implantable cardioverter-defibrillator]; MUSTIC-AF = Multisite Stimulation in Cardiomyopathies Atrial Fibrillation; MUSTIC-SR = Multisite Stimulation in Cardiomyopathies Sinus Rhythm; PATH-CHF = Pacing Therapies for Congestive Heart Failure; RR = relative risk.

reported statistically significant improvements in quality of life with cardiac resynchronization therapy (Leclercq C. Personal communication. November 2003).

Other Outcomes

Cardiac resynchronization therapy was associated with improvements (compared with control) in peak oxygen consumption of 0.7 mL/kg per minute (CI, 0.3 to 1.0 mL/kg per minute), in ejection fraction of 0.035 (CI, 0.015 to 0.055), and in QRS interval of 28 milliseconds (CI, 47 to 9 milliseconds).

Peri-Implantation Risks

Ten studies reported data on patients who died during implantation of a biventricular pacemaker: 13 of 3245 patients died (pooled risk, 0.4% [CI, 0.2% to 0.7%]; 1 peri-procedural death for every 240 patients undergoing implantation) (12–14, 18, 19, 21, 22, 25, 28; Leclercq C. Personal communication. May 2003). Device implantation was successful in 90% (CI, 89% to 91%) of attempts in 3673 patients from 17 studies.

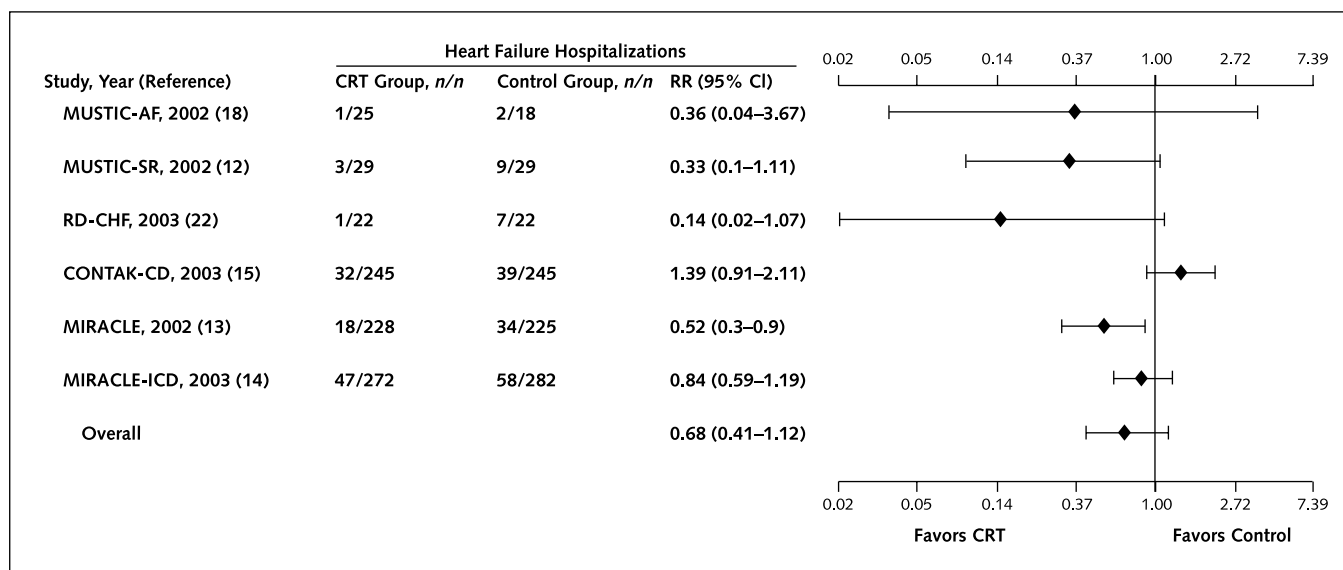
Postimplantation Risks

Over a median follow-up of 6 months, the cardiac resynchronization device malfunctioned with 7% (CI, 5% to 8%) of successful implants. Leads dislodged in 9% (CI, 7% to 10%) of patients (that is, 1 dislodgement for every 11 devices implanted), with no differences in studies that used specially designed left ventricular leads. Postimplantation infection (most commonly in the device pocket) occurred in 1.4% (CI, 0.8% to 2.3%) of patients, and 2% (CI, 1% to 3%) of patients had new arrhythmias on follow-up.

Sensitivity Analyses

We explored the effect of ICDs on the efficacy of cardiac resynchronization therapy by using meta-regression (a between-study nonrandomized comparison): The benefits of cardiac resynchronization therapy on all-cause mortality did not appreciably differ between patients with an ICD and those without an ICD ($P > 0.2$). Of note, the data from COMPANION (21) were not included in the meta-regression for ICDs because none of the COMPANION arms consisted of ICD alone. While the COMPANION data provide the only direct comparison between cardiac resynchronization therapy plus ICD versus cardiac

Figure 3. Heart failure hospitalizations with cardiac resynchronization therapy (CRT) versus controls.



CHF = congestive heart failure; CONTAK-CD = Guidant CONTAK CD CRT-D System Trial; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD = Multicenter InSync Randomized Clinical Evaluation ICD [implantable cardioverter-defibrillator]; MUSTIC-AF = Multisite Stimulation in Cardiomyopathies Atrial Fibrillation; MUSTIC-SR = Multisite Stimulation in Cardiomyopathies Sinus Rhythm; RR = relative risk.

resynchronization therapy alone (the chi-square test for all-cause mortality was not significant [$P = 0.13$]), the reductions in heart failure hospitalizations were similar in patients who received cardiac resynchronization therapy with and without ICDs (21). Thus, until detailed data from COMPANION subanalyses are made available, the most conservative conclusion to make at this stage is that the benefits of cardiac resynchronization therapy are probably similar with and without an ICD.

We also explored the relationship between the use of β -blockers or digoxin and the effect of cardiac resynchronization therapy on all-cause mortality. Both meta-regressions were nonsignificant ($P > 0.2$ for both), suggesting that use of these medications does not change the benefits of cardiac resynchronization therapy.

DISCUSSION

The participants in these trials were similar to those in other heart failure trials (32), and our analysis reveals that, when added to medical therapy in patients with reduced left ventricular ejection fraction, prolonged QRS duration, and symptomatic heart failure, cardiac resynchronization therapy reduces both all-cause mortality and heart failure hospitalizations by approximately one fourth. These benefits are similar to those reported for angiotensin-converting enzyme inhibitors, β -blockers, and aldosterone antagonists in recent trials (33–36). Cardiac resynchronization therapy also conferred statistically and clinically significant improvements in quality of life, functional status, and a variety of physiologic measurements. Indeed, a pooled 8-point improvement on the Minnesota Living with Heart Failure

Questionnaire is greater than the minimally clinically important difference established in placebo-controlled trials (37–39) and is greater than that seen in recent heart failure trials testing pharmacologic therapies (40, 41).

The survival benefits with cardiac resynchronization appear to be largely driven by reductions in progressive heart failure deaths and become apparent by 3 months after implantation. Although peri-implantation mortality rates are low, it is not surprising that the survival benefits are not apparent for several months because the benefits are thought to be mediated through morphometric remodeling of the left ventricle rather than acute changes in the neurohormonal system (42).

While we found a nonsignificant trend toward increased sudden cardiac death that was consistent across these trials, this trend was based on a small number of events (28 total) and the subclassification of cardiac deaths as sudden or nonsudden is notoriously difficult (43). Thus, we believe this finding is not interpretable without further trial data, particularly given the similar frequency of ventricular arrhythmia episodes between patients randomly assigned to control versus cardiac resynchronization in the MIRACLE-ICD trial (22% vs. 26%; $P > 0.2$) (14). On the other hand, 1 small study has shown that biventricular pacing can increase QT duration and may predispose to torsade de pointes, establishing a possible pathophysiologic mechanism for increased sudden cardiac deaths and emphasizing the importance of efforts to better define individual risk–benefit ratios for cardiac resynchronization in different subsets of patients (44). Regardless, the benefits of cardiac resynchronization are similar in patients with and

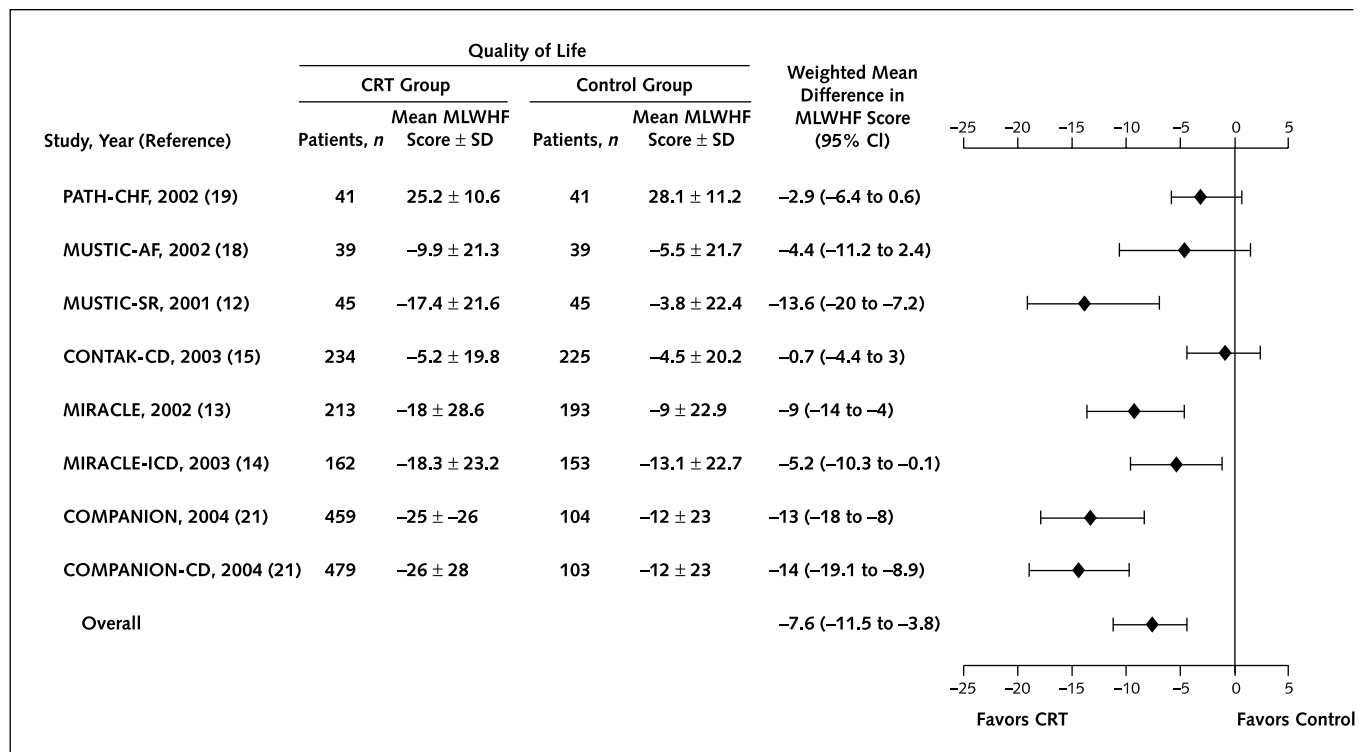
without ICDs, providing some reassurance that in patients who have indications for both, they may be administered together. The indications for an ICD for primary prevention in patients with heart failure not caused by ischemia remain uncertain pending publication of SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) (accessed at www.sicr.org/scdheft/index.html on 16 May 2004).

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% and are similar to the 0.7% reported in the Mode Selection in Sinus Node Dysfunction Trial for 2010 patients who underwent implantation of conventional dual-chamber pacemakers (45). Although few serious complications occurred, implantation of a biventricular pacemaker (in particular the left ventricular lead) is technically challenging, even in experienced hands (our systematic review identified a 10% failure rate). Furthermore, even if the device is successfully implanted, patients with these devices require close follow-up; 7% of devices malfunctioned and 9% of left-ventricular leads dislodged over a median follow-up of 6 months (a substantially higher rate than the 1% to 5% reported in the ICD trials) (9). Ongoing surveillance is required to 1) assess the

extent to which the reductions in heart failure hospitalizations seen in these trials with cardiac resynchronization may be offset by increased admissions for pacemaker revisions and 2) track changes in complications as device implanters, the tools for implantation, and the sophistication of the devices change over time.

A substantial limitation of the trials included in this analysis is the occurrence of randomization after implantation of the device in all but 1 trial. This design, as with the run-in period used in some pharmaceutical trials, does not affect the internal validity of the trials but does affect the generalizability of the results because these trials did not include patients who could not tolerate the procedure or those in whom implantation was unsuccessful. As a result, these trials probably overestimate the potential benefits from cardiac resynchronization. This further emphasizes the importance of ongoing surveillance registries to track complication rates (particularly given the marked paucity of data on the efficacy or complication rates with cardiac resynchronization therapy beyond 1 year) (46). Moreover, although the benefits of cardiac resynchronization therapy were qualitatively similar in all trials, there was substantial heterogeneity in the magnitude of benefits across trials despite the enrollment of similar patient populations and the

Figure 4. Changes in quality of life with cardiac resynchronization therapy (CRT) versus controls (based on the Minnesota Living with Heart Failure [MLWHF] Questionnaire).



CHF = congestive heart failure; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure; CONTAK-CD = Guidant CONTAK CD CRT-D System Trial; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD = Multicenter InSync Randomized Clinical Evaluation ICD [implantable cardioverter-defibrillator]; MUSTIC-AF = Multisite Stimulation in Cardiomyopathies Atrial Fibrillation; MUSTIC-SR = Multisite Stimulation in Cardiomyopathies Sinus Rhythm; PATH-CHF = Pacing Therapies for Congestive Heart Failure.

use of similar (and in many cases identical) devices. This finding suggests that cardiac resynchronization therapy does not always restore mechanical synchrony, even when lead placement is “successful” (47). Attempts to localize the most appropriate position for the pacing leads and to define which patients are most likely to benefit from cardiac resynchronization therapy remain research priorities (47, 48). The cardiac resynchronization literature is also limited in that few patients in these trials had bradyarrhythmias or atrial fibrillation. As a result, 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 patients with heart failure have atrial fibrillation or indications for conventional pacemakers (32). Finally, only selected cases and experienced providers participated in these trials; thus, the observed complication rates may not apply in other settings and, in particular, to clinicians less experienced with device implantation.

We have demonstrated that cardiac resynchronization therapy confers a 20% relative reduction in all-cause mortality (largely driven by a 40% reduction in deaths from progressive heart failure) and a 35% reduction in heart failure hospitalizations in patients with NYHA class III or IV symptoms despite medical management, reduced ejection fractions, and prolonged QRS duration on electrocardiogram. While preliminary data suggest similar relative (but smaller absolute) benefits in patients with NYHA class II symptoms, this conclusion is based on very few events. Further data are required before device indications are extended beyond those currently authorized by the FDA (that is, patients with NYHA class III or IV symptoms). Furthermore, because the trials enrolled few patients with indications for conventional pacemakers or with atrial fibrillation, the role of cardiac resynchronization therapy in these patients remains uncertain and requires further study. Approximately 10% of patients with heart failure have NYHA class III or IV symptoms, reduced ejection fraction, and a prolonged QRS duration, and up to half of these patients may also have indications for an ICD (49, 50). Thus, as many as 250 000 Americans may be eligible for cardiac resynchronization therapy and another 250 000 for a combined device with ICD capability. While cardiac resynchronization therapy should join the list of proven efficacious therapies for selected patients with advanced systolic heart failure, it requires technical expertise and has an uncertain cost-effectiveness ratio (in contradistinction to angiotensin-converting enzyme inhibitors, β -blockers, and spironolactone) (51). As such, it is not a panacea, and we believe that the optimization of medical therapy and the use of multidisciplinary teams to educate and follow patients with heart failure should continue to be emphasized as the cornerstones of management for this condition (52).

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APPENDIX

Search Strategies

Exact Search Strings

Appendix Tables 1 through 5 describe strategies for basic searches. Appendix Tables 6 through 9 describe strategies for safety review searches. Appendix Tables 10 through 16 describe strategies for efficacy review searches.

Electronic Databases

The search was designed by a medical librarian in consultation with a cardiologist, then performed systematically by the librarian. The following electronic resources were searched: the Cochrane Central Register of Controlled Trials (22 references identified), DARE (2 references), Cochrane Database of Systematic Reviews (2 references), EMBASE (4619 references from basic search, 1040 from safety search, 1415 from efficacy search), International Pharmaceutical Abstracts (1 reference), MEDLINE (9817 references from basic search, 2168 from safety search, 444 from efficacy search), PubMed (1558 references from basic search, 828 from safety search, 449 from efficacy search), and Web of Science (313 references from basic search, 17 from safety search, 27 from efficacy search). The total number of references with duplicates removed were 1709 (for the efficacy part of the review) and 1721 (for the safety part of the review).

Trial Registries

We also searched several trial registries using keywords from the searches below: www2.umdj.edu/~shindler/trials/trials_a.html, www.nhlbi.nih.gov/index.htm, www.controlled-trials.com/, <http://clinicaltrials.gov>, www.update-software.com/National/, www.centerwatch.com/search.asp, and www.cardiosource.com.

Two investigators independently reviewed each trial retrieved from the registries.

Companies

We contacted the companies that manufacture biventricular devices: Medtronic Inc. (Minneapolis, Minnesota), Guidant Corporation (Indianapolis, Indiana), and ELA Medical (Le Plessis-Robinson, 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*,

Appendix Table 1. MEDLINE Search: Cardiac Resynchronization for Heart Failure (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

adverse effects, *side effects*, *harm*, *etiology*, *aetiology*, *contraindications*, *causation*, *causality*, *predict*.

The search process also involved performing 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 in the Appendix Tables. They cover 1988 through June 2003.

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Appendix Table 2. EMBASE Search: Cardiac Resynchronization for Heart Failure (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

Appendix Table 4. PubMed Search: Cardiac Resynchronization for Heart Failure (Basic Search)†

Set	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*)

† Step 9 was deleted.

Appendix Table 3. Search of International Pharmaceutical Abstracts: Cardiac Resynchronization for Heart Failure (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

Appendix Table 5. Search of Web of Science: Cardiac Resynchronization for Heart Failure (Basic Search)†

Set	Total References Obtained, <i>n</i>	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	3268	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)

† TS = text word search.

Appendix Table 6. MEDLINE Search: Cardiac Resynchronization for Heart Failure (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

Appendix Table 7. EMBASE Search: Cardiac Resynchronization for Heart Failure (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

Appendix Table 8. PubMed Search: Cardiac Resynchronization for Heart Failure (Safety Search)

Set	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
#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*)

Appendix Table 9. Search of Web of Science: Cardiac Resynchronization for Heart Failure (Safety Search)†

Set	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)

† TS = text word search.

Appendix Table 10. MEDLINE Search: Cardiac Resynchronization for Heart Failure (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)

Appendix Table 11. EMBASE Search: Cardiac Resynchronization for Heart Failure (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

Appendix Table 12. Search of Cochrane Controlled Trials Register: Cardiac Resynchronization for Heart Failure (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

Appendix Table 14. Search of Cochrane Database of Systematic Reviews: Cardiac Resynchronization for Heart Failure (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

Appendix Table 13. Search of DARE (Database of Abstracts of Reviews of Effectiveness): Cardiac Resynchronization for Heart Failure (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

Appendix Table 15. PubMed Search: Cardiac Resynchronization for Heart Failure (Efficacy Search)†

Set	Search
#25	Search #19 AND #24
#24	Search #20 OR #21 OR #22 OR #23
#23	Search MULTICENTER STUDY
#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*)

† Step 9 was deleted.

Appendix Table 16. Search of Web of Science: Cardiac Resynchronization for Heart Failure (Efficacy Search)†

Set	Total References Obtained, <i>n</i>	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	3268	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)

† TS = text word search.

Appendix Table 17. Description of Studies Included in the Safety Review and Baseline Characteristics of Patients*

Study (Reference)	Duration of Treatment, <i>mo</i>	Sample Size, <i>n</i>	Mean Age ± SD, <i>y</i>	Ischemic Cause, %	Men, %	NYHA Class III or IV Symptoms, %	Atrial Fibrillation, %	Mean LVEF ± SD
Crossover trials								
MUSTIC-SR (12)	3	58	64 ± 9	37	74	100	0	0.23 ± 0.07
MUSTIC-AF (18)	3	43	65 ± 8	43	81	100	100	0.26 ± 0.10
PATH-CHF (19)	1	41	60 ± 7	29	50	100	0	0.21 ± 0.07
RD-CHF (22)	3	44	73 ± 8	NR	NR	100	52	0.25 ± 0.09
CONTAK-CD (15)	3	490	66 ± 11	69	84	68	0	0.22 ± 0.07
Filho et al. (28)†	6	24	55 ± 13	38	96	71	0	0.19 ± 0.05
Parallel-arm trials								
MIRACLE (13)	6	453	65 ± 11	54	68	100	0	0.22 ± 0.06
MIRACLE-ICD (14)	6	555	66 ± 12	35	81	65	14	0.21 ± 0.07
COMPANION (21)	12	1520	66	55	68	100	0	0.23
Cohort studies								
Cazeau et al. (25)	12	8	66 ± 5	50	88	100	38	0.22 ± 0.08
InSync Italian Registry (30)	12	117	67 ± 10	48	77	100	0	0.22 ± 0.06
Krahn et al. (23)	6	45	65 ± 10	69	82	94	33	0.19 ± 0.05
Kuhlkamp (24)	3	84	64 ± 9	NR	91	68	12	0.25 ± 0.07
Leclerq et al. (29)	6	37	68 ± 8	38	92	100	28	0.23 ± 0.05
Leclerq et al. (unpublished)	6	125	68 ± 9	38	88	100	29	0.21 ± 0.06
Leon et al. (26)	NR	20	70 ± 11	55	85	100	100	0.22 ± 0.07
Mortensen et al. (31)	3	189	66 ± 11	42	73	83	0	0.24 ± 0.07
Molhoek et al. (27)	6	40	64 ± 10	48	78	NR	10	0.24 ± 0.09

* CHF = congestive heart failure; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure; CONTAK-CD = Guidant CONTAK CD CRT-D System Trial; LVEF = left ventricular ejection fraction; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD = Multicenter InSync Randomized Clinical Evaluation ICD [implantable cardioverter-defibrillator]; MUSTIC-AF = Multisite Stimulation in Cardiomyopathies Atrial Fibrillation; MUSTIC-SR = Multisite Stimulation in Cardiomyopathies Sinus Rhythm; NR = not reported; NYHA = New York Heart Association; PATH-CHF = Pacing Therapies for Congestive Heart Failure.

† The trial by Filho and colleagues was not included in the efficacy review because it did not report the efficacy end points according to randomly assigned groups.