Annals of Internal Medicine | Review

Meta-analysis: Cardiac Resynchronization Therapy for Patients With Less Symptomatic Heart Failure

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Background: Cardiac resynchronization therapy (CRT) reduces morbidity and mortality in patients with advanced symptoms of heart failure.

Purpose: To assess the benefits and harms of CRT in patients with advanced heart failure and those with less symptomatic disease.

Data Sources: A search of electronic databases (1950 to December 2010), hand-searching of reference lists, and unpublished data from principal investigators. Searches were not limited to the English language.

Study Selection: Randomized, controlled trials of CRT compared with usual care and right or left ventricular pacing in adults with heart failure and a left ventricular ejection fraction of 0.40 or less.

Data Extraction: Two reviewers performed independent study selection, data abstraction, and quality assessment by using the Cochrane tool for assessing risk for bias.

Data Synthesis: There were 9082 patients in 25 trials. In patients with New York Heart Association (NYHA) class I and II symptoms, CRT reduced all-cause mortality (6 trials, 4572 participants; risk ratio [RR], 0.83 [95% CI, 0.72 to 0.96]) and heart failure hospitalizations (4 trials, 4349 participants; RR, 0.71 [CI, 0.57 to 0.87]) without improving functional outcomes or quality of life. In patients with NYHA class III or IV symptoms, CRT improved functional outcomes and reduced both all-cause mortality (19 trials, 4510 participants; RR, 0.78 [CI, 0.67 to 0.91]) and heart failure hospitalizations (11 trials, 2663 participants; RR, 0.65 [CI, 0.50 to 0.86]). The implant success rate was 94.4%; peri-implantation deaths occurred in 0.3% of trial participants, mechanical complications in 3.2%, lead problems in 6.2%, and infections in 1.4%.

Limitation: Subgroup analyses were underpowered and lack data for persons with NYHA class I symptoms, atrial fibrillation, chronic kidney disease, or right bundle branch block.

Conclusion: Cardiac resynchronization therapy is beneficial for patients with reduced left ventricular ejection fraction, symptoms of heart failure, and prolonged QRS, regardless of NYHA class.

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Heart failure is a common disorder, affecting approximately 2.5% of adults in North America and Europe (1, 2). Heart failure substantially reduces quality of life and has high morbidity (with frequent emergency department visits and heart failure hospitalizations) and mortality rates, which create a great economic burden even when patients receive optimal treatment (1, 3–7). In a previous systematic review of 4420 patients in 14 trials (7), McAlister and colleagues demonstrated a 22% relative risk reduction in all-cause mortality and a 37% relative risk reduction in heart failure hospitalization when cardiac resynchronization therapy (CRT) was added to optimal medical therapy. International guidelines recommend CRT for patients with left ventricular ejection fraction (LVEF) of 0.35 or less, New York Heart Association (NYHA) class III or IV symptoms despite medical treatment, wide QRS duration (>120 ms), and sinus rhythm (2, 8–10).

However, important questions remain regarding heart failure and CRT. First, because nearly all participants (91%) in the randomized, controlled trials (RCTs) identified in the previous systematic review had NYHA class III or IV symptoms (7), the effect of CRT in patients with less severe symptoms is unclear. Three RCTs (11–13) assessing the efficacy of CRT in patients with less severe heart failure symptoms have been published since the previous systematic review (7), and recently the European Society of Cardiology extended its recommendation for CRT to include patients with mildly symptomatic heart failure who have QRS duration of 150 ms or more (14). Second, patients with a narrow QRS duration and severe heart failure symptoms are not considered candidates for CRT, but mechanical and electrical dyssynchrony do not always coexist, raising questions about whether these patients may benefit from CRT (15, 16). Finally, pacing with a left ventricular lead (without placement of a concomitant right ventricular lead) may provide the same benefit as a 3-lead CRT device (17).

In this systematic review, we update the previous systematic review (7) and explore the benefits and harms of CRT in patients with less symptomatic heart failure, patients with a narrow QRS duration on electrocardiography,

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Context

Guidelines recommend cardiac resynchronization therapy (CRT) for patients with reduced left ventricular ejection fraction and advanced symptoms of heart failure.

Contribution

This meta-analysis of 25 trials includes new evidence that CRT reduces mortality and heart failure hospitalizations in patients with left ventricular systolic dysfunction, prolonged QRS duration, and milder symptoms. The relative magnitude of the benefits in patients with milder symptoms seemed to be similar to those in patients with New York Heart Association class III or IV symptoms.

Caution

Few trial participants had atrial fibrillation or asymptomatic (New York Heart Association class I) heart failure.

Implication

Some patients with reduced left ventricular ejection fraction and mild symptoms may benefit from CRT.

—The Editors

and the use of a left ventricular lead alone versus standard CRT.

METHODS

Data Sources and Searches

We updated and followed the protocol used for the previous systematic review (7). This included electronic literature searches supplemented by hand-searching reference lists of included studies and review articles, proceedings booklets from meetings, U.S. Food and Drug Administration reports, and contact with primary study authors and device manufacturers (**Appendix Table 1**, available at www.annals.org) (7). The search was not limited to studies published in English or to publication status. The search was last updated on 20 December 2010. **Appendix Table 2** (available at www.annals.org) shows the MEDLINE search strategy.

Study Selection

We included RCTs that 1) enrolled patients with heart failure and LVEF of 0.40 or less, regardless of their baseline NYHA functional class; 2) compared CRT with inactive pacing, right ventricular pacing alone, left ventricular pacing alone, implantable cardioverter-defibrillator (ICD) alone (for trials of CRT plus ICD vs. ICD alone), or usual care; 3) reported all-cause mortality, heart failure hospitalization, change in LVEF, or change in functional outcomes (NYHA class, quality of life, or 6-minute walk test); and 4) included more than 25 participants.

The primary literature search was done by 1 of the authors. Using standardized inclusion or exclusion forms, 2 of the authors then independently reviewed the full texts of all potentially relevant studies. Final decisions about study inclusion or exclusion were reached by consensus.

Data Extraction and Quality Assessment

Data extraction was done by 2 independent reviewers by using standardized data extraction forms. For crossover trials, data from the first period only (before crossover) were used. Quality assessment of all included studies was done by using the 6 domains of the Cochrane tool for assessing risk for bias (18).

Data Synthesis and Analysis

Primary and Secondary Outcomes

The primary outcome for this systematic review is all-cause mortality. Secondary outcomes include heart failure hospitalizations, quality of life, and functional outcomes (LVEF and 6-minute walk test). Because we expected duration of follow-up to differ among trials, we explored whether the risk ratios (RRs) for the primary outcome varied by duration of follow-up.

Subgroups and Sensitivity Analysis

A priori, we assessed the efficacy of CRT among studies that included patients with NYHA class I or II symptoms compared with NYHA class III or IV symptoms as a separate subgroup analysis; trials were classified as having patients who were predominantly (>50% but <100%) or exclusively (100%) in one NYHA subgroup or the other. Other prespecified subgroups were sex, age, ischemic etiology, QRS duration, year of enrollment, and whether patients received an ICD. Left ventricular lead–only pacing

Glossary: **Trial Abbreviations**

B-LEFT HF: Biventricular versus Left Univentricular Pacing with ICD Back-up in Heart Failure Patients
BELIEVE: Bi vs Left Ventricular Pacing: An International Pilot Evaluation on Heart Failure Patients with Ventricular Arrhythmias
CARE-HF: Cardiac Resynchronization–Heart Failure
COMBAT: Conventional Versus Biventricular Pacing in Heart Failure and Bradyarrhythmia
COMPANION: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure
DECREASE-HF: Device Evaluation of CONTAK RENEWAL 2 and EASYTRAK 2: Assessment of Safety and Effectiveness in Heart Failure
Greater-EARTH: Evaluation of Resynchronization Therapy For Heart Failure In Patients With A QRS Duration Greater Than 120 ms
HOBIPACE: Homburg Biventricular Pacing Evaluation
MADIT-CRT: Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy
MIRACLE: Multicenter InSync Randomized Clinical Evaluation
MIRACLE ICD: Multicenter InSync Randomized Clinical Evaluation ICD
MUSTIC AF: Multisite Stimulation in Cardiomyopathies–Atrial Fibrillation
MUSTIC SR: Multisite Stimulation in Cardiomyopathies–Sinus Rhythm
PATH-CHF: Pacing Therapies for Congestive Heart Failure
RAFT: Resynchronization/Defibrillation for Ambulatory Heart Failure
RethinQ: Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS
REVERSE: REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction
RHYTHM ICD: Resynchronization for Hemodynamic Treatment for Heart Failure Management
VecTOR: Ventricular Resynchronization Therapy Randomized Trial

trials versus biventricular lead trials were evaluated separately.

Statistical Analysis

For dichotomous outcomes (mortality and heart failure hospitalization), RRs and 95% CIs were calculated. For continuous outcomes (such as the 6-minute walk test and quality-of-life scores), weighted mean differences (WMDs) and 95% CIs were calculated. Intention-to-treat analyses were performed by using the same end point definitions as in the primary studies. We included results from primary study reports and not from their extended follow-up analyses, although these were reviewed for consistency of results. When reported, the components of a primary outcome were analyzed separately.

Because we expected studies to differ in length of follow-up and study participants, we decided a priori to use a DerSimonian–Laird random-effects model for all outcomes (18). The I^2 statistic was used to quantify heterogeneity; a value greater than 50% was considered to indicate substantial heterogeneity (19).

Meta-regressions were run to explore potential sources of heterogeneity among studies. The studies were weighted by size and variance and regressed against year of publication, age, sex, percentage of patients with key baseline characteristics of interest (ischemia, atrial fibrillation, and left bundle branch block), percentage in each NYHA class, mean QRS duration, and background ICD use. We examined the effect of duration of follow-up on the RR for all-cause mortality by using an additional meta-regression model.

Review Manager, version 4.2 (Cochrane Collaboration, Copenhagen, Denmark), was used to generate the forest plots and unadjusted RRs; meta-regression and other analyses were done by using R, version 2.12 (R Foundation for Statistical Computing, Vienna, Austria), using the metafor command (20).

Role of the Funding Source

The study was not supported by external funding.

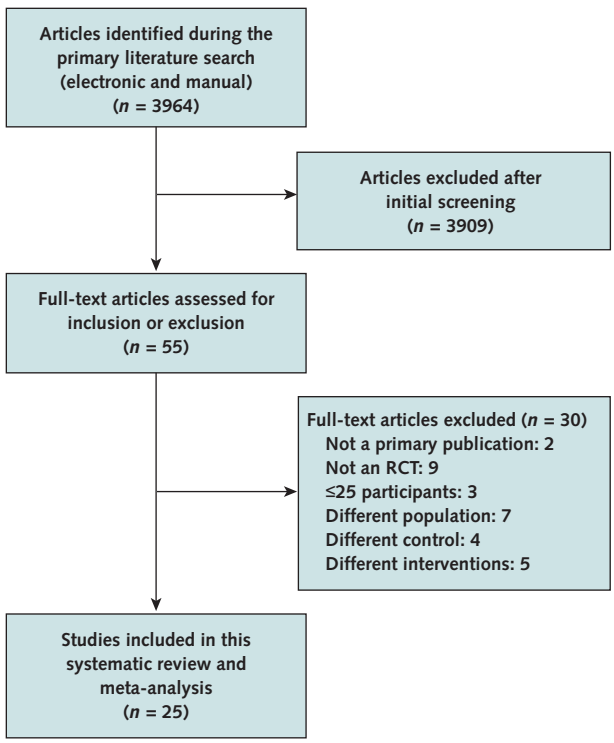
RESULTS

Qualitative Results

Study Selection and Evaluation

The primary literature search yielded 3964 studies (**Figure 1**). Of these, 11 RCTs (11–13, 17, 21–27) met the inclusion criteria and were added to the 14 trials (28–41) from the previous systematic review (7). All of the newly included trials were published, except for Greater-EARTH (27) (for expansions of all study names, see the Glossary). Greater-EARTH was presented at the 2010 Heart Rhythm Society meeting and was included because the principal investigator provided us with the unpublished data for this review. Additional data and clarifications were provided by the principal investigators of another 5 trials.

Figure 1. **Summary of evidence search and selection.**



For expansions of study names, see the Glossary. RCT = randomized, controlled trial.

Appendix Table 3 (available at www.annals.org) shows the funding sources and quality assessment of included studies. Fourteen trials were double-blind (11–13, 17, 21, 23, 25, 27–29, 31, 34–36), 8 trials were single-blind (22, 26, 30, 32, 33, 39–41), and 3 trials were open-label (24, 37, 38). Eighteen trials randomly assigned patients after successful device implantation (11, 17, 21–23, 25, 26, 29–36, 39–41), 6 trials did so before device implantation (12, 13, 24, 28, 37, 38), and timing was not clear in 1 trial (27). Sixteen trials used a parallel study design (11–13, 17, 21, 22, 24, 25, 28, 29, 31, 34–38), and 9 trials used a crossover study design (23, 26, 27, 30, 32, 33, 39–41).

Studies Included in the Systematic Review

Appendix Table 3 summarizes the baseline characteristics of 9082 patients (5080 patients in intervention group and 4002 in the control group) in the 25 trials. Cardiac resynchronization therapy was compared with usual care in 3 trials (24, 37, 38), right ventricular pacing in 5 trials (23, 26, 33, 39, 40), left ventricular pacing in 4 trials (17, 22, 25, 27), either right or left ventricular pacing in 1 trial (32), and backup (inactive) pacing in 4 trials (28, 30, 31, 41). Eight trials compared CRT plus ICD with ICD alone (11–13, 21, 29, 34–36).

The mean age of the participants ranged from 59 to 73 years, and the trials included predominantly men (**Appendix Table 3**). Four trials were restricted to patients with LVEF less than 0.30 (12, 13, 34, 41), 16 trials to those with LVEF less than 0.35 (17, 21, 22, 24, 25, 27–31, 33, 35–38, 40), and 4 trials to those with LVEF less than 0.40 (11, 23, 26, 39); in 1 trial, LVEF as an inclusion criterion was not clear (32). Twenty-four of the trials included only patients with a QRS duration of 120 ms or greater (mean QRS duration, 148 to 209 ms), whereas the RethinQ Study (21) included patients with a narrower QRS duration but with evidence of mechanical dyssynchrony on echocardiography (172 patients; mean QRS duration, 106 ms).

Three trials (2616 patients) included patients with NYHA class I or II symptoms exclusively (11, 12, 36), and 2 trials (158 patients) included predominantly patients with NYHA class I or II symptoms (78% [26] and 69% [27] of patients) but did not report outcomes separately for strata of NYHA classes. One trial (798 patients) included predominantly patients with NYHA class II symptoms (80%; the remaining 20% had class III symptoms) and reported outcomes separately for strata of NYHA classes, permitting us to split the data into appropriate NYHA subgroups (13). Of the remaining 19 trials, 11 (3445 patients) included patients with NYHA class III or IV symptoms exclusively (17, 21, 24, 25, 30–33, 35, 37, 38) and 8 (1065 patients) (22, 23, 28, 29, 34, 39–41) included predominantly patients with NYHA class III or IV symptoms (62% in 1 trial, 67% in 1 trial, and >70% in 6 trials) but did not report outcomes separately for strata of NYHA classes.

Quantitative Results

All-Cause Mortality

Pooled data from all 25 trials show that CRT reduced all-cause mortality by 19% (RR, 0.81 [95% CI, 0.72 to 0.90]); there was no appreciable statistical heterogeneity among trials ($I^2 = 0\%$). Excluding trials without events in 1 or both groups did not affect mortality estimates (RR, 0.80 [CI, 0.72 to 0.89]). In the 6 trials that predominantly included patients with NYHA class I or II symptoms, CRT reduced the risk for all-cause mortality (RR, 0.83 [CI, 0.72 to 0.96]; $I^2 = 0\%$) (**Figure 2**). Repeating this analysis for the 3 studies that exclusively included patients with NYHA class I or II symptoms (in addition to the subgroup of patients with NYHA class II symptoms from RAFT [13]) showed similar results (407 deaths in 4054 patients; RR, 0.80 [CI, 0.67 to 0.96]; $I^2 = 0\%$). In the 19 trials enrolling predominantly patients with NYHA class III or IV symptoms, CRT reduced the risk for all-cause mortality (RR, 0.78 [CI, 0.67 to 0.91]; $I^2 = 0\%$) (**Figure 2**). Repeating this analysis for the 11 studies that included exclusively patients with NYHA class III or IV symptoms (in addition to the subgroup of patients with NYHA class III symptoms from RAFT [13]) showed similar results (666 deaths in 3805 patients; RR, 0.80 [CI, 0.70 to 0.92]; $I^2 = 0\%$).

Four studies compared CRT with left ventricular pacing: Two included patients with NYHA class III or IV symptoms (17, 25); 1 included patients with NYHA class II, III, or IV symptoms (22); and 1 included patients with NYHA class I, II, or III symptoms (27). Left ventricular pacing alone did not affect all-cause mortality compared with CRT (RR, 0.83 [CI, 0.32 to 2.13]; $I^2 = 27\%$), although the number of events was small (28 deaths in 677 patients).

Because the trials had different durations of follow-up (ranging from 1 month to approximately 40 months), we examined the effect of follow-up duration on the RR of all-cause mortality. The RR (approximately 0.80) was constant over time (**Appendix Figure**, available at www.annals.org).

Cause-Specific Mortality

The mortality benefit of CRT was largely driven by a reduction in heart failure–related mortality in the 12 trials that reported this outcome (218 events in 3562 patients; RR, 0.64 [CI, 0.49 to 0.83]; $I^2 = 0\%$). However, the CRT and control groups did not differ in the risk for sudden cardiac death (12 trials, 175 events in 3592 patients; RR, 1.04 [CI, 0.77 to 1.41]; $I^2 = 0\%$) or noncardiac death (7 trials, 41 events in 1910 patients; RR, 0.85 [CI, 0.46 to 1.57]; $I^2 = 0\%$).

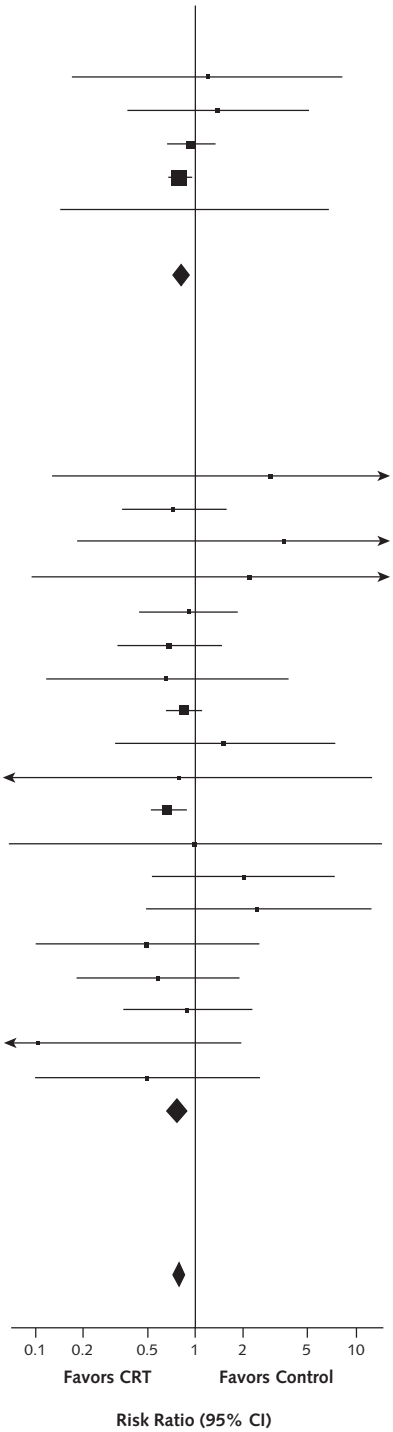
Heart Failure Hospitalization

Overall, CRT was associated with a reduction in the risk for hospitalization with heart failure (RR, 0.69 [CI, 0.58 to 0.82]; $I^2 = 50\%$) (**Figure 3**); no appreciable difference was found between trials enrolling predominantly patients with NYHA class III or IV symptoms (RR, 0.65 [CI, 0.50 to 0.86]; $I^2 = 57\%$) and those enrolling predominantly patients with NYHA class I or II symptoms (RR, 0.71 [CI, 0.57 to 0.87]; $I^2 = 37\%$), although the absolute rate of heart failure hospitalization was higher in the former trials (22% vs. 17% in the NYHA class I or II trials). Cardiac resynchronization therapy was associated with a reduction in heart failure hospitalization in the 2 studies exclusively of patients with NYHA class I or II symptoms (582 events in 3863 patients; RR, 0.69 [CI, 0.59 to 0.80]; $I^2 = 0\%$) and in the 8 trials that exclusively included patients with NYHA class III or IV symptoms (in addition to the subgroup of patients with NYHA class III symptoms from RAFT [13]) (635 events in 2361 patients; RR, 0.66 [CI, 0.51 to 0.87]; $I^2 = 66\%$). The effects of left ventricular pacing alone on heart failure hospitalization seemed to be similar to those of CRT (3 trials, 36 events in 371 patients; RR, 0.96 [CI, 0.50 to 1.87]; $I^2 = 8\%$).

Given the degree of statistical heterogeneity in the analyses of heart failure hospitalization, which was not explained by NYHA class at baseline, bivariate meta-regression models were used to explore the reasons for statistical heterogeneity. These models demonstrated that the

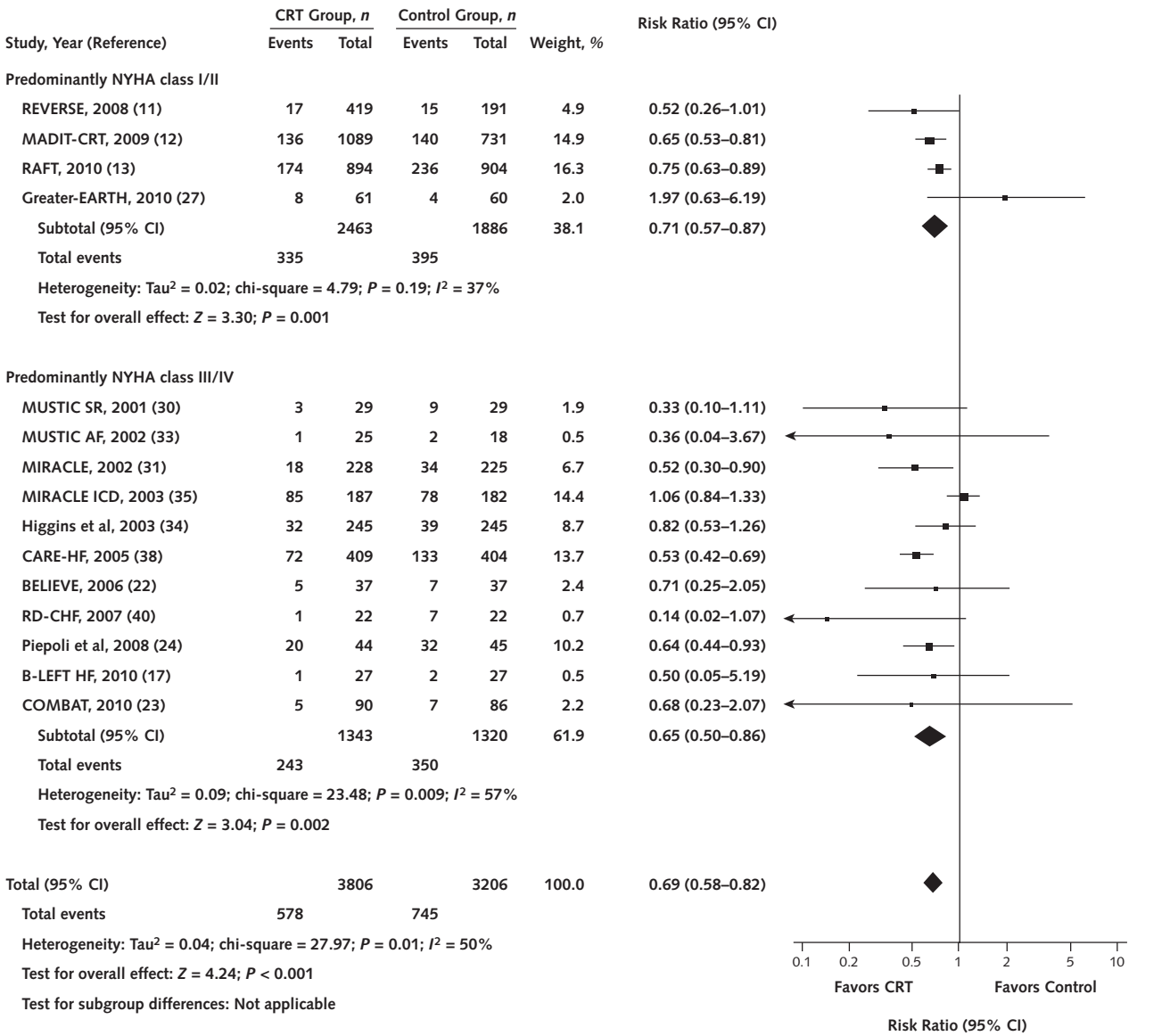
Figure 2. **All-cause mortality with CRT versus control.**

Study, Year (Reference)	CRT Group, *n* Events	CRT Group, *n* Total	Control Group, *n* Events	Control Group, *n* Total	Weight, %	Risk Ratio (95% CI)
Predominantly NYHA class I/II						
MIRACLE ICD II, 2004 (36)	2	85	2	101	0.3	1.19 (0.17–8.26)
REVERSE, 2008 (11)	9	419	3	191	0.7	1.37 (0.37–4.99)
MADIT-CRT, 2009 (12)	74	1089	53	731	9.7	0.94 (0.67–1.32)
RAFT, 2010 (13)	186	894	236	904	39.6	0.80 (0.67–0.94)
Greater-EARTH, 2010 (27)	2	61	2	60	0.3	0.98 (0.14–6.76)
van Geldorp et al, 2010 (26)	0	19	0	18		Not estimable
Subtotal (95% CI)		2567		2005	50.5	0.83 (0.72–0.96)
Total events	273		296			
Heterogeneity: Tau^2 = 0.00; chi-square = 1.46; P = 0.83; I^2 = 0%						
Test for overall effect: Z = 2.43; P = 0.01						
Predominantly NYHA class III/IV						
MUSTIC SR, 2001 (30)	1	29	0	29	0.1	3.00 (0.13–70.74)
MIRACLE, 2002 (31)	12	228	16	225	2.1	0.74 (0.36–1.53)
PATH-CHF, 2002 (32)	2	24	0	17	0.1	3.60 (0.18–70.54)
MUSTIC AF, 2002 (33)	1	25	0	18	0.1	2.19 (0.09–50.93)
MIRACLE ICD, 2003 (35)	14	187	15	182	2.3	0.91 (0.45–1.83)
Higgins et al, 2003 (34)	11	245	16	245	2.0	0.69 (0.33–1.45)
PATH-CHF II, 2003 (41)	2	43	3	43	0.4	0.67 (0.12–3.79)
COMPANION, 2004 (37)	131	617	77	308	18.6	0.85 (0.66–1.09)
RHYTHM ICD, 2005 (29)	6	119	2	60	0.5	1.51 (0.31–7.27)
VecTOR, 2005 (28)	1	59	1	47	0.1	0.80 (0.05–12.40)
CARE-HF, 2005 (38)	82	409	120	404	18.7	0.67 (0.53–0.86)
HOBIPACE, 2006 (39)	1	16	1	16	0.2	1.00 (0.07–14.64)
BELIEVE, 2006 (22)	6	37	3	37	0.7	2.00 (0.54–7.40)
RethinQ, 2007 (21)	5	87	2	85	0.4	2.44 (0.49–12.25)
RD-CHF, 2007 (40)	2	22	4	22	0.4	0.50 (0.10–2.45)
DECREASE-HF, 2007 (25)	6	205	5	101	0.8	0.59 (0.18–1.89)
Piepoli et al, 2008 (24)	7	44	8	45	1.3	0.89 (0.35–2.26)
B-LEFT HF, 2010 (17)	0	90	4	86	0.1	0.11 (0.01–1.94)
COMBAT, 2010 (23)	2	27	4	27	0.4	0.50 (0.10–2.50)
Subtotal (95% CI)		2513		1997	49.5	0.78 (0.67–0.91)
Total events	292		281			
Heterogeneity: Tau^2 = 0.00; chi-square = 11.61; P = 0.87; I^2 = 0%						
Test for overall effect: Z = 3.23; P = 0.001						
Total (95% CI)		5080		4002	100.0	0.81 (0.72–0.90)
Total events	565		577			
Heterogeneity: Tau^2 = 0.00; chi-square = 13.40; P = 0.94; I^2 = 0%						
Test for overall effect: Z = 4.00; P < 0.001						
Test for subgroup differences: Not applicable						



Studies are stratified by NYHA classes of included patients. Risk ratios were calculated by using Mantel–Haenszel random-effects methods. For expansions of study names, see the Glossary. CRT = cardiac resynchronization therapy; NYHA = New York Heart Association.

Figure 3. **Heart failure hospitalization with CRT versus control.**



Studies are stratified by baseline NYHA classes of included patients. Risk ratios were calculated by using Mantel–Haenszel random-effects methods. For expansions of study names, see the Glossary. CRT = cardiac resynchronization therapy; NYHA = New York Heart Association.

percentage of patients with ischemic heart failure enrolled in the trials explained most of the heterogeneity, because these patients seemed to derive less benefit from heart failure hospitalization than nonischemic patients. Each 5% increase in the percentage of patients with ischemic heart failure in an RCT was associated with an 8% relative reduction (CI, 3.9% to 12.8%) in the benefits of CRT on heart failure hospitalization.

Quality of Life

Quality of life was reported in 15 of the 25 trials. Overall, CRT was associated with an improvement in scores on the Minnesota Living with Heart Failure Questionnaire (MLHFQ) compared with control participants (14 trials, 4283 participants; WMD, 6.56 points [CI, 4.08 to 9.04 points]), but substantial statistical heterogeneity was found (I^2 = 72%) that was largely attributable to symptom status at baseline. Two of the 3 trials (787 participants) including patients with NYHA class I or II symptoms had better MLHFQ scores at baseline (mean scores, 40 [35] and 28 [11]) and did not show any appreciable improvement with CRT (WMD, 1.82 points [CI, −0.77 to 4.41 points]; I^2 = 0%). The remaining trial in patients with NYHA class I or II symptoms (12, 42) re-

ported no difference between the CRT and control groups in Kansas City Cardiomyopathy Questionnaire scores (mean change at 12 months, 13.9 vs. 12.1, respectively; $P = 0.059$). In contrast, in the 12 trials (3496 patients) including predominantly patients with NYHA class III or IV symptoms, MLHFQ scores were poorer at baseline and improved statistically and clinically with CRT (WMD, 7.39 points [CI, 4.87 to 9.91 points]; $I^2 = 65\%$). Results were similar when we repeated this analysis for the 9 trials (2773 participants) of patients with NYHA class III or IV symptoms exclusively (WMD, 6.93 points [CI, 3.90 to 9.96 points]; $I^2 = 71\%$). Only 1 of the 4 trials (148 participants) that compared CRT with left ventricular pacing alone evaluated this outcome (17), and no difference between the groups was reported (WMD, 0 points [CI, −6.27 to 6.27 points]).

6-Minute Walk Test

Overall, results of the 6-minute walk test improved in the CRT groups compared with control groups (15 trials, 3475 participants; WMD, 17.50 m [CI, 7.05 to 27.94 m]; $I^2 = 57\%$). Trials including predominantly patients with NYHA class I or II symptoms showed no improvement in the 6-minute walk test (3 trials, 890 participants; WMD, −4.08 m [CI, −17.79 to 9.63 m]; $I^2 = 0\%$), whereas trials including predominantly patients with NYHA class III or IV symptoms showed substantial improvement with CRT (12 trials, 2585 participants; WMD, 23.34 m [CI, 12.96 to 33.72 m]; $I^2 = 44\%$). Three trials comparing left ventricular pacing with CRT reported this outcome; no difference between the 2 pacing modalities was observed, although the CIs were wide (326 participants; WMD, −0.75 m [CI, −21.88 to 20.38 m]; $I^2 = 0\%$).

Improvement by at Least 1 NYHA Class

Patients assigned to receive CRT were significantly more likely than controls who did not undergo cardiac pacing to have improvement by at least 1 NYHA class (4 trials, 1476 participants; RR, 1.60 [CI, 1.34 to 1.92]; $I^2 = 45\%$), whereas the 2 studies that compared CRT with left ventricular pacing found no difference between the groups (245 patients; RR, 0.90 [CI, 0.74 to 1.08]; $I^2 = 0\%$). Of note, none of the trials of patients with NYHA class I or II symptoms reported this outcome.

LVEF

Cardiac resynchronization therapy improved LVEF compared with control patients who did not receive cardiac pacing (11 trials, 3202 participants; WMD, 0.0364 [CI, 0.0189 to 0.0539]; $I^2 = 89\%$); no appreciable difference was detected between trials in patients with predominantly NYHA class I or II symptoms (4 trials, 2165 participants; WMD, 0.0463 [CI, 0.0188 to 0.0739]; $I^2 = 92\%$) and trials in patients with predominantly NYHA class III or IV symptoms (7 trials, 1037 participants; WMD, 0.0297 [CI, 0.0097 to 0.0497]). In the 4 studies that compared CRT with left ventricular pacing for this outcome, the study groups did not differ (509 participants; WMD, 0.0078 [CI, −0.0058 to 0.0215]; $I^2 = 0\%$).

Safety

Appendix Table 4 (available at www.annals.org) shows the implantation success rate and rates of complications. The implantation success rate was 94.4% (CI, 93.8% to 94.8%). Mechanical complications (including coronary sinus dissection or perforation, pericardial effusion or tamponade, pneumothorax, and hemothorax) occurred in 3.2% (CI, 2.8% to 3.6%) of patients, device malfunction in 1.9% (CI, 1.5% to 2.4%), lead problems (including lead dislodgement or repositioning) in 6.2% (CI, 5.6% to 6.8%), and infections in 1.4% (CI, 1.1% to 1.7%). Peri-implantation death occurred in 0.3% of patients (CI, 0.2% to 0.5%).

Assessment for Publication Bias

We tested for publication bias by using a funnel plot for all-cause mortality. Although the funnel plot was asymmetrical, the area missing consisted of small positive studies; if anything, this indicates that our estimates of all-cause mortality may be conservative. A funnel plot for heart failure hospitalization was asymmetrical, indicating potential publication bias; the plot was missing small neutral or negative trials.

Discussion

In this systematic review, we confirm that CRT improves LVEF and reduces all-cause mortality and heart failure hospitalization in patients with milder symptoms of heart failure (NYHA class I or II), left ventricular systolic dysfunction, and prolonged QRS duration. The relative magnitude of these benefits (risk reductions of 17% for mortality and 29% for heart failure hospitalization) are similar to that seen in patients with NYHA class III or IV symptoms, left ventricular systolic dysfunction, and prolonged QRS duration. Our findings contrast with those of a recent meta-analysis (43) of 2 trials in patients with NYHA class I or II symptoms (compared with the 6 trials in our analysis) that report no survival benefit with CRT, but a significant reduction in a composite outcome of "any heart failure events."

Of note, 98% of the control patients in our analyses of trials including NYHA class I or II symptoms had an ICD; thus, the benefits of CRT that we found represent incremental benefits additional to the expected benefits from the ICD implanted in both groups in each study. However, CRT did not improve quality of life or functional outcomes, such as results of the 6-minute walk test, in patients with mildly symptomatic heart failure—in contrast to their marked beneficial effects on these outcomes (similar in magnitude to those of angiotensin-converting

enzyme inhibitors [44]) for patients with NYHA class III or IV symptoms at baseline. This is not surprising, given that patients with NYHA class I or II heart failure have less symptom burden and impairment of quality of life at baseline.

The improvements in LVEF that we documented for trial participants regardless of NYHA class are consistent with results from other studies (7, 36, 45, 46). Although data from the REVERSE trial and MADIT-CRT suggested that the benefits of CRT on left ventricular remodeling were greatest in patients with longer QRS durations and nonischemic heart failure (47, 48) and a substudy from MIRACLE also suggested greater left ventricular remodeling with CRT in patients with nonischemic disease (46), without access to individual-patient data, we could not explore whether this finding persisted in other trial data sets. Certainly, the benefits of CRT on the composite clinical outcome was greatest in patients in MADIT-CRT and RAFT who had a QRS duration greater than 150 ms. Of note, CRT is the only positive inotropic therapy that has been shown to improve both cardiac systolic function and patient survival.

An important question about CRT, as with any intervention that has been tested in only a selected range of patients and depends on specialized technical expertise to implant, is how generalizable the benefits demonstrated in RCTs will be when the device is used in clinical practice by less experienced clinicians working in smaller-volume centers (49–51). This is particularly relevant for CRT, because approximately 38% of the patients (18 of the RCTs) in our efficacy analysis were randomly assigned only after successful device implantation. As a result, these RCTs may overestimate the potential benefit from CRT and underestimate the risk, because patients who could not tolerate the procedure or in whom implantation was unsuccessful were not included in the trial data. We anticipate that data from the National Cardiovascular Data Registry and ongoing cohort studies will be vital in establishing the clinical effectiveness and safety of CRT and tracking changes over time as device implanters, the tools for implantation, and the sophistication of the devices change—complication rates for left ventricular lead placement may be higher in the community. Such data will also be important to inform future cost-effectiveness analyses of CRT; current estimates (52, 53) based on analyses using trial data and restricting use of CRT in their models to patients with NYHA class III or IV symptoms will not be applicable as indications for CRT expand.

Although we followed current recommendations for performing a systematic review and obtained unpublished data from several of the primary studies included in our meta-analysis, our study has limitations. Substantial statistical heterogeneity was present in some analyses and could not be explained by the variables considered in the meta-regressions; however, subgroup analyses and meta-regressions are post hoc analyses and generally underpowered. In addition, the conclusions about the implications for clinical practice are limited for some subgroups of patients who were excluded from or underrepresented in the trials: those with bradyarrhythmias, atrial fibrillation, chronic kidney disease, or right bundle branch block. Finally, most of the trial participants were younger and relatively healthier than patients with heart failure encountered in clinical practice.

What are the implications of our findings? Our data support the expansion of indications for CRT to less symptomatic patients with heart failure who have LVEF less than 0.35 and QRS duration greater than 120 ms and are in sinus rhythm (**Table**). However, 85% of less symptomatic patients in these trials had NYHA II symptoms, and high-quality evidence to support this therapy in patients with asymptomatic left ventricular dysfunction or NYHA class I symptoms is inconclusive.

Our data also illuminate other issues about CRT for which randomized trial evidence is sparse and thereby highlight research priorities. For example, whether CRT is as efficacious in patients with atrial fibrillation (54) as in those with sinus rhythm is unclear (55). This is an important research question for future randomized trials because less than 1% of participants in CRT trials had atrial fibrillation, but almost 30% of all CRT devices are implanted in patients with atrial fibrillation (56, 57). Moreover, although preliminary observations (58) suggest that CRT reduces symptom burden in patients with LVEF greater than 0.35, prolonged QRS, and NYHA class III or IV symptoms that are refractory to optimal medical therapy, an RCT is needed before practice recommendations can be made (59). Nonetheless, 10% to 15% of patients who received CRT devices in the United States and Europe have LVEF greater than 0.35 (56, 57, 60). Finally, the most pressing research priority for CRT should be to establish a uniform definition of "CRT response." A recent review pointed out the poor correlations among the 17 most frequently used definitions for CRT response and the fact that although 99% of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) participants would have been defined as CRT responders by at least 1 of these commonly used criteria, 94% would also have been defined as CRT nonresponders by at least 1 of the criteria (61).

Of note, our meta-regression analysis showed that inclusion of a higher proportion of patients with ischemic heart failure in the RCTs was associated with less benefit from CRT in reducing heart failure hospitalization, but no differential effect on mortality was observed. Studies in patients with NYHA class I or II symptoms (62) and class III or IV symptoms (46) have shown that an ischemic cause of heart failure is associated with less benefit from CRT. Thus, understanding which patients with ischemic heart disease should receive a CRT device, and the roles of scar tissue, wall thinning, limited myocyte viability, and

Table. **Summary of Current Evidence for CRT in Patients With Heart Failure**

Comparison	Patient Characteristics			Trials (Participants), *n (n)*	Quality of Evidence	Magnitude of Effect of CRT	Conclusion
	NYHA Class	ECG Criteria	LVEF				
CRT vs. usual care or right ventricular, left ventricular, or inactive pacing; CRT + ICD vs. ICD alone	I	QRS duration >120 ms; sinus rhythm	<0.40	4 (391 with NYHA I); all reported outcomes combined with NYHA class II	Low (post hoc meta-regression analysis)	Indeterminate	Inconclusive
	II	QRS duration >120 ms; sinus rhythm	<0.35	6 (4572)	High (several large RCTs); no heterogeneity	Reduce mortality: RR, 0.83 (95% CI, 0.72–0.96)	Definite benefit
				4 (4349)	High (3 large RCTs); moderate heterogeneity	Reduce HF hospitalizations: RR, 0.69 (CI, 0.57–0.87)	Definite benefit
				2 (787)	High (several RCTs); no heterogeneity	No effect on quality of life: WMD, 1.82 points (CI, −0.77 to 4.41 points)	Inconclusive
				4 (2165)	High (large RCT); substantial heterogeneity	Improves LVEF: WMD, 0.0463 (CI, 0.0188–0.0739)	Definite benefit
	III or IV	QRS duration >120 ms; sinus rhythm	<0.35	19 (4510)	High (several large RCTs)	Reduce mortality: RR, 0.79 (CI, 0.68–0.91)	Definite benefit
				11 (2663)	High (several large RCTs); substantial heterogeneity	Reduce HF hospitalization: RR, 0.65 (CI, 0.50–0.86)	Definite benefit
				12 (3496)	High (several large RCTs); substantial heterogeneity	Improves MLHFQ by 7 points (CI, 4.87–9.91)	Definite benefit
				7 (1037)	High (large several RCTs); substantial heterogeneity	Improves LVEF: WMD, 0.0297 (CI, 0.097–0.0497)	Definite benefit
	III or IV	QRS duration <130 ms; sinus rhythm	<0.35	1 RCT (172)	Low (small trial with wide CIs)	No effect on mortality (RR, 2.44 [CI, 0.49–12.25]) or hospitalization	Inconclusive; ongoing trials, EchoCRT (*n* > 1000) (NCT00683696) and Lesser-EARTH (*n* = 120) (NCT00900549)
	III or IV	QRS duration >120 ms; AF	<0.35	1 RCT limited to patients with AF	Low (small trial with wide CIs)	No difference between CRT and control	Inconclusive; ongoing studies, APAF (NCT00111527)
				4 trials included different proportion of patients with AF	Low (post hoc meta-regression analysis)		
	Any	Any QRS duration; bradyarrhythmia	Any	No RCTs identified	No available evidence	Not applicable	Inconclusive; ongoing trials, BLOCK-HF (NCT00267098)
CRT vs. LV pacing (both with ICD)	Any	Any	<0.35	4 RCTs; mostly small- to medium-sized, with low event rates	Low (small trials with wide CIs)	No difference in mortality, HF hospitalization, or functional outcomes	Inconclusive; ongoing study, Lesser-EARTH (NCT00900549)

AF = atrial fibrillation; APAF = Assessment of Cardiac Resynchronization Therapy in Patients With Permanent Atrial Fibrillation; BLOCK-HF = Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block; CRT = cardiac resynchronization therapy; ECG = electrocardiography; EchoCRT = Echocardiography Guided Resynchronization Therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; Lesser-EARTH = Evaluation of Resynchronization Therapy for Heart Failure; LV = left ventricular; LVEF = left ventricular ejection fraction; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NYHA = New York Heart Association; RCT = randomized, controlled trial; RR = relative risk; WMD = weighted mean difference.

subendocardial ischemia in making this decision, also warrant future research.

It had been estimated that CRT was indicated in fewer than 10% of symptomatic patients with heart failure who have left ventricular systolic dysfunction (63, 64). However, as our systematic review reveals, the evidence base has evolved substantially since these earlier estimates, and CRT may now be indicated for most of the 40% of patients with systolic heart failure who have a QRS duration greater than 120 ms (65). However, more than one third of current CRT recipients do not have functional or echocardiographic improvement after activation of their CRT (7), indicating that relying on RCT eligibility criteria to define which patients should undergo device implantation is imperfect. As such, we believe establishing criteria for case selection so that CRT devices are preferentially implanted in the patients who are most likely to benefit is of vital importance for researchers, clinicians, and policymakers.

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Appendix Table 1. Databases Searched

MEDLINE: in-process and other nonindexed citations
Ovid MEDLINE Daily and Ovid MEDLINE, 1950 to present
EMBASE
PubMed
Cochrane Central Register of Controlled Trials
Health Technology Assessment Database
International Pharmaceutical Abstracts
Web of Science (Science Citation Index Expanded)
National Library of Medicine Gateway
Conference Papers Index (CSA)
OCLC PapersFirst
OCLC ProceedingsFirst
ProQuest Dissertations and Theses
U.S. Food and Drug Administration Web site
Clinical trials Web sites:
- Australia New Zealand Clinical Trials Registry
- CenterWatch
- Clinical Center, National Institutes of Health
- ClinicalStudyResults.org
- ClinicalTrials.gov (National Institutes of Health)
- Current Controlled Trials (BioMed Central)
- Cardiosource (American College of Cardiology)
- www.theheart.org

Appendix Table 2. MEDLINE Search Strategy (November 2006–December 2010)

1. exp Heart Failure/
2. exp Ventricular Dysfunction, Left/
3. CHF.mp.
4. chronic heart failure.mp.
5. exp Heart Diseases/
6. congestive heart failure.mp.
7. exp Ventricular Dysfunction/
8. exp Cardiac Pacing, Artificial/or exp Pacemaker, Artificial/or cardiac resynchronization.mp.
9. exp Pacemaker, Artificial/or biventricular pacing.mp.
10. biventricular pacer.mp.
11. biventricular stimulation.mp.
12. multisite pacemaker.mp.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7
14. 8 or 9 or 10 or 11 or 12
15. 13 and 14
16. randomized controlled trial.pt.
17. clinical trial.pt.
18. randomi?ed.ti,ab.
19. placebo.ti,ab.
20. dt.fs.
21. randomly.ti,ab.
22. trial.ti,ab.
23. groups.ti,ab.
24. or/16-23
25. animals/
26. humans/
27. 25 not (25 and 26)
28. 24 not 27
29. 15 and 28
30. limit 29 to yr="2006-Current"

Appendix Table 3. Characteristics of Included Randomized, Controlled Trials and Baseline Characteristics of Patients

Study, Year (Reference)*	Duration	Funding Source	Risk for Bias	Group	Participants, *n*	Mean Age (SD), *y*	Men, %	Ischemic, %	NYHA Class, %				Mean LVEF (SD)	Mean QRS Duration (SD), *ms*	ECG Pattern, %		AF, %
									1	2	3	4			LBBB	RBBB	
MUSTIC SR, 2001 (30)	3 mo	Industry	High	CRT first	29	64 (11)	66	NR			100		0.23 (0.07)	172 (22)	87	NR	Excluded
				Inactive first	29	64 (8)	83	NR			100			175 (19)			
MUSTIC AF, 2002 (33)	3 mo	Industry	High	CRT first	25	65 (9)	84	NR			100		0.23 (0.07)	209 (21)†	NR	NR	100
				RV first	18	66 (9)	78	NR			100		0.30 (0.12)	208 (12)†			100
MIRACLE, 2002 (31)	6 mo	Industry	Unclear	CRT	228	64 (11)	68	50			90	10	0.22 (0.06)	167 (21)	NR	NR	Excluded
				Inactive	225	65 (11)	68	58			91	9	0.22 (0.06)	165 (20)			
PATH-CHF, 2002 (32)	1 mo	Industry	High	CRT first	24	59 (7)	46	42			88	12	0.21 (0.06)	174 (30)	87	13	Excluded
				Uni-V first	17	60 (5)	59	6			82	18	0.20 (0.07)	178 (34)	100	0	
PATH-CHF II, 2003 (41)	3 mo	Industry	High	CRT first	43	61 (9)	70	44		37		63	0.23 (0.07)	154 (18)	91	NR	Excluded
				Inactive first	43	58 (8)	63	33		28		72	0.23 (0.08)	157 (23)	86		
Higgins et al, 2003 (34)	3 mo	Industry	Low	CRT + ICD	245	66 (11)	85	71		32	60	8	0.21 (0.07)	160 (27)	54	14	Excluded
				ICD	245	66 (11)	83	67		33	57	10	0.22 (0.07)	156 (26)	55	12	
MIRACLE ICD, 2003 (35)	6 mo	Industry	Low	CRT + ICD	187	67 (11)	76	64			88	12	0.24 (0.07)	165 (22)	NR	13	Excluded
				ICD	182	68 (9)	78	76			89	11	0.24 (0.06)	162 (22)		13	
COMPANION, 2004 (37)	15 mo	Industry	High	CRT	617	67‡	67	54			87	13	0.20‡	160‡	69	NR	Excluded
				Usual care	308	68‡	69	59			82	18	0.22‡	158‡	70		
MIRACLE ICD II, 2004 (36)	6 mo	Industry	Unclear	CRT + ICD	85	63 (13)	88	55		100			0.24 (0.07)	166 (25)	NR	12	Excluded
				ICD	101	63 (12)	92	58		100			0.25 (0.07)	165 (23)		21	
CARE-HF, 2005 (38)	29.4 mo	Industry	Low	CRT	409	67 (60–73)§	74	40			94	6	0.25 (0.22–0.29)§	160 (152–180)§	NR	NR	Excluded
				Usual care	404	66 (59–72)§	73	36			93	7	0.25 (0.21–0.29)§	160 (152–180)§			
RHYTHM ICD, 2005 (29)	12 mo	Industry	Unclear	CRT + ICD	119	NR	NR	NR	1	5	87	7	0.26 (0.08)	169 (16)	NR	NR	Excluded
				ICD	59	NR	NR	NR	2	6	87	6	0.23 (0.06)	167 (15)			
VecTOR, 2005 (28)	6 mo	Industry	Unclear	CRT	59	67 (10)	63	NR		29	65	6	<0.35	>140	NR	NR	Excluded
				Inactive pacing	47												
BELIEVE, 2006 (22)	12 mo	Unclear	Low	CRT + ICD	33	67 (8)	88	58		42	58		0.26 (0.06)	176 (25)	NR	NR	Excluded
				LV + ICD	36	67 (7)	94	69		33	67		0.25 (0.06)	169 (31)			
HOBIPACE, 2006 (39)	3 mo	Government	Unclear	CRT	15	70 (8)	77	57	Mean (SD), 3.0 (0.6)				0.26 (0.08)	174 (42)	63	NR	37
				RV	15												
DECREASE-HF, 2007 (25)	6 mo	Industry	Unclear	Simultaneous and sequential BiV + ICD	205	66 (11)	68	66			98	2	0.23 (0.07)	167 (16)	94.1	0	Excluded
				LV + ICD	101	67 (10)	65	62			97	3	0.23 (0.07)	165 (15)	93	1	
RD-CHF, 2007 (40)	3 mo	Unclear	High	CRT first	25	73 (9)	100	56	Mean (SD), 3.2 (0.4)				0.24 (0.10)	212 (28)	NR	NR	56
				RV first	19	74 (6)	79	47					0.27 (0.09)	199 (21)			63
RethinQ, 2007 (21)	6 mo	Industry	Unclear	CRT + ICD	87	60 (12)	71	54			100		0.25 (0.05)	107 (12)	Excluded	Excluded	Excluded
				ICD	85	58 (14)	58	51			99		0.26 (0.06)	106 (13)			
Piepoli et al, 2008 (24)	12 mo	Unclear	Unclear	CRT	44	71 (7)	70	61			90	10	0.24 (0.01)	164 (18)	NR	NR	Excluded
				Usual care	45	73 (9)	73	56			89	11	0.23 (0.07)	160 (20)			
REVERSE, 2008 (11)	12 mo	Industry	Unclear	CRT on‖	419	63 (11)	78	56	18	82			0.27 (0.07)	153 (21)	NR	NR	Excluded
				CRT off‖	191	62 (12)	80	51	17	83			0.26 (0.07)	154 (24)			
MADIT-CRT, 2009 (12)	2.4 y	Industry	Unclear	CRT + ICD	1089	65 (11)	74	54	14	86			0.24 (0.05)	>150: 64.2%	70	13	Excluded
				ICD	731	64 (11)	76	55	16	85			0.24 (0.05)	>150: 65.1%	71	13	
B-LEFT HF, 2010 (17)	6 mo	Industry	Low	CRT + ICD	90	66 (10)	76	53			93	7	0.26 (0.06)	160 (19)	90	NR	Excluded
				LV + ICD	86	66 (9)	73	51			94	6	0.25 (0.06)	162 (20)	87		
COMBAT, 2010 (23)	3 mo	Industry	Unclear	RV-BiV-RV	27	57 (15)	68	23		16	52	32	0.29 (0.07)	154 (13)	NR	NR	Excluded
				BiV-RV-BiV	27	59 (13)	63	10		17	52	31	0.30 (0.09)	148 (16.4)			
RAFT, 2010 (13)	40 mo	Government and industry	Low	CRT + ICD	894	66 (9)	85	69		79	21		0.22 (0.05)	157 (24)¶	73	8	13
				ICD	904	66 (9)	81	65		81	19		0.22 (0.05)	158 (24)¶	71	10	13
Greater-EARTH, 2010 (27)	6 mo	Government	Unclear	BiV first (+ ICD)	61	62 (8)	72	48	8	59	33		0.24 (0.07)	157 (25)	NR	NR	NR
				LV first (+ ICD)	60	60 (10)	78	55	8	63	28		0.24 (0.06)	153 (22)			
van Geldorp et al, 2010 (26)	6 mo	Industry	Unclear	CRT first	19	64 (11)	79	26	26	47	26		0.36 (0.09)	196 (29)	NR	NR	63
				RV first	18	67 (10)	76	47	24	59	18		0.36 (0.11)	193 (23)			41

AF = atrial fibrillation; BiV = biventricular; CRT = cardiac resynchronization therapy; ECG = electrocardiography; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LV = left ventricular; LVEF = left ventricular ejection fraction; NR = not reported; NYHA = New York Heart Association; RBBB = right bundle branch block; RV = right ventricular; Uni-V first = 4 RV and 36 LV.

* For expansions of study names, see the Glossary.

† Paced QRS duration.

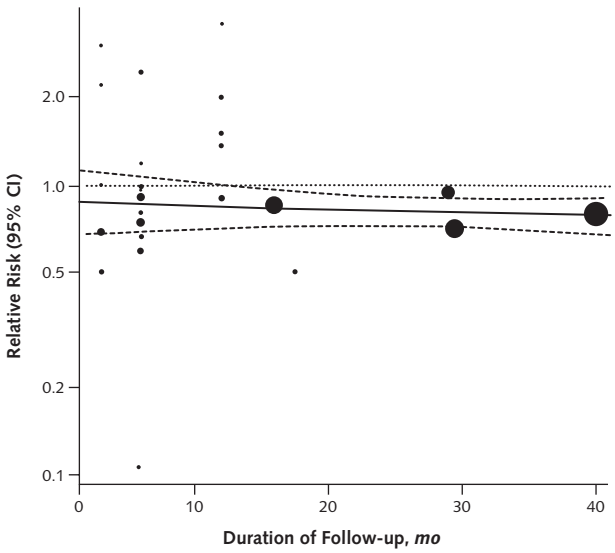
‡ Median.

§ Median (range)

‖ 83% with ICD in all patients.

¶ Intrinsic QRS duration (n = 826).

Appendix Figure. **Effect of follow-up duration on the efficacy of cardiac resynchronization therapy versus control for all-cause mortality.**



Circles represent trial size (number of participants). Dashed lines are 95% CIs. The dotted line represents a relative risk of 1.0.

Appendix Table 4. **Peri-implantation and Postimplantation Complication Rates in the Included Trials***

Study, Year (Reference)†	Implantation Success Rate, *n/N (%)* [95% CI]	Peri-implantation Death, *n/N (%)* [95% CI]	Mechanical Complications, *n/N (%)* [95% CI]‡	Device Malfunction, *n/N (%)* [95% CI]§	Lead Problems, *n/N (%)* [95% CI] ‖	Infection, *n/N (%)* [95% CI]
MUSTIC SR, 2001 (30)	58/64 (90.6) [80.7–96.5]	1/58 (1.7) [0.0–9.2]	2/58 (3.5) [0.4–11.9]	2/67 (3.0) [0.4–10.4]	8/67 (11.9) [5.3–22.2]	NR
MUSTIC AF, 2002 (33)	54/59 (91.5) [81.3–97.2]	0/59 (0.0) [0.0–6.1]	2/54 (3.7) [0.5–12.8]	NR	5/54 (9.3) [3.1–20.3]	NR
MIRACLE, 2002 (31)	528/571 (92.5) [90.0–94.5]	NR	35/571 (6.1) [4.3–8.4]	2/453 (0.4) [0.1–1.6]	30/524 (5.7) [3.9–8.1]	7/524 (1.3) [0.5–2.7]
PATH-CHF, 2002 (32)	41/41 (100) [91.40–100]	0/41 (0.0) [0.0–8.60]	NR	NR	NR	NR
PATH-CHF II, 2003 (41)	86/89 (96.6) [90.5–99.3]	NR	6/98 (6.1) [2.3–12.9]	NR	1/86 (1.2) [0.0–6.3]	1/92 (1.1) [0.0–5.9]
Higgins et al, 2003 (34)	501/501 (100) [99.2–100]	2/490 (0.4) [0.1–1.5]	22/448 (4.9) [3.1–7.3]	NR	31/448 (6.92) [4.8–9.7]	5/443 (1.1) [0.4–2.6]
MIRACLE ICD, 2003 (35)	379/429 (88.34) [84.92–91.22]	NR	25/364 (6.87) [4.49–9.97]	NR	46/364 (12.64) [9.4–16.5]	2/364 (0.6) [0.1–2.0]
COMPANION, 2004 (37)	1158/1294 (89.49) [87.69–91.11]	5/1294 (0.39) [0.13–0.90]	22/1212 (1.82) [1.14–2.74]	NR	NR	NR
MIRACLE ICD II, 2004 (36)	191/210 (91.0) [86.2–94.5]	1/191 (0.5) [0.0–2.9]	7/210 (3.3) [1.4–6.8]	4/191 (2.1) [0.6–5.3]	28/210 (13.3) [9.1–18.7]	NR
CARE-HF, 2005 (38)	390/409 (95.4) [92.8–97.2]	2/409 (0.49) [0.1–1.8]	24/409 (5.9) [3.8–8.6]	NR	24/409 (5.9) [3.8–8.6]	3/409 (0.7) [0.2–2.1]
RHYTHM ICD, 2005 (29)	183/205 (89.3) [84.2–93.2]	5/205 (2.4) [0.8–5.6]	33/205 (16.1) [11.4–21.9]	20/205 (9.8) [6.1–14.7]	22/205 (10.7) [6.9–15.8]	1/205 (0.49) [0.01–2.69]
VecTOR, 2005 (28)	120/144 (83.3) [76.2–89.0]	NR	NR	11/120 (9.17) [4.67–15.81]	8/120 (6.67) [2.92–12.71]	NR
BELIEVE, 2006 (22)	NR	NR	NR	NR	NR	NR
HOBIPACE, 2006 (39)	NR	NR	NR	1/30 (3.3) [0.1–17.2]	2/30 (6.7) [0.8–22.1]	NR
DECREASE-HF, 2007 (25)	342/358 (95.5) [92.8–97.4]	3/342 (0.9) [0.2–2.5]	NR	NR	NR	NR
RD-CHF, 2007 (40)	46/56 (82.1) [69.6–91.1]	NR	NR	1/44 (2.3) [1.0–12.0]	4/56 (7.1) [2.0–17.3]	3/44 (6.8) [1.4–18.7]
RethinQ, 2007 (21)	246/250 (98.4) [96.0–99.6]	2/250 (0.8) [0.1–2.9]	5/172 (2.9) [1.0–6.7]	2/172 (1.2) [0.1–4.1]	13/172 (7.6) [4.1–12.6]	6/172 (3.5) [1.3–7.4]
Piepoli et al, 2008 (24)	44/44 (100) [92.0–100]	NR	NR	1/44 (2.3) [0.1–12.0]	1/44 (2.27) [0.06–12.02]	NR
REVERSE, 2008 (11)	621/642 (96.7) [95.0–98.0]	NR	13/642 (2.0) [1.1–3.4]	1/642 (0.2) [0.0–0.9]	66/642 (10.3) [8.0–12.9]	NR
MADIT-CRT, 2009 (12)	1790/1820 (98.4) [97.7–98.9]	1/1820 (0.1) [0.0–0.3]	30/1820 (1.7) [1.1–2.3]	19/1820 (1.0) [0.6–1.6]	44/1820 (2.4) [1.8–3.3]	17/1820 (0.9) [0.6–1.5]
B-LEFT HF, 2010 (17)	180/186 (96.8) [93.1–98.8]	1/180 (0.6) [0.0–3.1]	NR	11/180 (6.1) [3.1–10.7]	35/180 (19.4) [13.9–26.0]	NR
COMBAT, 2010 (23)	64/68 (94.1) [85.6–98.4]	NR	NR	NR	2/60 (3.3) [0.4–11.5]	1/60 (1.7) [0.0–8.9]
RAFT, 2010 (13)	841/894 (94.1) [92.3–95.5]¶	1/1798 (0.1) [0.0–0.3]	30/1798 (1.67) [1.1–2.4]	NR	81/1798 (4.5) [3.6–5.6]	37/1798 (2.1) [1.5–2.8]
Greater-EARTH, 2010 (27)	NA	NA	NA	NA	NA	NA
van Geldorp et al, 2010 (26)	38/40 (95) [83.1–99.4]	NR	1/38 (2.6) [0.1–13.8]	NR	2/38 (5.2) [0.6–17.8]	NR
Total	7901/8374 (94.4) [93.8–94.8]	24/7708 (0.3) [0.2–0.5]	257/8099 (3.2) [2.8–3.6]	75/3968 (1.9) [1.5–2.4]	453/7372 (6.2) [5.6–6.8]	83/5931 (1.4) [1.1–1.7]

NA = not available; NR = not reported.
* Percentages indicate simple pooled risk.
† For expansions of study names, see the Glossary.
‡ Includes coronary sinus dissection or perforation, pericardial effusion or tamponade, pneumothorax, and hemothorax.
§ Includes pacing threshold problems, sensitivity issues, and inappropriate shocks.
‖ Includes lead dislodgment or repositioning.
¶ Successful left ventricular lead implantation.