Technology Assessment

Technology Assessment Program

Use of Cardiac Resynchronization Therapy in the Medicare Population

March 24, 2015
Final Report

Prepared for:

Agency for Healthcare Research and Quality
540 Gaither Road
Rockville, Maryland 20850

Use of Cardiac Resynchronization Therapy in the Medicare Population

Technology Assessment Report

Project ID: CRDT1013

March 24, 2015

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None of the investigators has any affiliations or financial involvement related to the material presented in this report.

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Suggested citation: Rickard J, Michtalik H, Sharma R, Berger Z, Iyoha E, Green AR, Haq N, Robinson KA. Use of Cardiac Resynchronization Therapy in the Medicare Population. (Prepared by the Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA 290-201-200007-1) Rockville, MD: Agency for Healthcare Research and Quality. March 24, 2015.

Acknowledgments

We would like to thank Allen Zhang and Elisabeth Haberl Nannes for their assistance in data abstraction, Lisa Wilson for conducting meta-analysis and Eric Vohr for copy editing. We would also like to thank the Peer Reviewers, the Task Order Officers, and representatives from CMS.

Peer Reviewers

We wish to acknowledge individuals listed below for their review of this report. This report was reviewed in draft form by individuals chosen for their expertise and diverse perspectives. The purpose of the review was to provide candid, objective, and critical comments for consideration by the EPC in preparation of the final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

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Structured Abstract

Objectives: To assess the benefits and harms of cardiac resynchronization with (CRT-D) and compared to an ICD alone, CRT without a defibrillator (CRT-P) compared with optimal medical therapy and CRT-D compared with CRT-P in patients with an EF ≤35% and a QRS duration ≥120 ms. We also sought to assess predictors of response to CRT-D and CRT-P.

Data Sources: We searched MEDLINE, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 1995, as this is the date of first article reporting use of CRT through October 20th, 2014.

Review Methods: Paired investigators independently screened search results to assess eligibility. Investigators abstracted data sequentially and assessed risk of bias independently. Investigators graded the strength of evidence as a group.

Results: CRT-D was found to be effective in reducing heart failure hospitalizations, inducing ventricular reverse remodeling, improving quality of life, and increasing six-minute hall walk distances compared to an ICD alone with a high strength of evidence. In a meta-analysis of minimally symptomatic patients, CRT-D reduced LVESV (ml) (mean difference -22.55, 95% CI -40.66 to -9.56). This analysis was comprised primarily on NYHA class II patients; therefore, the applicability to NYHA class I patients is unclear. In a meta-analysis of patients with advanced heart failure (NYHA class III-IV), CRT-D improved quality of life scores (as measured by the Minnesota Living with Heart Failure Questionnaire) (mean difference -10.91, 95% CI -12.03 to -7.27) compared to an ICD alone. CRT-P was found to be effective in improving all-cause survival and reducing heart failure hospitalizations compared to optimal medal therapy alone with a moderate level of evidence. CRT-P was also found to induce reverse ventricular remodeling and increase six-minute hall walk distances compared to optimal medical therapy alone. These findings were primarily noted in NYHA class III-IV patients. The applicability of these findings to NYHA class I-II patients is unclear. Determining predictors of response to CRT was limited by the likely presence of reporting bias. Nevertheless, a left bundle branch (LBBB) morphology, non-ischemic cardiomyopathy (NICM), and female gender were generally associated with improved outcomes following CRT-D. Sinus rhythm (as compared to atrial fibrillation) and a wider QRS duration were associated with improved outcomes following CRT-D albeit with a lower strength of evidence. There is insufficient evidence to determine predictors of outcomes in patients undergoing CRT-P. There is insufficient evidence to determine the effectiveness of CRT-D versus CRT-P. Compared to CRT-P, device infection was slightly more common in patients receiving CRT-D.

Conclusions: There is convincing evidence that CRT-D is effective with regard to improvements in multiple clinical outcomes compared to an ICD alone in patients with an LVEF≤35% and a QRS duration ≥120ms. Similarly, there is convincing evidence that CRT-P is effective in improving multiple clinical endpoints compared to optimal medical therapy alone in the same population. The certainty of these findings varies based on NYHA class. Female gender, LBBB, a wider QRS duration, sinus rhythm, and non-ischemic cardiomyopathy are associated with improved outcomes following CRT although the likely presence of reporting bias qualifies these results. More data are needed for several questions including the efficacy of CRT in patients with a non-LBBB morphology or atrial fibrillation and the comparison of outcomes in patients receiving a CRT-D vs. CRT-P device.

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Executive Summary

Background

Chronic heart failure (CHF) is a major public health problem in the United States affecting an estimated 4.9 million Americans, causing high rates of hospitalization, poor quality of life, and 300,000 deaths each year.[1]

Cardiac resynchronization (CRT) is a pacing modality utilizing a left ventricular (LV) pacing lead with the goal of re-synchronizing myocardial contraction in patients with CHF. CRT was originally indicated in patients with significant LV dysfunction, defined as a left ventricular ejection fraction (LVEF) ≤ 35%, New York Heart Association (NYHA) class III-IV heart failure symptoms, and a QRS duration ≥120ms on optimal medical therapy.[2-4]More recently, the indications for CRT expanded to include patients with minimally symptomatic heart failure (NYHA class II).[5,6] The appropriateness of CRT in patients with NYHA class I symptoms is unclear.[1] The vast majority of candidates for CRT devices also have an indication for an implantable cardiac defibrillator (ICD), therefore, the large majority of patients receiving CRT in the United States receive a CRT device with a defibrillator (CRT-D) as opposed to a CRT pacemaker (CRT-P). CRT-P devices are occasionally placed in patients who wish to avoid ICD shocks or in patients with an indication for frequent ventricular pacing due to conduction disease who have an LVEF between 36-50 percent.

Scope and Key Questions

We conducted a systematic review on the efficacy for both CRT-D and CRT-P. The questions were nominated by the Centers for Medicare and Medicaid (CMS).We sought to address the following questions for patients with an LVEF ≤35% and a QRS duration≥120ms:

- What is the effectiveness and safety of CRT-D compared to an ICD alone?
- What is the effectiveness and safety of CRT-P compared to optimal medical therapy alone?
- What is the comparative effectiveness and safety of CRT-D versus CRT-P?
- What are the clinical predictors of response in patients deemed appropriate candidates for CRT-D devices?
- What are the clinical predictors of response in patients deemed appropriate candidates for CRT-P devices?

Methods

With input from key informants, we refined the questions, including eligibility criteria, and developed a protocol (PROSPERO registration CRD42014009981).

We searched MEDLINE, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 1995, as this is the date of first article reporting use of CRT through October 20th, 2014. We also reviewed the reference lists of all included articles, requested information from device manufacturers and searched Clinicaltrials.gov.

Citations were screened independently by two reviewers using predefined eligibility criteria. One reviewer completed data abstraction and a second reviewer checked abstraction for completeness and accuracy. Data when available by subgroups (females, QRS duration >150 ms, left bundle branch block, atrial fibrillation and non-ischemic cardiac conditions) were also abstracted. Two reviewers independently assessed risk of bias for individual studies. We used the Cochrane Collaboration's tool for assessing the risk of bias of controlled studies.[7] For nonrandomized studies, we used the Newcastle Ottawa Scale [8] and for predictor studies, we used Quality In Prognosis Studies (QUIPS) tool.[9] Differences between reviewers were resolved through consensus.

All studies were summarized qualitatively. We conducted meta-analyses for an outcome when there were sufficient data (at least 3 studies of the same design) and studies were sufficiently homogenous with respect to key variables (population characteristics, intervention, and outcome measurement) using profile likelihood estimate for random effects model. We identified substantial statistical heterogeneity in the trials as an I-squared statistic with a value greater than 50 percent. All meta-analyses were conducted using STATA 12.1 (College Station, TX).

We graded the strength of evidence using the scheme recommended by the AHRQ EPC Methods Guide for Conducting Comparative Effectiveness Reviews.[10] For this report, we graded the strength of evidence for the outcomes we classified during protocol development as the most important or critical outcomes, including quality of life as assessed by the Minnesota Living with Heart Failure Inventory Score (MLHFQ), left ventricular end systolic volume, hospitalizations for heart failure and, all- cause mortality.

Results

We included 60 studies, reported in 86 articles (see Figure A).

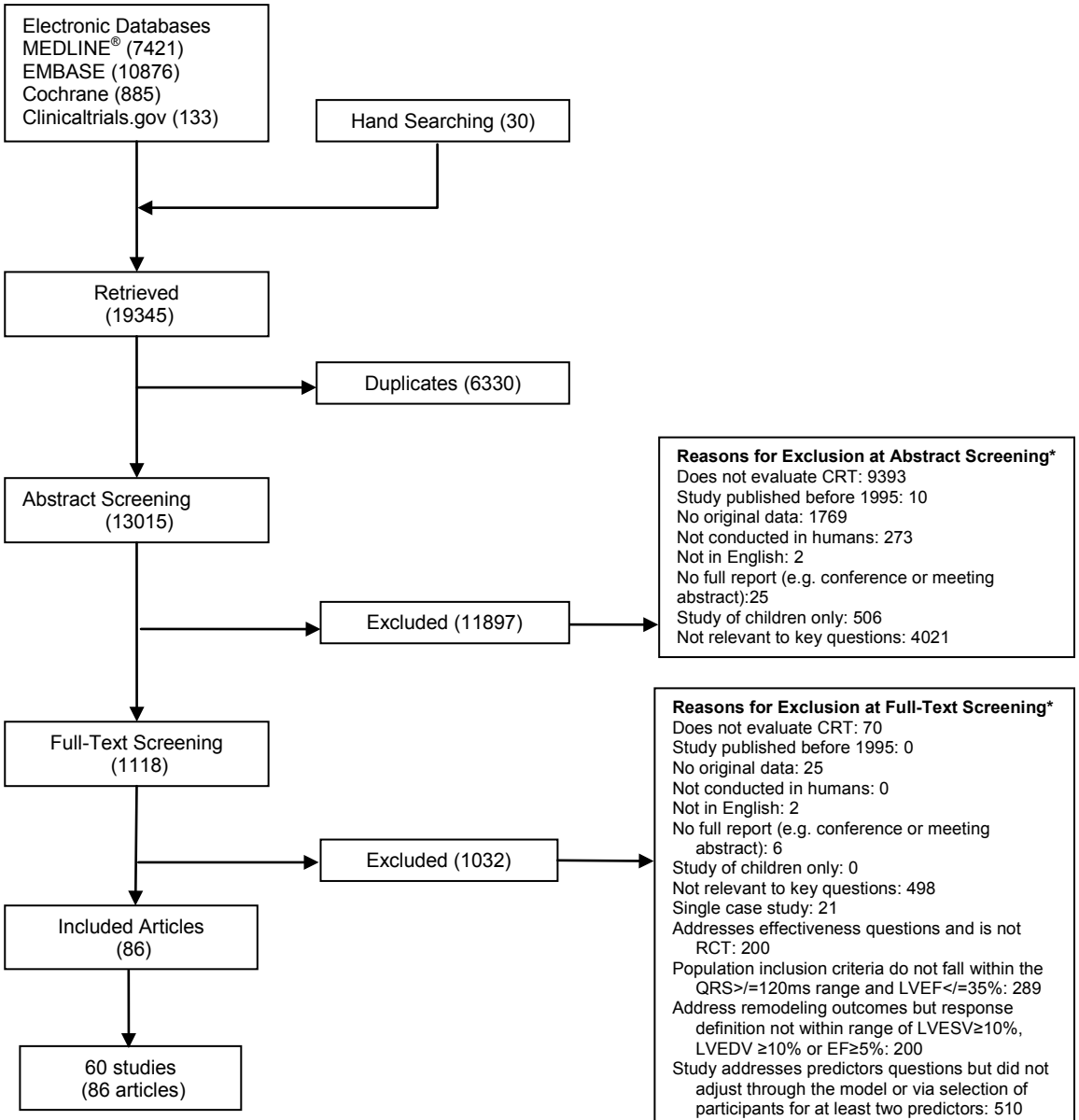
Eight trials assessed the effectiveness of CRT-D with 7 providing data about all-cause mortality. We found moderate evidence of a benefit with CRT-D compared with ICD alone for survival in minimally symptomatic patients. There is insufficient evidence about the effect of CRT-D on all-cause mortality in patients with NYHA III-IV. CRT-D was noted to reduce heart failure hospitalizations, an effect seen primarily in patients with left bundle branch block (LBBB) morphology (6 trials; n=4736; high strength of evidence). There was also a high strength of evidence for CRT-D inducing ventricular reverse remodeling compared to ICD alone (5 trials; n=2936). A meta-analysis of three trials found a mean difference in mean change from baseline in left ventricular end systolic volume (LVESV) of -22.55 favoring CRT-D (95% CI -40.66 to -9.56). Quality of life, as measured by MLHFQ, was not different for minimally symptomatic patients (NYHA I-II) (-0.83 95% CI -9.27 to 5.30) but showed improvement with CRT-D compared to ICD alone in those with NYHA class III-IV symptoms (-10.37 95% CI -12.95 to -7.27) (high strength of evidence). CRT-D also increased six-minute hall walk distances compared to an ICD alone and improved clinical composite score. The prevalence of harms associated with CRT-D devices were as follows: cardiac perforation/tamponade (0.1-1.4%), pocket hematoma (0.9-2.8%), pneumothorax (1.3-2.8%), device infection (0.9-2.8%), and lead dislodgement (2.4% to 9.8%). No conclusions could be drawn about the association between CRT-D implant and subsequent ventricular arrhythmias or inappropriate shocks.

We identified six trials, which assessed the efficacy of cardiac resynchronization therapy with a pacemaker (CRT-P) compared to optimal medical therapy alone (OMT). Three trials with longer followup showed improved survival (all-cause mortality) with CRT-P but those with shorter duration did not find an effect (moderate strength of evidence).There was moderate strength of evidence that CRT-P reduced heart failure hospitalizations and low strength of evidence that CRT-P, compared with OMT, induced ventricular reverse remodeling. Evidence about MLHFQ was insufficient to draw conclusions, and the effect of CRT-P on six-minute hall walk distances compared to optimal medical alone was similarly unclear. Harms associated with CRT-P were as follows: cardiac perforation/tamponade (0-1.6%), pocket hematoma (0.2-9.5%), pneumothorax (0.5-1.5%), device infection (0.7-4.8%), and lead dislodgement (1.7-17%).

Determining predictors of response to CRT was limited by the likely presence of reporting bias. Nevertheless, a left bundle branch block (LBBB) morphology, non-ischemic cardiomyopathy (NICM), and female gender were generally associated with improved outcomes following CRT-D. Sinus rhythm (as compared to atrial fibrillation) and a wider QRS duration were associated with improved outcomes following CRT-D albeit with a lower strength of evidence. There is insufficient evidence to determine predictors of outcomes in patients undergoing CRT-P. However, of the outcomes that were assessed, the ICD function would impact only the mortality endpoint. Therefore similar conclusions as to those noted for CRT-D can be drawn for CRT-P devices for the other, non-mortality endpoints.

The availability of only one trial, with methodological limitations, means that there is insufficient evidence to determine the effectiveness of CRT-D vs. CRT-P. Compared to CRT-P, device infection was slightly more common in patients receiving CRT-D. There was insufficient evidence to draw conclusions on any other harms comparing the two devices.

Figure A. Summary of the literature search and screen



* Total number of reasons for exclusion exceeds the number of citations excluded, because citations could be excluded for more than one reason

Discussion

Key Findings and the Strength of Evidence

Efficacy and Safety of CRT-D (KQ1a, KQ2)

There is convincing evidence that CRT-D devices are effective in reducing heart failure symptoms, improving myocardial function, and reducing hospitalizations for heart failure in patients with an LVEF≤35% and a QRS duration ≥120 ms compared to therapy with an ICD alone. Specifically, we found moderate strength of evidence for benefit of CRT-D versus ICD alone for all-cause mortality in minimally symptomatic patients. This statement is derived from data looking primarily at NYHA class II patients. The applicability of this finding to NYHA class I patients, a population significantly under-represented in studies, is unclear. There is insufficient evidence to determine whether CRT-D devices are effective in improving survival compared to an ICD alone in an advanced heart failure population (NYHA III-IV).

In terms of pre-specified subgroups, there is generally strong evidence that in CRT-D patients (compared to an ICD alone), female gender, a left bundle branch block, and non-ischemic cardiomyopathy are associated with superior outcomes. Sinus rhythm (as opposed to a history of atrial fibrillation) and a wider QRS complex and also associated with superior outcomes in patients undergoing CRT-D implant compared to an ICD alone although the data for this are less compelling. (Table A.)

Efficacy and Safety of CRT-P (KQ3a, KQ4)

There is moderate evidence that CRT-P, compared to optimal medical therapy, is effective in improving survival, reducing LVESV, and reducing hospitalizations for heart failure in patients with an LVEF≤35% and a QRS duration ≥120 ms compared to optimal medical therapy alone**.** These data are largely derived from patients with NYHA class III-IV heart failure. The applicability of these findings to patient with NYHA class I-II heart failure is unclear. We found insufficient evidence about the effect of CRT-P on quality of life, as measured with the MLHFQ, compared to optimal medical therapy alone.

Efficacy and Safety of CRT-D versus CRT-P (KQ5, KQ6)

Only one included trial contained both CRT-D and CRT-P arms, and direct comparisons between those arms were lacking. Therefore, there is insufficient evidence to determine the effectiveness of CRT-D compared to CRT-P. In comparing harms between CRT-D and CRT-P devices, there was also insufficient evidence to draw any conclusions except for device infections, which appear to be slightly more common for CRT-D devices.

Predictors of Response: CRT-D and CRT-P (KQ1b, KQ3b)

The evidence regarding predictors of a favorable response following CRT varied considerably based on outcome. In addition, the high likelihood of reporting bias qualifies these results. Age was not an important predictor of outcomes in patients receiving CRT-D devices. However, data for very elderly patients (> 75 years of age) were limited. Non-ischemic cardiomyopathy, female gender, and a left bundle branch block morphology were strongly associated with improved outcomes. A history of atrial fibrillation and a narrower QRS duration were predictive of poorer outcomes although the evidence for this was less robust. There was inadequate evidence to determine the predictive nature of chronic kidney disease, left atrial volume, baseline LVEF, body mass index, and left ventricular end-diastolic volume on outcomes following CRT-D implant. There was also insufficient evidence to draw conclusions as to the predictive nature of baseline characteristics in patients receiving a CRT-P device. However, of

the outcomes that were assessed, the ICD function would impact only the mortality endpoint. Therefore similar conclusions as to those noted for CRT-D can likely be drawn for CRT-P devices for the other, non-mortality endpoints.

Table A. Summary of the strength of evidence for key effectiveness outcomes

Comparisons	All-cause mortality	Hospitalizations for heart failure	Left ventricular end systolic volume (or index)	Minnesota Living with Heart Failure Questionnaire
Cardiac resynchronization therapy with defibrillator vs. ICD alone	Moderate In patients with minimally symptomatic CHF (primarily class NYHA class II), data from the RAFT trial (a larger, slightly more symptomatic population, with a longer followup) demonstrates a mortality benefit, The MADIT-CRT trial did not report a mortality benefit with CRT-D in primarily NYHA class II patients. Long-term followup of a subset of patients demonstrated a mortality benefit in patients with LBBB but not with a non-LBBB and did not report a mortality comparison for the group as a whole. The other trials assessing mortality in minimally symptomatic patients were either too small in size or followup to add significant additional evidence. The trials assessing mortality in patients with NYHA class III-IV symptoms were limited in terms of followup and size, therefore there is insufficient evidence to determine the effect of CRT-D on mortality compared to an ICD alone.	High The large RAFT and MADIT-CRT trials showed a reduction in CHF events for CRT-D compared to an ICD alone. Subgroup analyses from both trials demonstrate the effect to be primarily in patients with LBBB morphology.	High The trials were consistent in demonstrating a reduction in LVESV with CRT-D compared to an ICD alone. Meta-analysis of trials in patients with NYHA I-II (primarily NYHA class II patients), mean difference -22.55 (95% CI, -40.66 to -9.56).	High The current data suggest that CRT-D does not improve QOL in minimally symptomatic patients compared to an ICD alone. The data does suggest a significant improvement in QOL in patients with NYHA class III-IV CHF (mean difference -10.91 (95% CI -12.03 to 7.27).
Cardiac resynchronization therapy with pacemaker vs. optimal medical therapy	Moderate Studies showed statistically significant differences in mortality favoring CRT-P.	Moderate Studies showed fewer hospitalizations in the CRT-P group	Low CRT-P significantly reduced LVESV compared with optimal medical therapy alone.	Insufficient
Cardiac resynchronization therapy with pacemaker or with defibrillator	Insufficient	Low Compared with optimal medical therapy, CRT-P and CRT-D were associated with 44% and 41% reduction in heart failure hospitalizations (not significantly different).	Insufficient	Insufficient

Relationship of Findings to Existing Literature

Our current review differs from prior reviews in that only studies with patients with an LVEF≤35% and a baseline QRS duration≥120 ms undergoing biventricular pacing were included. These criteria were developed in consultation with our key informants and largely mirror the current appropriate use criteria for CRT from United States guidelines.[1] This eliminated the REVERSE, BLOCK CHF, and HOBIPACE trials which included patients with an LVEF>35%.[11-13] The criteria also excluded all trials looking at the effects of CRT in a narrow QRS duration population,[14-16] and studies of LV only pacing.[17,18] We considered the appropriate control for the CRT-D effectiveness question to be an ICD alone given the compelling data demonstrating improvements in mortality with an ICD that evolved concomitantly with studies of CRT effectiveness. We considered the appropriate control for CRT-P to be optimal medical therapy alone to assess the impact of cardiac resynchronization. We did not assess the comparison of CRT-D to optimal medical therapy as we determined this to be an inappropriate comparison, given the known improvements in mortality by defibrillation. Also, in contrast to several previous reviews, we included only RCTs to assess the questions regarding effectiveness.

In terms of minimally symptomatic patients, the results of our review largely agree with those of prior reviews, which focused on the same population. Similarly, the current review is in agreement with the systematic review performed in 2007 by Mcallister et al., which included studies primarily involving an advanced heart failure population.[19] Our review arrived at somewhat different conclusions in terms of the efficacy of CRT-D vs. CRT-P compared to that by Jiang et. al.[20] Given that we considered only RCTs for determination of effectiveness, only the COMPANION trial was included in our review, which likely explains the discrepancy in conclusions.[3]

In our systematic analysis of predictors of outcomes following CRT, many studies assessing the capacity for baseline characteristics to predict responses (defined in many different ways) were identified. The large majority of studies were small (<100 patients) and not properly controlled. At a minimum, we pre-specified that a cohort study addressing our questions about predictors of response to CRT had to include at least gender and either QRS duration or morphology in a multivariate model to address confounding factors. Such criteria eliminated many studies. Despite this, the positive predictive effect noted with LBBB, female gender, non-ischemic cardiomyopathy, a wider QRS duration, and normal sinus rhythm on multiple outcomes was supportive of the similar findings noted from the pre-specified subgroup analyses of the RCTs. There are other potential predictors we did not consider (e.g. lead position). Given the large number of potential predictors in the literature, a review of all predictors was not practical. Our predictors were chosen based on prevailing knowledge of the most important predictors, identified in consultation with our key informants.

Finally, we did not conduct individual patient data meta-analysis to assess predictors meaning that our analyses may suggest that clinically relevant subgroup effects exist, but we are unable to quantify the effects reliably or precisely.

Applicability

The generalizability of these results is slightly limited. Race was reported very infrequently, prohibiting an assessment of applicability based on racial differences. The majority of patients included in the RCTs were male, although a large focus in sub-studies has been given to the role of CRT in women, given the heightened response to therapy seen in this population. The average age in the RCTs and cohort studies was in the mid 60s although many patients included were in

the age range of the elderly Medicare population. There has not been an RCT that specifically enrolled Medicare eligible patients. Also, data for very elderly patients (> 75 years of age) are limited. In cohort studies and subgroup analyses from the RCTs, age was not found to be an important predictor of outcomes. Taken together, the results of our review are generalizable to the Medicare population although given the absence of dedicated RCTs, a definitive statement of generalizability to this population is not possible.

Limitations of the Comparative Effectiveness Review Process

In addressing the questions of efficacy of CRT-D and CRT-P, several studies potentially of interest were excluded since they were non-randomized. For the questions about the predictors of response to CRT, many retrospective cohort studies were excluded because of a mixed population of CRT-D and CRT-P devices. Attempts were made to contact the authors of such studies to obtain the device-specific data but, in many cases, this was unsuccessful. In addition, many cohorts that contained outcomes of interest were excluded due to failure to control for gender and QRS duration and/or morphology, important baseline confounders. Finally, we did not include prior or conduct new individual patient data meta-analyses to assess predictors. Therefore, our analyses may suggest that clinically relevant subgroup effects exist, but we are unable to quantify the effects reliably or precisely.

Limitations of the Evidence Base

Multiple, well-conducted RCTs were identified addressing the questions about the efficacy of CRT-D and CRT-P. The majority of patients enrolled in the clinical trials had NYHA class II-IV heart failure symptoms. The applicability of the current findings to class I patients is less clear. In contrast, only the COMPANION trial contained both CRT-D and CRT-P arms.[3] However, a direct comparison of the CRT-D to CRT-P arms was not reported for several outcomes. For the questions examining predictors of response to CRT many of the included cohort studies were relatively small. While all studies controlled for gender and either QRS duration or morphology based on our pre-specified inclusion criteria, the remaining variables in the model varied widely between studies. Similarly, many studies used statistical criteria to create their multivariate adjustments, rather than pre-specifying clinical factors known to be important.

Research Gaps

There is convincing evidence that CRT-D results in reverse ventricular remodeling and improvements in quality of life compared to an ICD alone. However, only two trials showed a mortality benefit of CRT-D over ICD alone. The RAFT trial primarily contained patients with NYHA class II symptoms.[6] Long term follow up of the MADIT-CRT trial suggested a mortality benefit in the LBBB subgroup alone but did not report mortality for the cohort as a whole.[21] Whether CRT-D results in improved survival compared to an ICD alone in patients with advanced heart failure is unclear.

Several subgroup analyses from RCTs as well as cohort studies demonstrate superior outcomes in patients with a native LBBB compared to a non-LBBB. Subgroup analysis from the MADIT-CRT trial suggested possible harm for CRT-D versus an ICD alone in non-LBBB patients.[5,21] Subgroup analyses from other RCTs suggested little benefit of CRT in non-LBBB patients (but no convincing trend towards harm).[6] One important issue with the assessment of CRT efficacy according to QRS morphology is the interaction between QRS duration, another

variable with impact on outcome, and morphology. Patients with a LBBB tend to have wider QRS durations than patients with non-LBBBs. Several retrospective studies have attempted to determine the relative impact on outcomes of QRS duration within various QRS morphology groups in patients receiving a CRT device with mixed results.[22,23] There has not been an RCT, which compares CRT to a control in patients with a non-LBBB morphology. Given the lack of such a trial, the ability to conclude definitively that CRT is ineffective or, in fact harmful, in patients with non-LBBB morphology is limited.

Similarly, subgroup analyses from RCTs suggest limited benefit of CRT in patients with atrial fibrillation. Outside the small MUSTIC-AF study, data focused on the AF population are lacking.[24] Therefore, the ability to definitively conclude a lack of benefit in patients with AF receiving CRT is not possible.

The effectiveness of CRT-D versus CRT-P in patients with an LVEF≤35% has not been adequately addressed. The COMPANION trial, which included both arms, did not directly compare the CRT types and is therefore inadequate to answer this question definitively.[3]

Conclusion

We performed a systematic review to evaluate the efficacy and safety of CRT-D and CRT-P devices as well as predictors of outcomes following implant of such devices. There is convincing evidence that CRT-D is effective with regard to improvements in multiple outcomes compared to an ICD alone in patients with an LVEF≤35% and a QRS duration ≥120ms. These findings are based on patients primarily with NYHA class II-IV heart failure. The applicability of these findings to patients with NYHA class I symptoms is unclear. Similarly, there is convincing evidence that CRT-P is effective in improving multiple endpoints compared to optimal medical therapy alone in the same population. These data are primarily derived from NYHA class III-IV and the applicability to patients with NYHA class I and II is less clear. Female gender, LBBB, a widened QRS duration, sinus rhythm, and non-ischemic cardiomyopathy are associated with improved outcomes following CRT.

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Introduction

Chronic heart failure (CHF) is a major public health problem in the United States affecting an estimated 4.9 million Americans, with 550,000 new cases diagnosed annually.[1] CHF patients have high rates of hospitalization, poor quality of life, and account for 300,000 deaths in the United States each year.[1] The annual cost of CHF in 2010 was estimated at $39.2 billion or approximately 2 percent of the total United States healthcare budget.[2] Targeted interventions for this commonly encountered condition are needed, aimed at improving quality of life, reducing hospitalizations, and decreasing mortality.

Left ventricular (LV) activation delay, as approximated by widening of the QRS complex on a twelve lead electrocardiogram, is present in approximately one-quarter to one-third of heart failure patients. Such delay leads to inefficient myocardial hemodynamics, which may impair cardiac function further. Cardiac resynchronization (CRT) is a pacing modality utilizing an LV pacing lead with the goal of re-synchronizing myocardial contraction in patients with CHF, depressed systolic function, and significant LV activation delay. CRT is thought to produce a reduction in intraventricular dyssynchrony and more favorable hemodynamics by placement of a pacing lead, either endovascularly via a coronary sinus tributary, or epicardially with direct placement on the lateral LV wall via a thoracotomy. CRT was originally indicated in patients with significant LV dysfunction, defined as a left ventricular ejection fraction (LVEF) $\leq$ 35%, with New York Heart Association (NYHA) class III-IV heart failure symptoms, and with a QRS duration $\geq$120ms on optimal medical therapy.[3-5]More recently, the indications for CRT expanded to include patients with less advanced heart failure.[6,7] In addition, the most recent guidelines for CRT implantation have called to attention the importance of both QRS duration and morphology.[1]

Multiple large scale clinical trials have been conducted to assess the effects of CRT. Early trials of CRT compared CRT pacemakers with optimal medical therapy alone in patients with advanced CHF.[3,5,8]With the concomitant development of the implantable cardiac defibrillator (ICD), comparisons used in the large clinical trials changed to compare patients with ICDs with and without CRT.[6,7] Currently, the vast majority of candidates for CRT devices also have an indication for an ICD; therefore, the large majority of patients receiving CRT in the United States receive a CRT defibrillator (CRT-D) as opposed to a CRT pacemaker (CRT-P). CRT-P devices are occasionally placed in patients who wish to avoid ICD shocks (such as in the geriatric population who may be more interested in quality of life compared to life prolongation) or in patients with an indication for frequent right ventricular pacing due to conduction disease who have an LVEF between 36-50 percent.

The early trials of CRT focused on "softer" or more subjective endpoints including changes in quality of life scores, NYHA functional class, and six minute hall walk distances.[3,8] More objective or "harder" endpoints were included in subsequent studies including ventricular remodeling, myocardial oxygen consumption, CHF hospital admissions, and all-cause mortality.[4,7] CRT has been one of the most important therapeutics for the treatment of CHF over the past 20 years, but not every patient who meets the guideline criteria for CRT appears to respond to this therapy. While the percentage of "non-responders" to CRT fluctuates greatly primarily based on how one defines "response", it is generally estimated that between 30-40 percent of patients receiving CRT derive what may appear to be little benefit.[9] Prediction of response to CRT is an important goal in order to tailor this therapy to patients most apt to derive benefit.[9] In addition, the specter of patient harm in certain subgroups has been raised.[10]

The impact of bundle branch block morphology and duration on patient outcomes receiving CRT devices continues to be an important area of research.[11-13] The new 2013 United States guidelines for the implantation of CRT capable devices take both bundle branch block morphology and QRS duration into consideration in determining appropriateness for CRT device implantation.[14,15] It is not yet clear how these new guidelines may impact response rates, but any improvement is expected to be incremental, with the issue of non-responders not completely resolved. Not all potential causes of non-response were considered in the new guidelines.[16]

Scope and Key Questions

We conducted a systematic review on the efficacy for both CRT-D and CRT-P. The questions were nominated for the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) Program by the Centers for Medicare and Medicaid (CMS) and thus focus on the Medicare population. We developed analytic frameworks to illustrate the different questions and outcomes we considered (Figures 1, 2 and 3). We sought to address the following Key Questions (KQ):

KQ1a: Is cardiac resynchronization therapy with defibrillator (CRT-D) effective in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with an LVEF≤35% and a QRS duration≥120ms?

KQ1b: What are the clinical predictors of response in Medicare eligible patients who are deemed appropriate candidates for CRT-D devices?

KQ2: What are the adverse effects or complications associated with CRT-D implantation in the Medicare population?

KQ3a: Is cardiac resynchronization therapy in the absence of defibrillator capacity (CRT-P) effective in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with LVEF≤35% and a QRS duration≥120ms?

KQ3b: What are the clinical predictors of response in Medicare eligible patients who are deemed appropriate candidates for CRT-P devices?

KQ4: What are the adverse effects or complications associated with CRT-P implantation in the Medicare population?

KQ5: What is the effectiveness of CRT-D versus CRT-P in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with LVEF≤35% and a QRS duration≥120ms?

KQ6: What are the adverse effects or complications associated with CRT-D versus CRT-P implantation in the Medicare population?

Figure 1. Analytic framework for use of cardiac resynchronization therapy with defibrillator (CRT-D) in the Medicare population

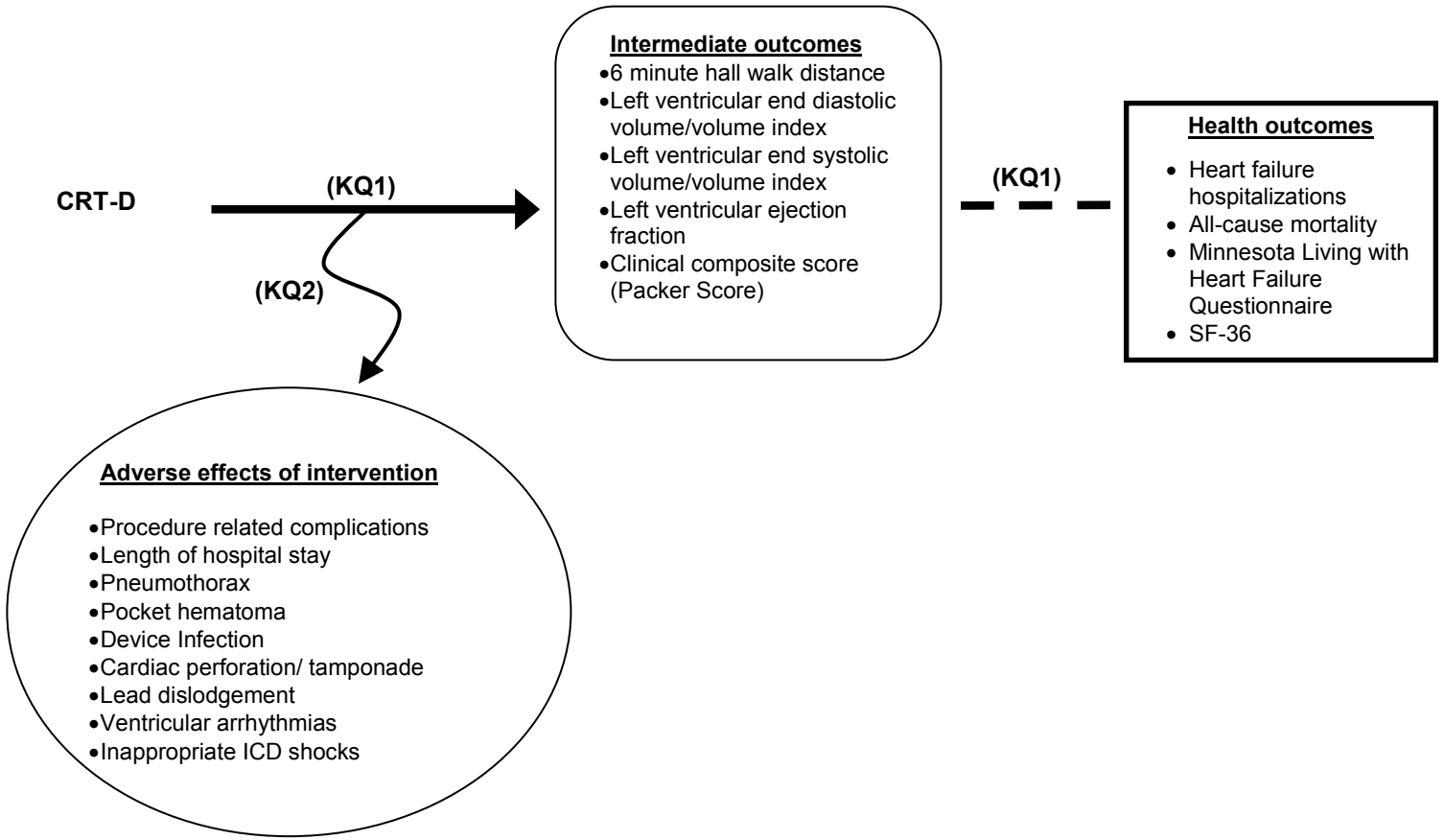


Figure 2. Analytic framework for use of cardiac resynchronization therapy without defibrillator capacity (CRT-P) in the Medicare population

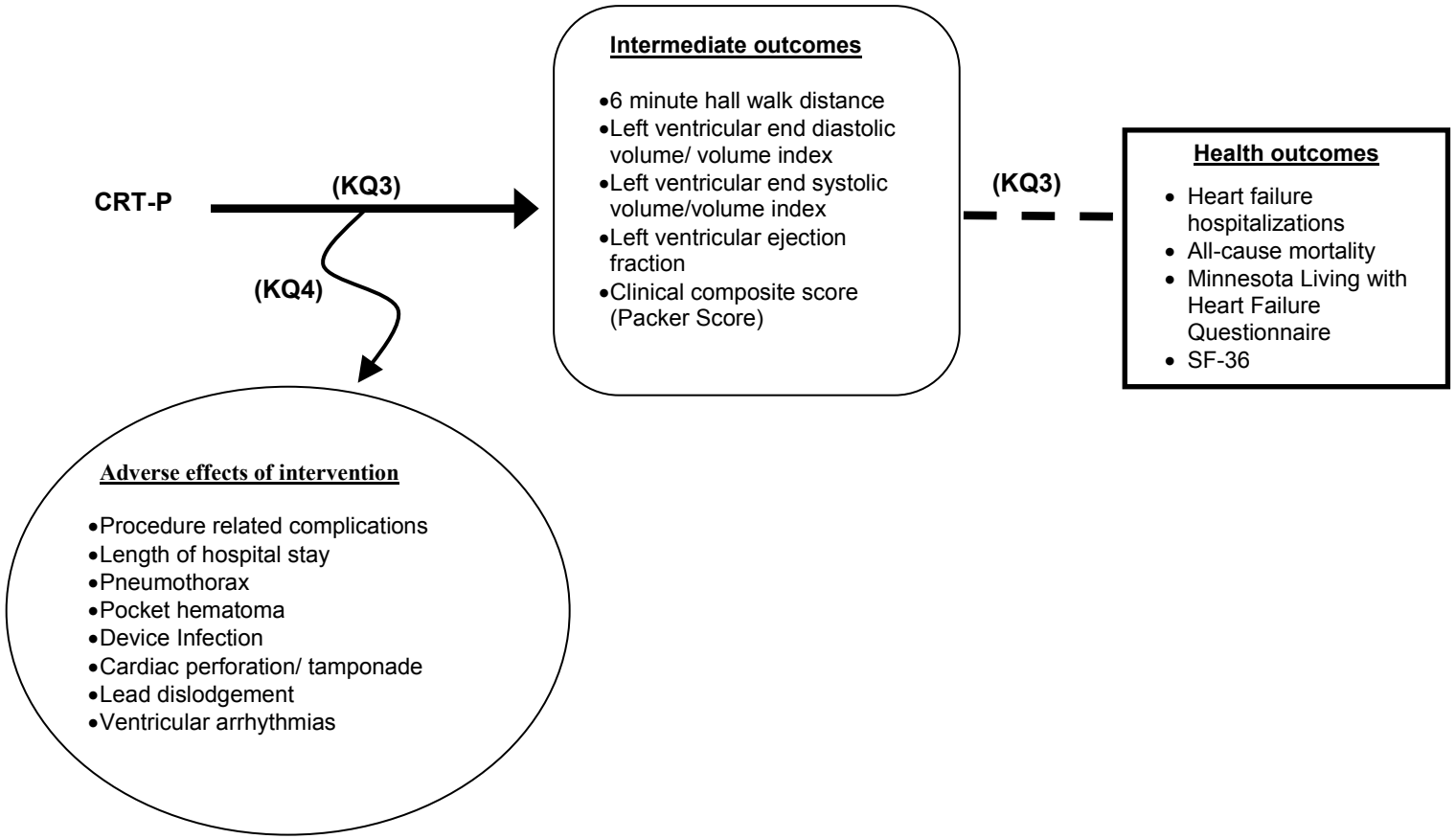
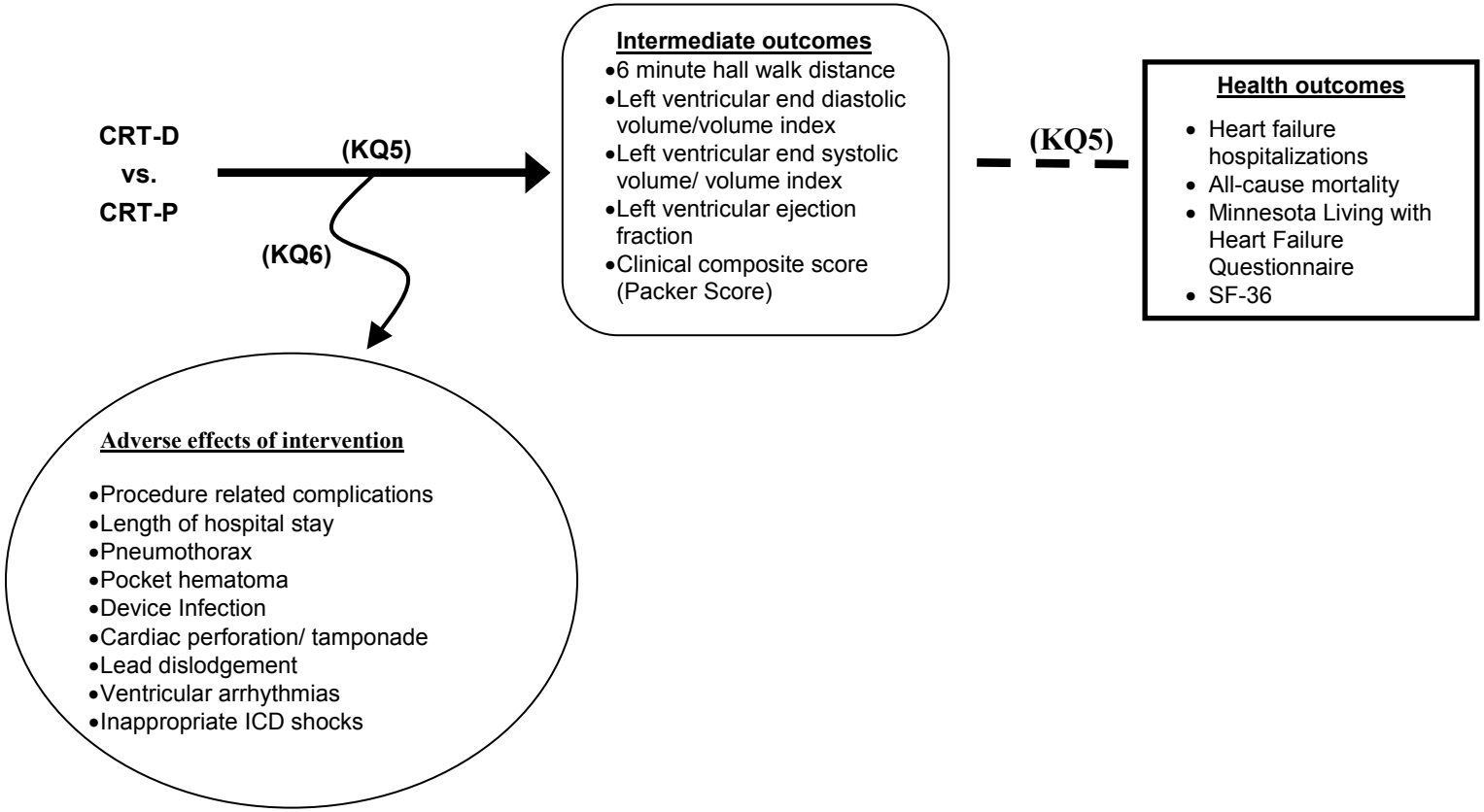


Figure 3. Analytic framework for use of cardiac resynchronization therapy with defibrillator capacity (CRT-D) versus cardiac resynchronization therapy without defibrillator capacity (CRT-P) in the Medicare population



Methods

The methods for this Technology Assessment follow the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[17]

Protocol Development

Representatives from the Coverage and Analysis Group at CMS posed the questions for this review. With feedback from these representatives, from AHRQ representatives and from our key informants, we refined these questions and developed a protocol for this systematic review. Our protocol was registered on PROSPERO (CRD42014009981).

Search Strategy

We searched MEDLINE, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 1995, as this is the date of first article reporting use of CRT through October 20th, 2014. We developed a search strategy based on medical subject headings (MeSH®) terms and text words of key articles (Appendix B). We also reviewed the reference lists of all included articles. In addition, we requested Scientific Information Packets from device manufacturers (Table 3). We had no language restrictions in the search strategies. Additionally, on January 22nd, 2015, we searched Clinicaltrials.gov to identify relevant registered trials.

Study Selection

Study selection was based on predefined eligibility criteria of patient populations, interventions, outcome measures, and study design (see Table 1 and 2). Abstracts were screened independently by two reviewers, and were excluded if both reviewers agreed that one or more of the exclusion criteria was met (see Appendix C Abstract Screen Form). Differences between reviewers regarding abstract eligibility were resolved through consensus. We used DistillerSR (Evidence Partners, 2010) to manage the screening process.

Citations promoted on the basis of the abstract screen underwent another independent screen using the full-text of the articles. Additional exclusion criteria were applied at this level (see Table 2 and Appendix C Article Screen Form). Differences regarding citation eligibility were resolved through consensus.

Data Abstraction and Data Management

We created and pilot tested data extraction forms in Excel (Microsoft, Redmond, WA) (Appendix C). Reviewers extracted information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, gender, race/ethnicity, etc.), eligibility criteria, interventions, outcome measures and the method of ascertainment, and the results of each outcome, including measures of variability. Data when available by subgroups (females, QRS duration >150 ms, left bundle branch block, atrial fibrillation and non-ischemic cardiac conditions) were also abstracted. For studies reporting patient data, including outcomes, undifferentiated as to CRT-D or CRT-P we contacted the authors for clarification and data (see Data Synthesis).

One reviewer completed data abstraction and a second reviewer checked the first reviewer's abstraction for completeness and accuracy. We resolved differences between reviewer pairs through discussion and, as needed, through consensus among our team.

Table 1. PICOTS (population, interventions, comparators, outcomes, timing, setting) for each Key Question

	Effectiveness **KQ1a: CRT-D** **KQ3a: CRT-P** **KQ5: CRT-D vs CRT-P**	**Harms** **KQ2: CRT-D** **KQ4: CRT-P** **KQ6: CRT-D vs CRT-P**	**Clinical predictors** **KQ1b: CRT-D** **KQ 2b: CRT-P**
Population	• Age ≥ 18 • Subjects with a left ventricular ejection fraction ≤35% and a QRS duration ≥120 ms.		
Interventions	• Cardiac resynchronization therapy with a defibrillator (CRT-D) • Cardiac resynchronization without a defibrillator (CRT-P)	• Cardiac resynchronization therapy with a defibrillator (CRT-D) • Cardiac resynchronization without a defibrillator (CRT-P)	• Cardiac resynchronization therapy with a defibrillator (CRT-D) • Cardiac resynchronization without a defibrillator (CRT-P)
Comparisons	• CRT-D: Implantable Cardioverter Defibrillator (ICD) • CRT-P: Optimal medical therapy • CRT-D versus CRT-P	• CRT-D: Implantable Cardioverter Defibrillator (ICD) • CRT-P: Optimal medical therapy • CRT-D versus CRT-P	• CRT-D: Implantable Cardioverter Defibrillator (ICD) • CRT-P: Optimal medical therapy
Outcomes	• 6 minute hall walk distance • Minnesota Living with Heart Failure Questionnaire • SF-36 • Left ventricular end systolic volume/volume index • Left ventricular end diastolic volume/volume index • Left ventricular ejection fraction • Clinical composite score (Packer Score) • Hospitalizations for heart failure • All- cause mortality	• Procedure related complications • Length of hospital stay • Pneumothorax • Pocket hematoma • Device Infection • Cardiac perforation/ tamponade • Lead dislodgement • Ventricular arrhythmias • Inappropriate ICD shocks (CRT-D only) • Death (within a week)	• Age • Gender • Cardiomyopathy subtype • History of atrial fibrillation • QRS duration • QRS morphology • Chronic kidney disease • Left atrial volume • Left ventricular ejection fraction • Body mass index • Baseline left ventricular end diastolic volume
Type of study	Randomized controlled trials	Any study design except case report	Any study design except case report
Timing and setting	CRT-D and CRT-P at 3-6 months, 1 year, and ≥2 year end-points KQ2,4 and 6 (harms) Outcomes (above) from CRT-D and CRT-P at any time point	Any time point	Any time point

Table 2. List of exclusion criteria at the abstract and article screening level

	Abstract screening level	Article screening level
Exclusion criteria	• Does not evaluate CRT • Study published before 1995 • No original data (systematic reviews, meta-analysis, editorial, commentary) • Not conducted in humans • Not in English • No full report (e.g. conference or meeting abstract) • Study of children only • Not relevant to key questions	• Does not evaluate CRT • Study published before 1995 • No original data (systematic reviews, meta-analysis, editorial, commentary) • Not conducted in humans • Not in English • No full report (e.g. conference or meeting abstract) • Study of children only • Not relevant to key questions.
Additional exclusion criteria at the article screening level		• Single case study • Addresses effectiveness questions (KQ1a, 3a, and 5) only and is not RCT • Population inclusion criteria do not fall within the QRS duration ≥120ms range and LVEF≤35% • Address remodeling outcomes but response definition not within range of LVESV≥10%, LVEDV ≥10% or EF≥5% • Study does not adjust via model or participant selection for at least 2 predictor of gender, QRS duration and/or morphology (LBB or not) and does not include at least 30 patients

Table 3. List of CRT device manufacturers

Manufacturer	Device
Boston Scientific	COGNIS® CRT-D
	ENERGEN™ CRT-D
	INCEPTA™ CRT-D
	PUNCTUA™ CRT-D
	INVIVE™ CRT-P
BIOTRONIK	Lumax 300 HF-T CRT-D
	Lumax 340 HF-T CRT-D
	Lumax 540 HF-T CRT-D
	Stratos LV-T CRT-P
	Evia HFT-T CRT-P
Medtronic	Viva™ XT CRT-D
	Viva™ S CRT-D
	Protecta® XT CRT-D
	Protecta® CRT-D
	Consulta® CRT-D
	Concerto® II CRT-D
	Maximo® II CRT-D
	InSync Sentry® CRT-D
	InSync II™ Marquis CRT-D
	InSync III® CRT-P
	Consulta® CRT-P
	Syncra™ CRT-P
St. Jude Medical	Promote™ Plus CRT-D
	Quadra Assura™ CRT-D
	Unify Assura™ CRT-D
	Unify Quadra™ CRT-D
	Unify™ CRT-D
	Anthem™ CRT-P
SORIN GROUP	PARADYM™ CRT
	Paradym™ RF SonR® CRT-D
	Paradym™ RF CRT-D

Risk of Bias Assessment

Two reviewers independently assessed risk of bias for individual studies. We used the Cochrane Collaboration's tool for assessing the risk of bias of controlled studies.[18] For nonrandomized studies, we used the Newcastle Ottawa Scale [19] and for predictor studies, we used Quality In Prognosis Studies (QUIPS) tool.[20] Differences between reviewers were resolved through consensus.

Data Synthesis

For each key question, we created a detailed set of evidence tables containing all information abstracted from eligible studies. We followed these steps for studies which reported data for both devices (CRT-D and CRT-P) in one arm or group or for which the type of device was unclear:

1. If the type of device is not specified, we contacted the study authors to request information about type of device.
2. If the number of patients receiving each device is not specified, we contacted the study authors to request information about the number of patients receiving each device.
3. If the number of patients receiving each device is not specified, and the outcomes are not presented separately, we contacted the study author to request device-specific outcome data.
4. If the number of patients receiving each device is specified, but the outcomes are not presented separately, we attributed the reported outcomes to the device received by ≥ 90 percent of the patients.
5. If the number of patients receiving each device is specified and the outcomes are not presented separately and no more than 90 percent of the patients received any one type of device or all devices were received by an equal number of patients, we contacted the study authors to request device-specific outcome data.

All studies were summarized qualitatively. We conducted meta-analyses for an outcome when there were sufficient data (at least 3 studies of the same design) and studies were sufficiently homogenous with respect to key variables (population characteristics, intervention, and outcome measurement) using profile likelihood estimate for random effects model. We identified substantial statistical heterogeneity in the trials as an I-squared statistic with a value greater than 50 percent. We planned to assess publication bias using Begg's and Eggers tests (with alpha of 0.10) including evaluation of the asymmetry of funnel plots for each comparison of interest for the outcomes where meta-analyses are conducted. Criteria for testing for funnel plot asymmetry was at least 10 studies of unequal sizes contributing quantitative data for which there is no apparent relationship between study size and between study clinical or methodological diversity. All meta-analyses were conducted using STATA 12.1 (College Station, TX).

Strength of the Body of Evidence

We graded the strength of evidence using the scheme recommended by the AHRQ EPC Methods Guide for Conducting Comparative Effectiveness Reviews.[21] For this report, we graded the strength of evidence for the outcomes we classified during protocol development as the most important or critical outcomes, including quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire, left ventricular end systolic volume, hospitalizations for heart failure and, all- cause mortality. We considered five domains: study limitations, directness,

consistency, precision, and reporting bias. We classified evidence pertaining to the KQs into four basic categories: 1) "high" grade; 2) "moderate" grade; 3) "low" grade; and 4) "insufficient" grade (Table 4).

Investigators writing each section completed the strength of evidence grading. The team members reviewed grading and discussed the process they used to grade the evidence throughout the report writing process.

Table 4. Strength of evidence grades and definitions

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding judgment.

Applicability

Applicability was assessed separately for the different outcomes for the entire body of evidence guided by the PICOS framework as recommended in the Methods Guide for Comparative Effectiveness Reviews of Interventions.[17] We considered important population characteristics (e.g., gender, race, ethnicity), comorbidities (e.g. atrial fibrillation, bundle branch pathologies), and intervention (e.g. therapy, co-intervention) that may cause heterogeneity of treatment effects and effect generalizability of the findings.

Peer Review and Public Comment

The draft report was peer reviewed and posted for public comment from November 27th, 2014, through December 11th, 2014. Comments received from invited reviewers and through the public comment website were compiled and addressed. A disposition of comments will be posted on the AHRQ Web site 3 months after the release of the final technology assessment.

Results

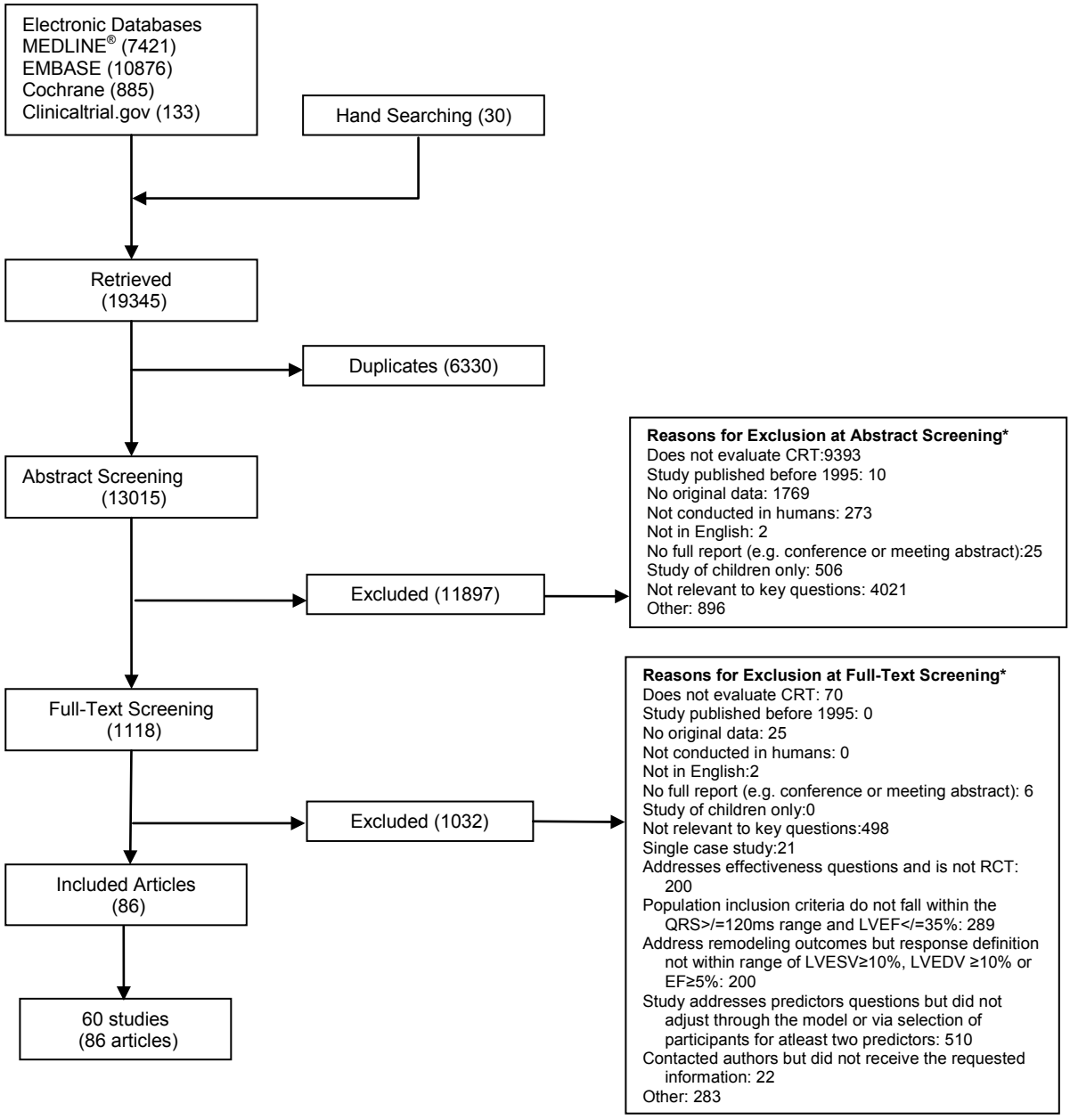
Results of the Search

Figure 4 summarizes the results of our searching and screening. We identified 13,015 unique citations and excluded 10,805 of these during the abstract screen. During the full-text screening, we excluded 1032 citations (See Appendix D for list of excluded articles with reason (s) for exclusion). Sixty studies reported in eighty six articles are included in this review.

Scientific information packets (SIPs)

As part of the grey literature search, device manufacturer companies were asked to provide information about pertinent studies conducted with their products (published, unpublished, and ongoing clinical trials). One company responded that no relevant studies had been conducted. Two companies provided scientific information packets, with potentially relevant studies; these citations were checked against our existing citation database, yielding ten new citations, none of which met our eligibility criteria. (Appendix F)

Figure 4. Summary of the literature search and screen



* Total number of reasons for exclusion exceeds the number of citations excluded, because citations could be excluded for more than one reason

Overview of included studies by outcomes

We list the number and type of studies identified as addressing each comparison of interest, by type of outcome assessed. List of RCTs, and other analyses and reports from these trials, are shown in Table 6.

Table 5. List of included studies by outcomes

Comparison	Effectiveness	Harms	Clinical predictors
CRT–D vs. Implantable cardioverter defibrillator alone	8 trials (reported in 16 articles)	24 studies (reported in 27 articles) 6 trials and 18 cohort	11 studies (reported in 14 articles) 2 trials and 9 cohort
CRT–P vs. Optimal medical therapy	6 trials (reported in 16 articles)	11 studies (reported in 13 articles) 5 trials and 6 cohort	2 studies 2 cohort
CRT-D vs CRT-P	1 trial (reported in 3articles)	9 studies 2 trials and 7 cohort	NA

CRT-D: Cardiac resynchronization therapy with defibrillator, CRT-P: Cardiac resynchronization therapy with pacemaker, NA: not applicable

Table 6. List of trials included in the review

Trial with Primary Publication	Secondary Analyses and Other Reports from Trials
CARE HF (Cardiac Resynchronization-Heart Failure)-Cleland,2004[5]	Cleland,2006[22] Cleland,2007[23] Cleland,2009[24] Ghio,2009[25] Gras,2007[26] Wikstrom,2009[27] Cleland,2012[28]
COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) -Bristow,2004[4]	Anand, 2009[29] Carson,2005[30]
MADIT CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) trial- Moss,2009[6]	Arshad,2011[31] Barsheshet,2011[32] Goldenberg,2011[33] Hsu,2012[34] Ouellet,2012[35] Penn, 2010[36] Solomon,2010[37] Tompkins, 2013[38] Zareba,2011[10] Jamerson,2014[39] Ruwald,2014[40] Goldenberg,2014[41]
MIRACLE (Multicenter InSync Randomized Clinical Evaluation)-	Sutton,2003[42] Abraham,2002[3]
MIRACLE-ICD (Multicenter InSync ICD Randomized Clinical Evaluation) -Young,2003[43]	-
MIRACLE-ICD II (Multicenter InSync ICD Randomized Clinical Evaluation II)- Abraham,2004[44]	-
MUSTIC (Multisite Stimulation in Cardiomyopathy)-Cazeau,2001[8]	Leclercq,2002[45]
MASCOT (Management of Atrial fibrillation Suppression in AF-HF Comorbidity Therapy)	Schuchert,2013[46]
RAFT (Resynchronization–Defibrillation for Ambulatory Heart Failure Trial) -Tang,2010[7]	Birnie,2013[47] Gilis,2014[48] Healey,2012[49]
SMART AV (Smart Delay Determined AV Optimization)	Cheng, 2012[50] Gold,2011[51]
Other trials	
Diab, 2011[52]	
Garikipati,2014[53]	
Higgins,2003[54]	
Leclercq,2007[55]	
Lozanzo,2000[56]	
Pinter,2009[57]	
Pokushalov,2010[58]	

Organization of Results Chapter

We present our results by outcomes. Each section follows the format listed below:

Study Characteristics
Population Characteristics
Outcomes

A. Effectiveness

- All- cause mortality (Key outcome)
- Heart failure hospitalizations (Key outcome)
- Left ventricular end systolic volume/volume index (Key outcome)
- Minnesota Living with Heart Failure Questionnaire (Key outcome)
- SF-36
- Left ventricular ejection fraction
- Left ventricular end diastolic volume/volume index
- Clinical composite score (Packer Score)
- 6 minute hall walk distance

B. Harms

- Procedure related complications
- Length of hospital stay
- Pneumothorax
- Pocket hematoma
- Device Infection
- Cardiac perforation/ tamponade
- Lead dislodgement
- Ventricular arrhythmias
- Inappropriate ICD shocks (CRT-D only)
- Death (within a week)

C. Clinical predictors

- Age
- Gender
- Cardiomyopathy subtype
- History of atrial fibrillation
- QRS duration
- QRS morphology
- Chronic kidney disease
- Left atrial volume
- Left ventricular ejection fraction
- Body mass index
- Baseline left ventricular end diastolic volume

Effectiveness of Cardiac Resynchronization Therapy with Defibrillator (CRT-D)

Table 7. Evidence addressing effectiveness and harms of CRT-D

	Effectiveness of cardiac resynchronization therapy	Harms of cardiac resynchronization therapy
Number of included studies	8 trials (reported in 16 articles)	24 studies (reported in 27 articles) 6 were RCTs and the rest were prospective or retrospective cohorts.
Study characteristics	• The number of patients enrolled ranged from 73-1,820 • The percentage of women was between 9.1-25.3% • The mean age ranged from 63.0-67.6 years old • All trials reported NYHA class • The mean LVEF ranged from 21-26% • The proportion of participants with LBBB ranged from 54 -72.9% • The mean QRS duration was generally similar amongst the trials	• The number of patients enrolled ranged from 73 -1,820 • The percentage of women in the studies ranged from 9.0-35% • The mean age ranged from 60- 82.68 years old • All studies reported NYHA class • The mean LVEF ranged from 20-32.1% • The proportion of participants with LBBB ranged from 54-94% • The mean QRS duration ranged from 125.2-170ms
Outcomes (number of included studies)	• All-cause mortality: 7 trials • Hospitalizations for heart failure: 6 trials • Left ventricular end systolic • volume/volume index : 5 trials • Minnesota Living with Heart Failure Questionnaire: 5 trials • Left ventricular ejection fraction: 6 trials • Left ventricular end diastolic volume/volume index: 4 trials • Clinical composite score (Packer Score): 2 trials • 6 minute hall walk distance: 4 trials	• Procedure related complications: 3 studies • Length of hospital stay: 1 study • Pneumothorax: 6 studies • Pocket hematoma: 5 studies • Device Infection: 9 studies • Cardiac perforation/ tamponade: 8 studies • Lead dislodgement: 8 studies • Ventricular arrhythmias: 13 studies • Inappropriate ICD shocks (CRT-D only): 6 studies • Death (within a week): 2 studies
Key findings	CRT-D devices are effective in reducing heart failure symptoms, improving myocardial function, and reducing hospitalizations for heart failure We found a moderate strength of evidence for the benefit of CRT-D versus ICD alone for all-cause mortality in patients with NYHA class II symptoms. The applicability of these findings to patients with NYHA class I symptoms is unclear. There is insufficient evidence to determine whether CRT-D devices are effective in improving survival compared to an ICD alone in an advanced heart failure population (NYHA III-IV)	Prevalence of harms associated with CRT-D devices were as follows: cardiac perforation/tamponade (0.1-1.4%), pocket hematoma (0.9-2.8%), pneumothorax (1.3-2.8%), device infection (0.9-2.8%), and lead dislodgement (2.4 -9.8%). No conclusions could be drawn about the association between CRT-D implant and both ventricular arrhythmias and inappropriate shocks. Death within one week of implantation was 0% although only two studies reported this outcome.

Study Characteristics

Eight trials (reported in 16 articles) addressed the effectiveness of CRT-D.[6,7,10,31,32,37,38,41,43,44,47,49,52,54,56,57] The studies used largely consistent comparators when assessing patients with an implantable cardioverter defibrillator (ICD) and active biventricular pacing versus an ICD and no active biventricular pacing (Evidence Table 1).

One trial separated patients into two groups based on the presence or absence of baseline ventricular dyssynchrony.[52] Patients with dyssynchrony all received a CRT-D device. The trial randomized patients without dyssynchrony to a CRT-D device or an ICD alone. Another trial started as a crossover design with patients crossing over between active CRT-on versus CRT-off.[54] The study changed protocol after the trial started to a parallel arm design. Two studies did not report funding status (Table 8).[52,56]

Table 8. Study characteristics of trials assessing effectiveness of CRT-D

Author, year	Number of patients	Length of followup	Device manufacturer name/ device model	Comparison	NYHA class	Funding source
MADIT-CRT						
Arshad, 2011[31]	Women: 453 Men: 1,367	12 months remodeling ; 2.4 years mortality and CHF	Boston Scientific devices	CRT-D vs. ICD alone	I: 14.8% II: 85.2%	Industry
Barsheshet, 2011[32]	Ischemic: 1,046 Non-ischemic: 774	12 months remodeling ; 2.4 years mortality and CHF	Boston Scientific devices	CRT-D vs. ICD alone	I: 14.4% II: 85.6%	Industry
Goldenberg, 2014[41]	LBBB: CRT-D: 394 ICD:240 Non-LBBB: CRT-D:133 ICD: 87	7 years	Boston Scientific devices	CRT-D vs. ICD alone	I: 14.5% II: 85.5%	Industry
Moss, 2009[6]	CRT-D: 1,089 ICD: 731	12 months remodeling ; 2.4 years mortality and CHF	Boston Scientific devices	CRT-D vs. ICD alone	I: 14.6% II: 85.4%	Industry
Solomon, 2010[37]	CRT-D: 749 ICD: 623	12 months	Boston Scientific devices	CRT-D vs. ICD alone	I: 84.7% II: 15.3%	Industry
Tompkins, 2013[38]	CRT-D: 132 ICD: 87	12 months remodeling ; 3 years mortality	Boston Scientific devices	CRT-D vs. ICD alone	I: 21.0% II: 79.0%	Industry
Zareba, 2011[10]	LBBB: 1,281 RBBB: 228 NSIVCD: 308	12 months remodeling ; 2.4 years mortality and CHF	Boston Scientific devices	CRT-D vs. ICD alone	I: 14.5% II: 85.5%	Industry
MIRACLE-ICD						
Young, 2003[43]	CRT: 187 Control: 182	6 months	Model Insync 7272	CRT-on vs. CRT-off	III: 88.9% IV: 11.1%	Industry
MIRACLE-ICD II						
Abraham, 2004[44]	CRT: 85 Control: 101	6 months	Model Insync 7272	CRT-on vs. CRT-off	Class II	Industry
RAFT						
Birnie, 2013[47]	LBBB: 1,175 RBBB: 141 NSIVCD: 167	40 months	Medtronic devices	CRT-D vs. ICD alone	II: 81.5% III: 19.5%	Industry and Canadian Institute of Health Research
Healey, 2012[49]	CRT-D: 114 ICD: 115	40 months	Medtronic devices	CRT-D vs. ICD alone	II: 72.1% III: 27.9%	Industry and Canadian Institute of Health Research

Author, year	Number of patients	Length of followup	Device manufacturer name/ device model	Comparison	NYHA class	Funding source
Tang, 2010[7]	CRT-D: 894 ICD: 904	40 months	Medtronic devices	CRT-D vs. ICD alone	II: 80.0% III: 20.0%	Industry and Canadian Institute of Health Research
Other trials						
Diab, 2011[52]	CRT-D (no dyssynchrony) 22 ICD: 21	6 months	Not reported	CRT-D vs. ICD alone	III: 90.4% IV: 9.9%	Not reported
Higgins, 2003[54]	CRT: 245 Control: 245	6 months	Model 1822 Ventak CHF device or the 1823 CONTAK CD device	CRT-on vs CRT-off	II: 32.6% III: 58.5% IV: 9.0%	Industry
Lozano, 2000[56]	CRT: 109 Control: 113	3 months	Not reported	CRT-D on vs. off	II: 35% III: 57% IV: 8%	Not reported
Pinter, 2009[57]	CRT: 36 Control: 36	6 months	Model1823 CONTAK CD CHF or the H135 CONTAK RENEWAL HF	CRT-on vs. CRT-off	Class II	Industry

CRT=cardiac resynchronization therapy; CRT-D=cardiac resynchronization therapy with defibrillator; NYHA=New York Heart Association

Participant Characteristics

The number of patients enrolled in the trials ranged from 73 to 1,820. The percentage of women was between 9.1 to 25.3 percent. The mean age ranged from 63.0 to 67.6 years old. Only one trial (MADIT-CRT) reported the racial distribution of subjects.[6] This study included approximately 90 percent Caucasian patients. In terms of cardiomyopathy subtype, the proportion of patients with ICM ranged from 54.9 percent in the ICD arm of the MADIT-CRT trial [6] to 75.8 percent in the ICD arm of the MIRACLE-ICD trial.[43] In the MADIT CRT-Trial,[6] 28 percent of women had ICM compared to 64 percent of men.[31]

Three trials reported on history of atrial fibrillation (AF) in study participants.[6,44,57] The incidence of AF ranged from 5.6 percent in the CRT-on arm in the study by Pinter et al. (2009) to 16.7 percent in the CRT-off arm in the same study.[57] The MADIT-CRT[6],MIRACLE-ICD[43], and MIRACLE-ICD II[44] trials excluded patients with atrial arrhythmias <1 month prior to implant, and the trial by Higgins et al. (2003) excluded patients with any history of AF.[54] Six trials reported mean QRS duration.[7,43,44,52,54,57]

The MADIT-CRT trial dichotomized QRS duration into ≥150ms or <150ms categories.[6] In subgroup analyses from MADIT-CRT, women and men had a similar QRS duration (158±17ms vs. 158±20ms, respectively).[31] Patients with a left bundle branch block (LBBB) had a mean QRS duration of 163±19ms, right bundle branch block (RBBB) 153±15ms, and non-specific intraventricular conduction delay (NSIVCD) 142±14ms.[10] In the RAFT trial, patients with LBBB had a mean QRS duration of 161.0±23.5ms, RBBB 159.9±19.3ms, and NSIVCD 138.6±18.4ms.[47] The mean QRS duration was generally similar amongst the trials with only the smaller trial by Diab et al. (2011) as an outlier.[52]

Four trials reported the incidence of LBBB ranging from 54 to 72.9 percent.[6,7,54,57] One study reported no QRS morphology data.[52] Two trials[43,44] reported on the incidence of RBBB. While these two studies excluded paced patients, given a lack of data on the number of NSIVCD patients, we could not determine the number of LBBB patients from these two studies. Six trials reported the number of RBBB patients, ranging from 7.6 percent in the CRT arm of the RAFT trial[7] to 20.8 percent in the CRT-off arm from the MIRACLE-ICD II trial.[44] Three trials reported patients with NSIVCD ranging from roughly 11 to 32 percent.[7,10,54]

Only the RAFT trial included patients with a paced rhythm prior to CRT.[7] These patients represented 7.4 to 7.6 percent of the patients in this trial. All paced patients in the RAFT trial had a QRS duration >200ms.[7]

The NYHA class was a key inclusion criteria in all trials. Three trials included only patients with NYHA class III-IV symptoms.[43,52,57] One trial included primarily class III patients, however roughly one-third of the patients in this study were NYHA class II.[54] The trial by Lozano et al. (2000) included patients with class II, III, and IV symptoms.[56] The RAFT trial included primarily NYHA class II patients, although roughly 20 percent were NYHA class III.[7] The MIRACLE-ICD trial included only NYHA class II patients.[43] The MADIT-CRT study enrolled only patients with NYHA class I or II symptoms, of which NYHA class II represented roughly 85 percent.[6]

All trials reported the mean left ventricular ejection fraction (LVEF) and it was similar across studies ranging from 21-26 percent. Only two trials reported serum creatinine.[6,57] Mean serum creatinine ranged from 1.1-1.2 mg/dl. These trials were homogeneous in patient population with the major exception of NYHA class (Evidence Table 4).

Risk of Bias

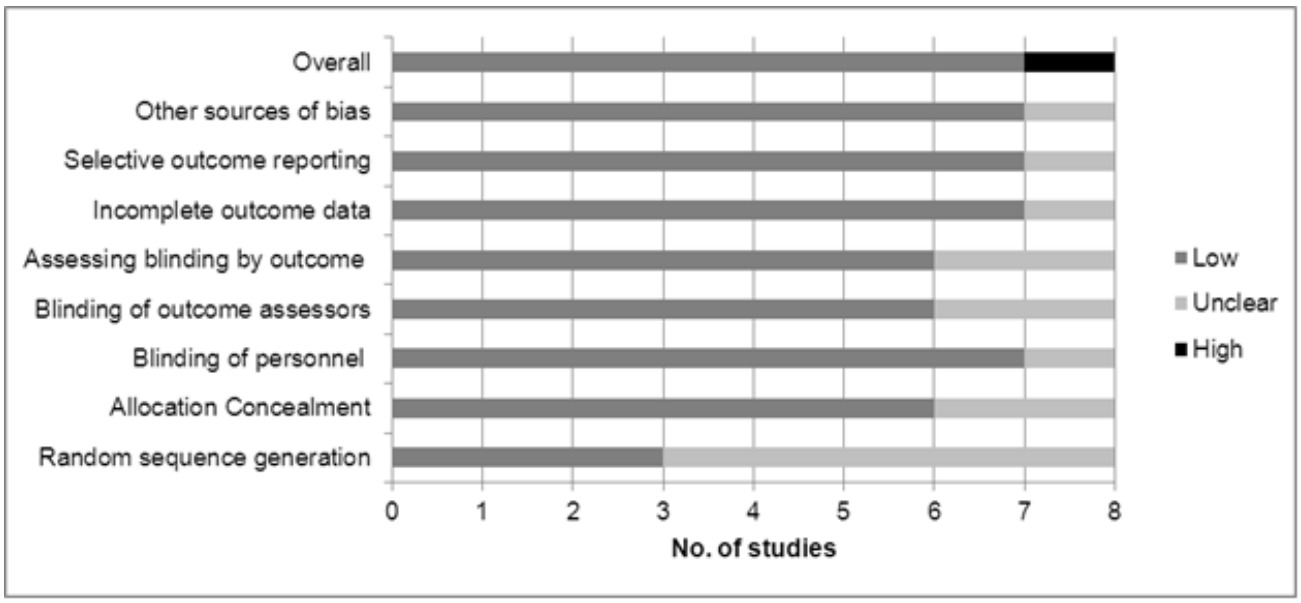
The majority of trials did not report whether they performed random sequence generation; therefore, we cannot rule out selection bias. In the MADIT-CRT trial, the treating physicians were aware of study-group assignments introducing possible performance bias.[6,10,31,32,37,38] The RAFT trial conducted 6-minute hall walk tests and administered QOL questionnaires [7]. However, this outcome was only reported as a secondary analysis limited to patients with permanent AF.[49] Despite these limitations, overall, the included RCTs have a low risk of bias (Table 9 and Figure 5).

Table 9. Summary of risk of bias for trials assessing effectiveness of CRT-D

Author, year	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessors	Assessing blinding by outcome	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall quality
MADIT CRT Trial									
Arshad,2011[31] Barsheshet,2011[32] Goldenberg, 2014[41] Moss,2009[6] Solomon,2010[37] Tompkins, 2013[38] Zareba,2011[10]	?	-	-	-	-	-	-	-	-
MIRACLE-ICD									
Young,2003[43]	-	-	-	-	-	-	-	-	-
MIRACLE-ICD II									
Abraham,2004[44]	-	-	-	-	-	-	-	-	-
RAFT									
Tang,2010[7] Birnie,2013[47]Healey,2012[49]	?	-	-	-	-	-	-	-	-
Other trials									
Diab, 2011[52]	-	-	-	-	-	-	-	-	-
Higgins,2003[54]	?	?	-	?	?	-	-	-	-
Lozanzo,2000[56]	?	?	?	?	?	?	?	?	+
Pinter,2009[57]	?	-	-	-	-	-	-	-	-

+=High
-=Low
?=Unclear

Figure 5. Summary of risk of bias for trials assessing effectiveness of CRT-D



Effectiveness Outcomes

The most common outcomes assessed were all-cause mortality and heart failure hospitalizations (Table 9). Multiple studies also measured indices of reverse ventricular remodeling changes including LVEF, LVESV, LVEDV, left ventricular end-systolic volume indexed to body surface areas (LVESVi), and left ventricular end-diastolic volume indexed to body surface areas (LVEDVi). Six studies assessed quality of life (QOL) as measured by the MLHFQ. Five reported functional capacity changes by noting variations in 6-minute hall walk distances, and two studies measured symptomatic improvement via the same clinical composite score which assigned patients to one of three groups (worsened, improved, or unchanged) (Table 10).

Table 10. Outcomes reported in the trials assessing effectiveness of CRT-D

Author, year	All-cause mortality	HF hospitalization	LVESV	LVESVi	MLHFQ	LVEF	LVEDV	LVEDVi	Clinical composite score	6MHWD
MADIT-CRT										
Moss,2009[6]	X	X	X			X	X			
Goldenberg, 2014[41]	X									
Tompkins, 2013[38]	X		X				X			
Solomon, 2010[37] (other endpoints are redundant from MADIT-CRT[6]				X				X		
Arshad,2011[31]	X	X		X		X		X		
Zareba, 2011[10]	X	X	X			X	X			
Barsheshet, 2011[32]	X	X	X			X	X			
MIRACLE-ICD										
Young,2003[43]	X	X (part of combined endpoint)	X		X	X	X		X	X
MIRACLE-ICD II										
Abraham,2004[44]	X	X	X		X	X	X		X	X
RAFT										
Tang, 2010[7]	X	X								
Birnie, 2013[47]	X	X								
Healey, 2012[49]	X	X			X					X
Other trials										
Diab, 2011[52]	X	X	X		X	X				
Higgins, 2003[54]	X	X			X	X				X

Author, year	All-cause mortality	HF hospitalization	LVESV	LVESVi	MLHFQ	LVEF	LVEDV	LVEDVi	Clinical composite score	6MHWD
Pinter, 2009[57]			X		X	X	X			X
Lozano, 2000[56]	X									

HF= heart failure; LVESV=left-ventricular end-systolic volume; LVEVi=left-ventricular end-systolic volume indexed to body surface area; MLHFQ = Minnesota Living with Heart Failure Questionnaire; LVEF=left-ventricular ejection fraction; LVEDV=left ventricular end-diastolic volume; LVEDVI=left-ventricular end-diastolic volume indexed to body surface area; 6MHWD=6-minute hall walk distance

All-cause Mortality

Seven trials (reported in 14 articles) assessed the all-cause mortality outcome.[6,7,10,31,32,38,41,43,44,47,49,52,54,56] Three trials included patients with primarily minimally symptomatic CHF [6,7,44], two included patients with primarily advanced CHF [43,52] and two included both populations.[54,56] In the MADIT-CRT trial over a mean followup of 2.4 years, 3.3 percent of the CRT group died compared with 2.5 percent in the ICD alone arm (HR:1.0, 95% CI, 0.69 to 1.44, p=0.99).[6] In long term follow up of 854 patients from MADIT-CRT (1,818 were originally followed) patients with a LBBB undergoing CRT derived a significant improvement in mortality compared to an ICD alone (log rank p=0.002) but those with a non-LBBB did not (log rank p=0.2).[41] Long term mortality data comparing CRT-D to an ICD alone in the cohort as a whole were not reported. In another analysis from MADIT-CRT trial, women derived a significant benefit in survival from CRT-D compared to an ICD alone (log rank p=0.02), whereas men did not (log rank p=0.83) (Table 11).[31]

In a separate analysis from MADIT-CRT, in patients with RBBB, with or without a left anterior fascicular block [LAFB]), there was no difference in survival in patients receiving CRT-D compared with an ICD alone (log rank p=0.374).[38]

Lastly, in one analysis from MADIT-CRT trial (stratified by cardiomyopathy subtype), patients with ICM had no statistically significant difference in survival with CRT-D versus ICD (HR: 0.99, 95% CI, 0.65 to1.52, p=0.984).[32] Patients with non-ischemic cardiomyopathy (NICM) had no statistically significant difference in survival with CRT-D versus ICD (HR: 0.87, 95% CI, 0.45 to 1.67, p=0.669).[32] In the RAFT trial (primarily NYHA class II patients), the 5-year actuarial rate of death in the CRT-D arm was 28.6 versus 34.6 percent in the ICD alone arm (HR: 0.75, 95% CI, 0.562 to 0.91, p=0.0003).[7]

In patients with permanent AF, there was no difference in survival between patients in the CRT-D arm and ICD alone arm (HR: 1.04, 95% CI, 0.66 to 1.62, p=0.88).[49] RAFT reported other pre-defined subgroups of interest, but they were not broken down by survival alone and thus precluded analysis. Grouped by bundle branch block morphology, patients with a LBBB had improved survival with CRT-D compared to an ICD alone (HR: 0.664, 95% CI, 0.516 to 0.853, p=0.0013).[47] There was no statistically significant difference between the CRT-D and ICD arms for patients with RBBB (HR: 0.544, 95% CI, 0.264 to1.121, p=0.095) or NSIVCD (HR: 0.930, 95% CI, 0.491 to 1.1761, p=0.0825).[47] In MIRACLE-ICD II (enrolling patients with NYHA class II), two patients in each group died at 6-month followup.[44]

In terms of the trials of patients with more advanced CHF symptoms, in the MIRACLE-ICD trial the cumulative survival at 6 months was 92.2 percent in the ICD arm and 92.4 percent in the CRT-D arm (log rank p=0.96).[43] In the trial by Diab et al. (2011) (enrolling NYHA class III-IV), there were two deaths in the ICD arm and none in the CRT arm at a followup of 6 months.[52] In the trial by Higgins et al. (2003) (which contained mixed NYHA class population), there were 11 deaths in the CRT-D arm compared with 16 deaths in the ICD arm at 6 months followup.[54] In the trial by Lozano et al. (2000) enrolling a mixed NYHA population (the majority of which were NYHA class III), the survival rate at 3 months in the CRT-on cohort was 93 percent versus 86 percent in the CRT-off cohort—a result that was not statistically significant (p=0.18).[56]

In summary, in patients with less symptomatic CHF, data from the RAFT trial demonstrate a mortality benefit, which conflicts with the originally reported median 2.4 year followup of the MADIT-CRT trial, which did not. Long term followup of the MADIT-CRT trial demonstrated a mortality benefit in LBBB but not in non-LBBB. Whether CRT-D produced a mortality

improvement in the cohort as a whole was not reported and many patients in the original trial were lost to followup. The other trials assessing mortality in minimally symptomatic patients were either too small in size or followup to add significant additional evidence. Given this, the strength of evidence that CRT-D improves mortality in patients with minimally symptomatic CHF is moderate (Table 12). The trials assessing mortality in patients with NYHA class III-IV symptoms were limited in terms of followup and size, therefore there is insufficient evidence to determine the effect of CRT-D on mortality compared to an ICD alone. Three reasonably homogenous trials (RAFT, MADIT-CRT, and MIRACLE-ICD II) reported mortality, however the 6-month followup in MIRACLE-ICD II is limiting. Therefore, there are too few trials to perform a meta-analysis. Women appear to have improved survival compared to men with CRT-D compared to an ICD alone, although we need more data to confirm this finding.

The evidence on bundle branch block morphology and survival in patients receiving CRT-D is conflicted and limited to patients with less symptomatic CHF.

Heart Failure (HF) Hospitalizations

Six trials (reported in 11 articles) assessed HF hospitalization outcomes.[6,7,10,31,32,43,44,47,49,52,54] In the RAFT trial, over the duration of followup, 19.5 percent in the CRT arm were hospitalized for HF compared to 26.1 percent in the ICD arm (HR: 0.68, 95% CI, 0.56 to 0.83, p<0.001).[7] In patients with permanent AF from this trial, 19.3 percent of patients in the CRT-D arm were hospitalized for HF versus 27.8 percent in the ICD arm, a result of borderline significance (p=0.052).[49] The RAFT trial reported other pre-defined subgroups of interest, but they were not broken down by HF hospitalization alone, thus precluding analysis. Grouped by bundle branch block morphology, patients with a LBBB had fewer HF hospitalizations with CRT-D compared to an ICD alone (HR: 0.603, 95% CI, 0.469 to 0.774, p<0.001]).[47] There was no statistically significant difference in HF hospitalizations between the CRT-D and ICD arm for patients with RBBB (HR: 1.142, 95% CI, 0.580 to 2.249, p=0.705, 95% CI, 264 to 1.121, p=0.095) or NSIVCD (HR: 1.021, 95% CI, 0.574 to 1.81, p=0.944).[47]

In the MADIT CRT trial, over the duration of followup, there were 151 HF events (13.9 %) in the CRT arm and 167 HF events (22.8 %) in the ICD arm (HR: 0.59, 95% CI, 0.47 to 0.74, p<0.001).[6] In an analysis from MADIT-CRT trial, both women and men derived fewer heart hospitalizations with CRT-D compared to an ICD alone (HR: 0.30, 95% CI, 0.18 to 0.50, p<0.001 and HR: 0.65, 95% CI, 0.50 to 0.84, respectively p=0.001).[31] In another analysis from the MADIT-CRT trial, stratified by QRS morphology, patients with a LBBB morphology had fewer HF events with CRT-D versus an ICD alone (HR: 0.41, 95% CI, 0.31to 0.54, p<0.001).[10] Patients with a RBBB had no statistically significant difference in CHF events with CRT-D versus ICD (HR: 0.88, 95% CI, 0.46 to 1.67, p=0.690).[10] Patients with a NSIVCD morphology had no statistically significant difference in HF events with CRT-D versus ICD (HR: 1.31, 95% CI, 0.78 to 2.16, p<0.306).[10] In another analysis from the MADIT-CRT trial (stratified by cardiomyopathy subtype), patients with both ICM from NICM had fewer HF events with CRT-D compared to an ICD alone (HR: 0.58, 95% CI,0.45 to 0.77, p=<0.001 and HR: 0.50, 95% CI, 0.35 to 0.75, p=0.001, respectively).[32]

The MIRACLE-ICD trial did not report HF hospitalizations alone (without combination with all-cause survival).[43] A study by Diab et al. (2011) hospitalized two patients in the CRT arm (both in the dyssynchrony present arm) and two in the ICD arm for HF over 6 months of followup.[52] In the study by Pinter et al. (2009), the authors reported percentages only for all-cause hospitalizations and stated that the reasons for hospitalization were the same in both

groups.[57] In the study by Higgins et al. (2003) there was a non-statistically significant 15 percent reduction in HF progression in patients receiving CRT versus control (p=0.35).[54]

Both the large RAFT and MADIT-CRT trials showed a reduction in HF events for CRT-D compared to an ICD alone. Subgroup analyses from both trials demonstrate the effect to be primarily in patients with LBBB morphology. The definition for HF events in MADIT-CRT incorporated both inpatient and outpatient CHF management. There are too few trials to perform a meta-analysis.

The overall the strength of evidence that CRT-D results in fewer hospitalizations for CHF compared to an ICD alone is high (Table 12).

Left Ventricular End Systolic Volume/Volume Index

Five trials (reported in 8 articles) reported change in LVESV.[6,10,32,38,43,44,52,54] In the MADIT-CRT trial there was a significant decrease in LVESV in the CRT-D arm compared to the ICD arm alone (57ml vs. 18ml, p<0.001), respectively.[6]

In an analysis from the RAFT trial (grouped by bundle branch block morphology), patients with a LBBB had a significant reduction in LVESV compared to those receiving an ICD alone (62.1±31.5ml vs. 18.3±16.5ml, p<0.01).[47] Patients with a non-LBBB morphology (RBBB and NSIVCD grouped together), derived a significant reduction in LVESV with CRT-D compared to ICD alone (45.7±27.3ml vs. 17.5±16.1, p<0.01).[47]

In an analysis from MADIT-CRT (stratified by cardiomyopathy subtype), patients with both ICM and NICM demonstrated reductions in LVESV with CRT-D versus an ICD alone compared to baseline (-29%±14 vs. -10%±9 and -37%±16 vs. -11%±9).[32] This effect was greater in patients with NICM compared with ICM.

In the MIRACLE-ICD trial the median change in LVESV in the control group was -8.2ml (-19.1 to 0.6) compared with -22.2ml (-32.8 to -10.7) in the CRT-D arm (p=0.06).[43] In the MIRACLE-ICD II trial the mean change in LVESV in the CRT arm compared with control was (-42ml vs. -14ml, p=0.01, respectively).[44]

In the trial by Pinter et al. (2009) the mean change in the CRT-on arm was -21±45ml versus -5+22ml in the CRT-off arm—a change which was not statistically significant.[57] In the study by Diab et al. (2011) the change in LVESV was dichotomized into reduction ≥15 percent from baseline.[52] Amongst patients with no dyssynchrony at baseline, patients with CRT were more likely to have a reduction in LVESV from baseline of at least 15 percent compared to patients receiving an ICD alone (57% vs. 11%, p=0.002).

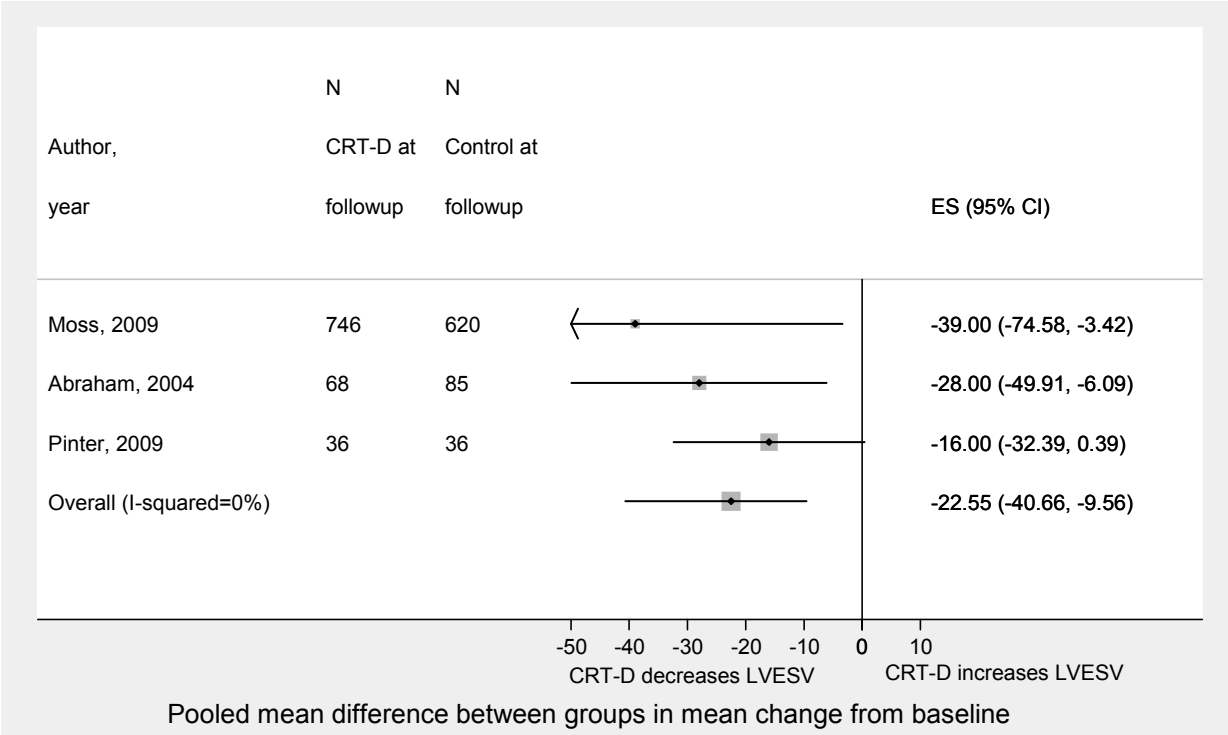
The MADIT-CRT trial also reported changes in LVESVi.[6,37] At 12-month followup, patients receiving CRT-D derived a greater improvement in LVESVi compared to patients receiving an ICD alone (-28.7±15.5 vs. -9.1±8.2, p=0.0001).[37] In an analysis from MADIT-CRT, both women and men derived improvements in LVESVI compared to an ICD alone (ml/body surface area, -31 vs. -10 and -27 vs. -8). This reduction was greater in women compared to men (p<0.001).[31]

The trials were generally consistent in demonstrating a reduction in LVESV with CRT-D compared to an ICD alone. This effect was noted across multiple subgroups including patients with non- LBBB block morphologies. We performed a meta-analysis incorporating the three trials, which enrolled minimally symptomatic CHF. This meta-analysis demonstrated a clear benefit in terms of LVESV reduction favoring CRT-D compared to an ICD alone (Mean difference: -22.55, 95% CI, -40.66 to -9.56) (Figure 6).

There were not enough trials enrolling patients NYHA class III-IV CHF to perform meta-analysis. Nevertheless, the data are consistent in favoring CRT-D over an ICD alone in terms of

LVESV reduction this population. The strength of evidence is high favoring CRT-D over an ICD alone in terms of LVESV reduction (Table 12).

Figure 6. Meta-analysis of left ventricular end-diastolic volume comparing CRT-D with ICD alone in minimally symptomatic patients (NYHA I-II)



Minnesota Living with Heart Failure Questionnaire

Five trials (reported in 6 articles) reported quality of life via the MLHFQ.[43,44,49,52,54,57] In the trial by Higgins et al. (2003) there was a non-significant improvement in MLHFQ score with CRT-D versus an ICD alone (-7±2 vs. 5±2, p=0.43).[54] When divided by NYHA class I/II vs. II/IV subgroups, patients with advanced CHF (NYHA class III/IV) had a significant improvement in MLHFQ score with CRT-D versus an ICD alone (-16±3 vs. -5±3, p=0.017) whereas patients with less symptomatic CHF (NYHA class I and II) had no significant difference (-1±2 vs. -4±2, p=0.26).

In the MIRACLE-ICD trial, there was a significant improvement in MLHFQ scores in the CRT-D arm compared to the control arm (-17.5 [-21 to -14] vs. -11 [-16 to -7], p=0.02).[43]

In the trial by Diab et al. (2011) there was an improvement in MLHFQ score in patients receiving CRT-D with dyssynchrony present at baseline (-29), without dyssynchrony at baseline (-16), and in patients without dyssynchrony receiving an ICD alone (-8).[52] While a global p-value was presented comparing all three arms, the impact of baseline dyssynchrony makes this difficult to interpret.

In the trial by Pinter et al. (2009) there was no statistically significant change in MLHFQ scores between patients with CRT-on vs. -off (-7.8±20.1 vs. -0.2±13.5, p=non-significant).[57]

In the MIRACLE-ICD II trial there was no significant change in MLHFQ scores between patients in the control arm and those receiving CRT (-10.7±21.7 vs. -13.3±25.1, p=0.49).[44]

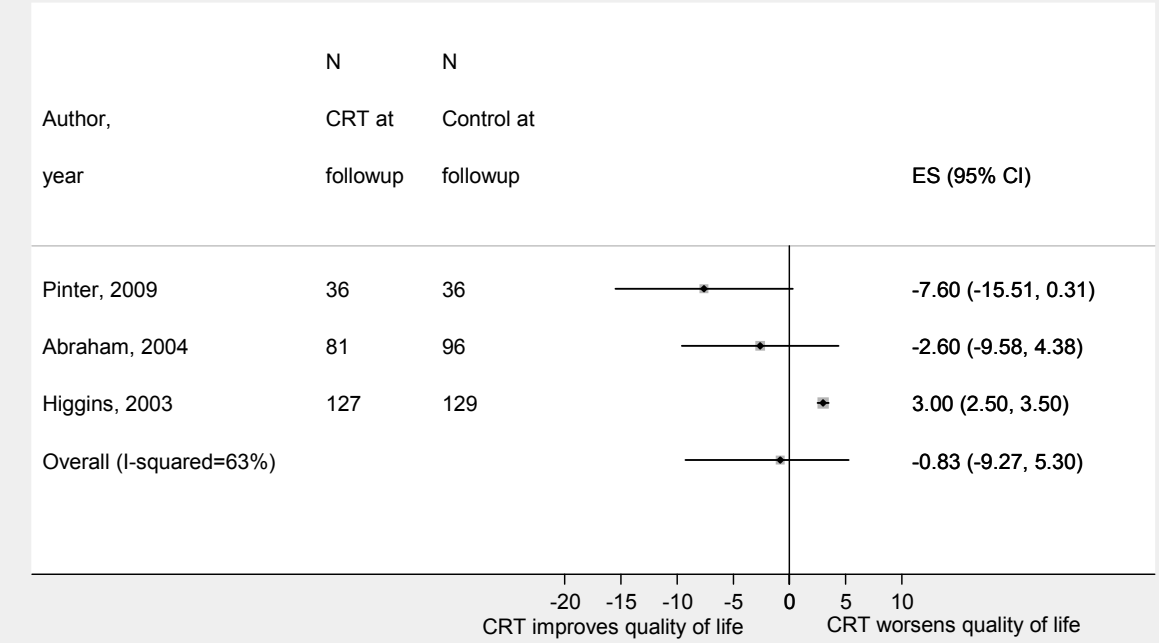
In the permanent AF subgroup from the RAFT trial there was a non-significant improvement in MLHFQ scores with CRT-D compared to an ICD alone (-11±18 vs. -5±21, p=0.057).[49]

The trial by Pinter et al. (2009) also reported data from the SF-36 health survey. Of 10 metrics incorporating subscales of physical and mental function, only changes in general health scores were different between patients with CRT-on and -off (-5.8±14.9 vs. -5.8±13.9, p=0.02).[57]

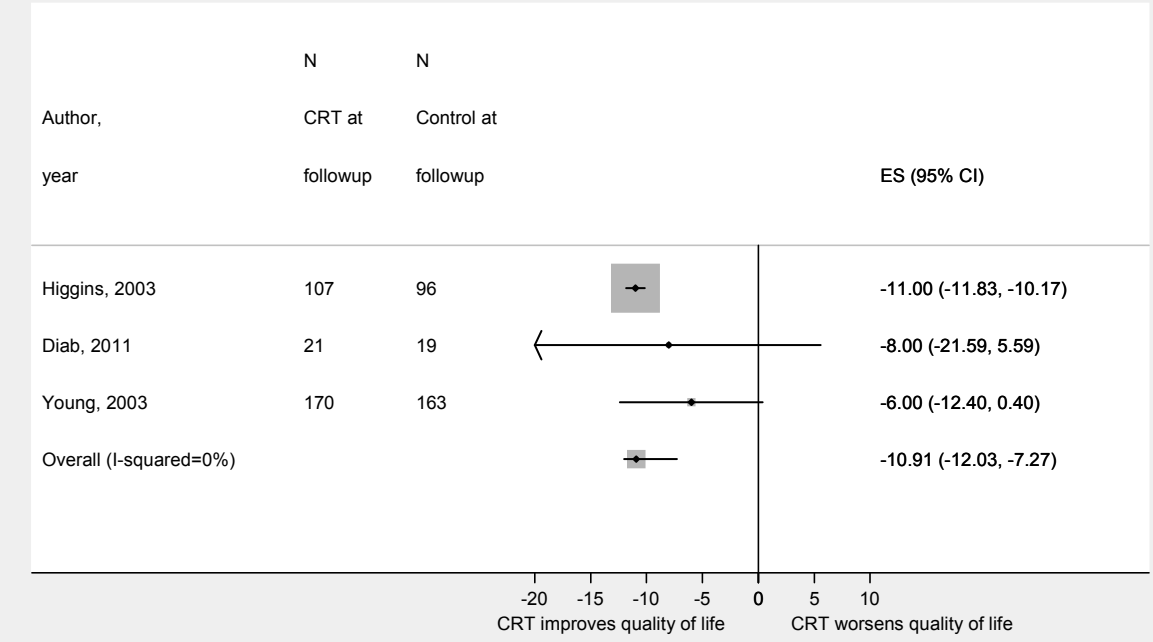
The current data suggest that CRT-D does not improve quality of life in minimally symptomatic patients compared to an ICD alone, though the meta-analysis should be interpreted with caution given the substantial heterogeneity (0.83, 95% CI, -9.27 to 5.30) (Figure 7a). The data does suggest a significant improvement in quality of life in patients with NYHA class III-IV CHF with a high strength of evidence supporting this conclusion (mean difference-10.91, 95% CI, -12.03 to -7.27) (Figure 7b and Table 12).

Figure 7a and b. Meta-analysis of quality of life, as measured with the Minnesota Living with Heart Failure Questionnaire, comparing CRT-D with ICD alone in (a) minimally symptomatic patients (NYHA I-II) and (b) in patients with advanced heart failure (NYHA III-IV)

7a. Meta-analysis NYHA class I-II



7b. Meta-analysis NYHA class III-IV



Left Ventricular Ejection Fraction

Six trials (reported in 9 articles) reported change in LVEF.[6,10,31,32,43,44,52,54,57] In the MADIT-CRT trial, there was a significant improvement in LVEF in the CRT arm compared to the ICD arm (11% vs. 3%, p<0.001).[6] In an analysis from MADIT-CRT, both women and men had improvement in LVEF with CRT-D compared to an ICD alone, although the magnitude was significantly greater in women.[31]

In another analysis from MADIT-CRT (stratified by QRS morphology), patients with an LBBB morphology had significant improvement in LVEF (3.4%±3.0 in the ICD arm compared to 11.9%±5.1 in the CRT-D arm, p<0.01).[10] The analysis grouped RBBB and NSIVCD patients as "non- LBBB". This cohort similarly showed an improvement in LVEF with CRT-D versus ICD alone (8.8%±4.9 vs. 3.4%±3.1, p<0.01).[10] The improvement in LVEF was larger in patients with LBBB compared with non- LBBB. In subgroup analyses (stratified by cardiomyopathy subtype), patients with both ICM and NICM showed improvement in LVEF with CRT-D compared to an ICD alone (10.5%±5 vs. 3%±3 and 12%±5 vs. 3%±3).[32] The effect was greater in patients with NICM.

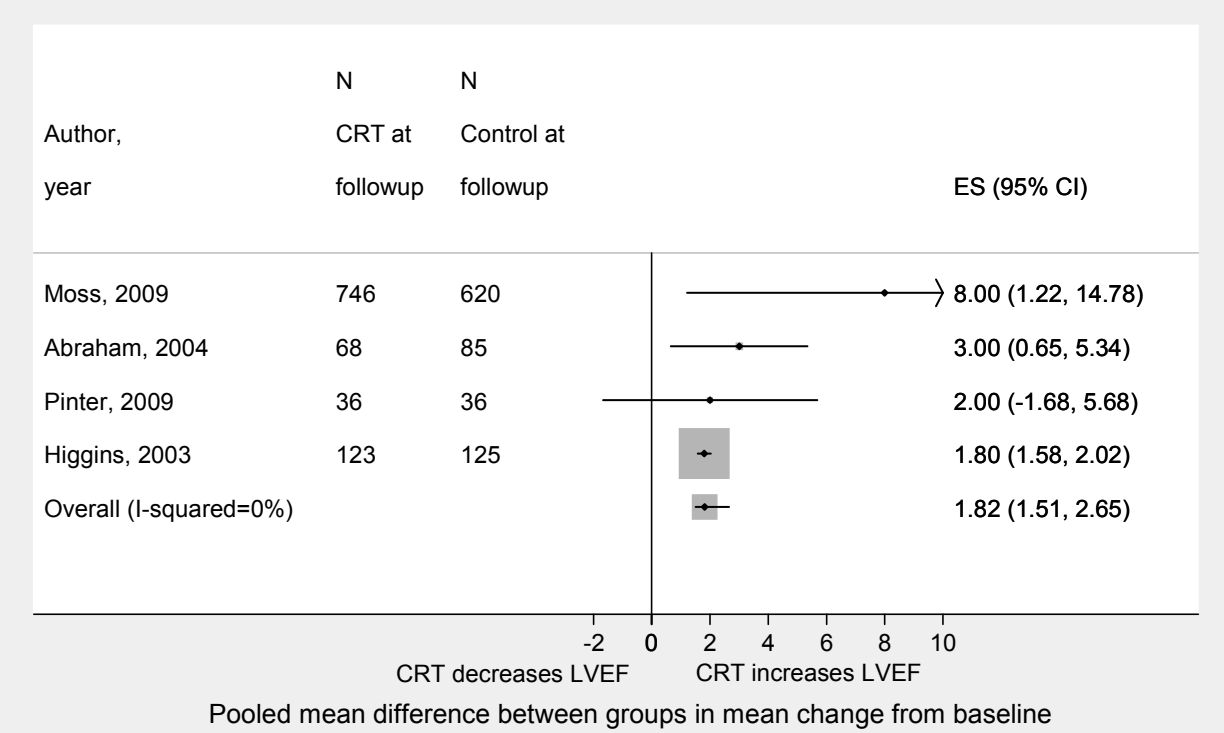
In the MIRACLE-ICD trial, the median change in LVEF in the CRT arm was 2.1 percent (95% CI, 0.12 to 4.1) compared to 1.7 percent (95% CI, 0.7 to 2.4, p=0.12).[43] In the MIRACLE-ICD II trial, the mean change in LVEF in the CRT arm was 3.8 percent vs. 0.8 percent in the ICD arm (p=0.02).[44]

In the trial by Higgins et al. (2003) the mean change in LVEF in CRT patients was 5.1 percent ±0.7 versus 2.8 percent ±0.7 in the ICD arm (p=0.02).[54] In the trial by Pinter et al. (2009) the change in LVEF in the CRT-on arm was 3.9 percent ±8.9 vs. 1.9 percent ±6.8 in the CRT-off arm, which was not statistically different.[57]

In the study by Diab et al. (2011) the change in LVEF was dichotomized into improvement ≥15 percent from baseline rather than used as a continuous variable.[52] The study made a comparison between CRT-D vs. ICD alone in patients who lacked baseline dyssynchrony. The proportion of patients demonstrating >15 percent improvement in LVEF was greater in the CRT arm than the ICD alone arm (p=0.007).

The majority of studies, including the very large MADIT-CRT trial, were consistent in demonstrating an improvement in LVEF with CRT compared to ICD alone.[6] This effect existed across multiple subgroups including patients with non-LBBB morphologies. The study by Higgins et al. (2003) reported separately the changes in LVEF in the NYHA class I-II cohort and class III-IV cohorts.[54] We performed a meta-analysis incorporating the four trials enrolling patients with minimally symptomatic CHF. In pooled analysis a clear benefit in terms of LVEF improvement existed favoring CRT-D over an ICD alone (1.82, 95% CI, 1.51 to 2.65) (Figure 8). There were not enough trials enrolling patients NYHA class III-IV to perform meta-analysis.

Figure 8. Meta-analysis of left ventricular ejection fraction comparing CRT-D with ICD alone in minimally symptomatic patients (NYHA I-II)



Left Ventricular End Diastolic Volume/Volume Index

Four trials (reported in 7 articles) reported change in LVEDV.[6,10,32,38,43,44,57] In the MADIT-CRT trial, there was a significant decrease in LVEDV in the CRT-D arm compared to the ICD arm alone (52ml vs. 15ml, p<0.001).[6]

In an analysis from the RAFT trial, grouped by bundle branch block morphology,[47] patients with a LBBB had a significant reduction in LVEDV compared to an ICD alone (56.7±34.1ml vs. 14.8±14.5ml, p<0.01). Patients with a non- LBBB morphology (RBBB and NSIVCD grouped together), derived a significant reduction in LVEDV with CRT-D compared to ICD alone (41.0±28.13ml vs. 14.4±14.2ml, p<0.01).

In an analysis from MADIT-CRT stratified by cardiomyopathy subtype, patients with both ischemic cardiomyopathy and NICM demonstrated reductions in LVEDV with CRT-D versus an ICD alone compared to baseline (-18%±10 vs. -5%±5 and -24%±12 vs. -7%±6).[32] This effect was greater in patients with NICM compared with ICM.

In the MIRACLE-ICD trial the median change in LVEDV in the control group was -5.7ml (-16.2 to 1.8) compared with -19.9m (-39.7 to -6.3) in the CRT-D arm (p=0.06).[43] In the MIRACLE-ICD II trial the mean change in LVEDV in the CRT arm compared with control was (-42ml vs. -16ml, p=0.04).[44]

In the study by Pinter et al. (2009) the mean change in the CRT-on arm was -16±44ml vs. -13±47ml in the CRT-off arm, a change, which was not statistically significant.[57]

The MADIT-CRT trial also reported changes in LVEDV indexed to body surface area (LVESDi).[6,37] At 12-month followup, patients receiving CRT-D derived a greater improvement in LVEDVi compared to patients receiving an ICD alone (-26.2±16.5 vs. -7.4±7.2, p=0.0001).[37]

In an analysis from MADIT-CRT, both women and men derived improvements in LVEDVI compared to an ICD alone (ml/body surface area) (-29 vs. -9 and -22 vs. -7). This reduction was greater in women compared to men ($p<0.001$).[31]

The trials were consistent in demonstrating a reduction in LVEDV with CRT-D compared to an ICD alone. This effect existed across multiple subgroups including patients with non-LBBB morphologies. However, given differences in NYHA class amongst patients included in these trials, there were not enough trials enrolling patients of similar NYHA class to perform a meta-analysis.

Clinical Composite Score

Two trials reported a clinical composite score.[43,44] In each trial, the score categorized patients as improved, worsened, or unchanged following CRT. In the MIRACLE-ICD trial, 42.9, 23.6, and 33.5 percent of patients in the control arm were improved, unchanged, or worsened respectively compared with 52.4, 15.0, and 32.6 percent in the CRT-D arm ($p=0.06$).[43] In the MIRACLE-ICD II trial, 36, 34, and 31 percent of patients in the control arm were improved, unchanged, or worsened respectively compared with 58, 22, and 17 percent in the CRT-D arm ($p=0.06$).[44]

The current data suggest that CRT-D likely results in greater improvement in clinical composite score compared with an ICD alone. Still more data are needed to confirm this finding.

6-Minute Hall Walk Distance

Four trials (reported in 5 articles) reported changes in 6-minute hall walk distance (6MHWD).[43,44,49,54,57]

In the MIRACLE-ICD trial there was no statistically significant change in median 6MHWD in the control arm compared to the CRT-D arm (53m (43-75) versus 55m (44-79), $p=0.36$).[43,43]

In the trial by Pinter et al. (2009) there was no statistically change in 6MHWD between the CRT-on and -off arms (53.3±113.3m vs. 27.3±71.1m, p=non-significant).[57] In the trial by Higgins et al. (2003) there was a significant improvement in 6MHWD in the CRT-D arm compared to the ICD alone arm (35±7m vs. 15±7m, $p=0.043$).[54] This effect was limited to the patients with advanced CHF symptoms (NYHA class III-IV).

In the MIRACLE-ICD II trial, there was no difference in change in 6MHWD in the CRT arm compared to the control arm (38±109m vs. 33m±98m, $p=0.59$).[44]

In the permanent AF cohort from the RAFT trial there was no difference in change in 6MHWD between patients receiving CRT-D versus an ICD alone (19±84m vs. 16±76m, $p=0.88$).[49]

We performed a meta-analysis incorporating the three trials which included minimally symptomatic patients and reported changes in 6MHWD.[44,54,57] In this analysis, CRT-D resulted in a significant improvement in 6MHWD compared to an ICD alone (7.04, 95% CI, 3.12 to 11.84) (Figure 9). Not enough studies of patients with NYHA class III-IV symptoms reporting 6MWWD were available for meta-analysis. The two trials of this population reported opposite conclusions.

In conclusion, the data suggest that CRT-D is effective in improving 6MHWD in patients with minimally symptomatic CHF compared to those receiving an ICD alone. We need more data to determine the impact of CRT-D versus an ICD alone in terms of changes in 6MHWD in patients with advanced CHF.

Figure 9. Meta-analysis of 6-minute hall walk distance comparing CRT- D with ICD alone in minimally symptomatic patients (NYHA I-II)

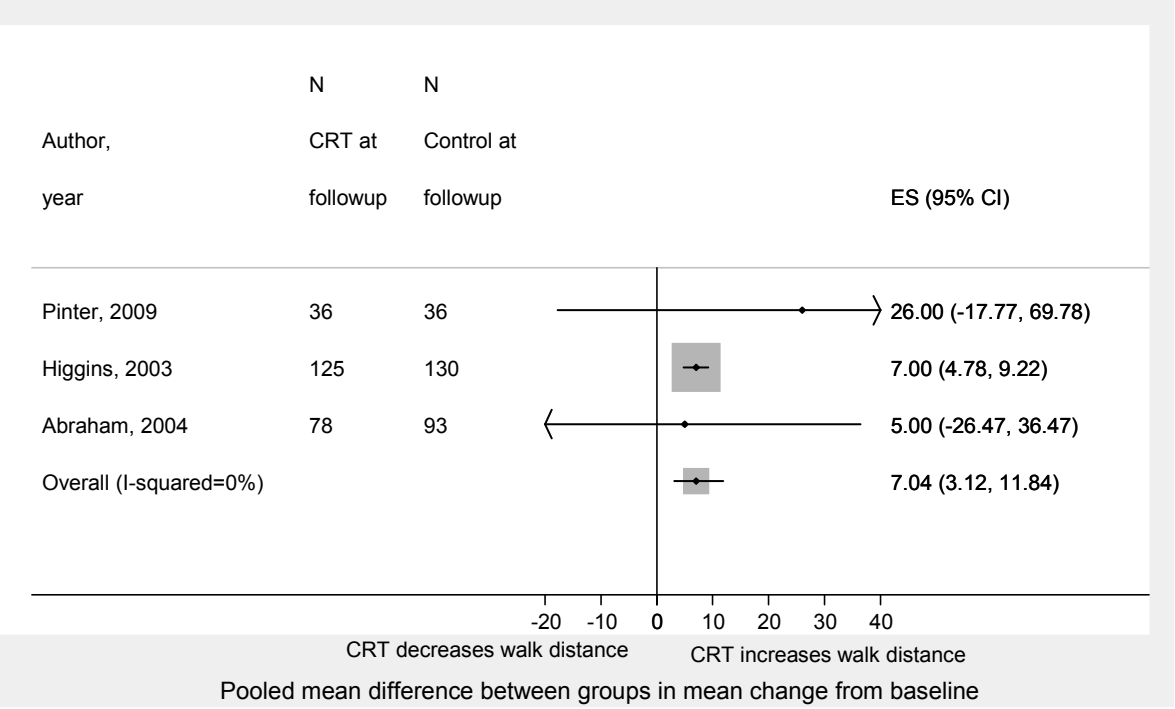


Table 11. Summary of CRT-D effectiveness outcomes reported by subgroup

Female (no. of trial)	LBBB (no. of trial)	QRS duration >150ms (no. of trial)	Non ischemic cardiac conditions (no. of trial)	Atrial fibrillation (no. of trial)
All-cause mortality				
1 Trial Beneficial in women	2 trials Beneficial in LBBB	NR	1 trial No difference in survival	1 trial No difference in survival
Hospitalizations for heart failure				
1 Trial Beneficial in women	2 trials Beneficial in LBBB patients	NR	1 trials Beneficial in NICM patients	1 trials Beneficial in patients with AF
Minnesota Living with Heart Failure Questionnaire				
NR	NR	NR	NR	1 trial No difference in outcome
6-minute hall walk distance				
NR	NR	NR	NR	1 trial No difference in outcome
Left ventricular end systolic volume/volume index				
1 trial Beneficial in women	1 trial Beneficial in LBBB patients	NR	1 trials Beneficial in NICM patients	1 trial Non-significant improvement with CRT-D
Left ventricular ejection fraction				
1 trial Beneficial in women	1 trial Beneficial in LBBB patients	NR	1 trials Beneficial in NICM patients	NR
Left ventricular end diastolic volume/volume index				
1 trial Beneficial in women	1 trial Beneficial in LBBB patients	NR	1 trials Beneficial in NICM patients	NR

CRT-D- Cardiac Resynchronization Therapy with Defibrillator, LBBB-Left bundle branch block, NR-Not Reported, NICM-Non Ischemic Cardiomyopathy

Table 12. Strength of evidence for key effectiveness outcomes of CRT-D

Key outcomes	No. Studies (number of patients)	Study limitations	Directness	Consistency	Precision	Reporting bias	Strength of evidence Finding
All-cause mortality	7 (5812)	Low	Direct	Inconsistent	Precise	Undetected	Moderate In patients with minimally symptomatic CHF (primarily class NYHA class II), data from the RAFT trial (a larger, slightly more symptomatic population, with a longer followup) demonstrates a mortality benefit, The MADIT-CRT trial did not report a mortality benefit with CRT-D in primarily NYHA class II patients. Long-term followup of a subset of patients demonstrated a mortality benefit in patients with LBBB but not with a non-LBBB and did not report a mortality comparison for the group as a whole. The other trials assessing mortality in minimally symptomatic patients were either too small in size or followup to add significant additional evidence. The trials assessing mortality in patients with NYHA class III-IV symptoms were limited in terms of followup and size, therefore there is insufficient evidence to determine the effect of CRT-D on mortality compared to an ICD alone.
Heart failure hospitalizations	6 (4736)	Low	Direct	Consistent	Precise	Undetected	High The large RAFT and MADIT-CRT trials showed a reduction in HF events for CRT-D compared to an ICD alone. Subgroup analyses from both trials demonstrate the effect to be primarily in patients

Key outcomes	No. Studies (number of patients)	Study limitations	Directness	Consistency	Precision	Reporting bias	Strength of evidence Finding
							with an LBBB morphology
Left ventricular end systolic volume (or index)	5 (2938)	Low	Direct	Consistent	Precise	Undetected	High The trials were consistent in demonstrating a reduction in LVESV with CRT-D compared to an ICD alone. Meta-analysis of trials in patients with NYHA I-II (primarily NYHA class II patients), mean difference -22.55 (95% CI, -40.66 to -9.56).
Minnesota Living with Heart Failure Questionnaire	5 (2895)	Low	Direct	Inconsistent	Precise	Selective outcome reporting (not reported in main RAFT cohort)	High The current data suggest that CRT-D does not improve QOL in minimally symptomatic patients compared to an ICD alone. The data do suggest a significant improvement in QOL in patients with NYHA class III-IV CHF (mean difference -10.91 (95% CI, -12.03 to 7.27)).

Harms of Cardiac Resynchronization Therapy with Defibrillator (CRT-D)

Study Characteristics

Twenty-four studies (reported in 27 articles) reported on the harms of CRT-D.[6,35,39,40,43,44,48,54,57,59-76] There were eight RCTs (reported in 9 articles) [6,35,39,40,43,44,48,54,57] and the rest were prospective or retrospective cohorts. The largest study included 7090 patients[62] and the smallest included 45,[60] both of which were cohort studies. Followup ranged from 30 days[6,39] to 3 years[64]. Ten studies were industry-supported.[6,35,43,44,48,57,59,62,66,75] One study was supported by grant from the AHRQ.[72]The remaining studies did not report their funding source or reported that they received no external funding (Evidence Table 1).

Population Characteristics

The percentage of women in the studies ranged from 9.0 percent in the study by Kuehlkamp et al. (2002)[69] to 35 percent in the study by Nian-Sang et al. (2010)[63] The mean age ranged from 60 years in the primary prophylaxis arm of the study by Theuns et al.[65] to 82.68 years old in the study by Strimel et al. (2011)[64] (a study in an octogenarian population). One study did not report the mean age.[63] Only two studies reported racial distribution of participants, and 90 percent were white in both.[6,35]

Eighteen studies (reported in 21 articles) reported the proportion of patients with ICM ranged from 26 to 79 percent.[6,39,40,43,44,48,54,57,60,62-64,67-69,71-76]Five studies did not report on the proportion with ICM.[35,59,61,65,66] The proportion of patients with AF ranged from 11.1[6] to 42 percent.[65] Eleven studies did not report the proportion of patients with AF.[35,43,44,54,60,63,64,67,71,73,74]

The proportion of patients in NYHA Class IV ranged from 1.6[68] to 11.1[43] percent. The proportion of patients in NYHA Class III ranged from 19.2[48] to 89[65] percent. The proportion of patients in NYHA Class II ranged from 6[59] to 100[44] percent. The proportion of patients in NYHA Class I ranged from 0.0 to 7.1 percent.[64] Six studies did not report the breakdown of NYHA class of participants.[6,35,62,63,71,73] The MADIT-CRT trial included only patients with NYHA class I-II heat failure.[6,39,40]

The mean LVEF ranged from 20[70] to 32.1[63] percent. Four studies did not report the mean LVEF.[48,54,60,67] The proportion of participants with LBBB ranged from 52.6%[54] to 94[60] percent. Thirteen studies did not report on the proportion of participants with LBBB.[43,44,57,62-67 71,73,75,76]

The mean QRS interval ranged from 125.2ms[63] to 170ms.[69] Eight studies did not report the mean QRS interval.[6,35,57,64,65,67,68,70,73] The mean creatinine ranged from 1.05mg/dl to 1.4mg/dl. Eighteen studies did not report on renal function.[43,44,48,54,60-67,69,71,73-76] In general, the patient populations were generally homogenous with the major exception being NYHA class, which varied considerably across studies (Evidence Table 5).

Risk of Bias

The majority of the RCTs did not report whether they performed random sequence generation; therefore, selection bias cannot be ruled out. In the MADIT-CRT trial and all of its sub-studies [6,10,31,32,37-40] the treating physicians were aware of study-group assignments

introducing possible performance bias. Despite these limitations, overall, the included RCTs had a low risk of bias (Figure 10 and Table 13).

In the cohort studies, there was some heterogeneity in terms of comparability of the cohorts to a typical CHF population receiving CRT-D devices. The study by Strimel et al. (2011) focused on an elderly population with a mean age of 82.68 years old.[64] In the study by Nian-sang et al. (2010) the average age was 57 years old, the mean LVEF was 32.1 percent, and the mean QRS duration was 125.2ms.[63] In the study by Bossard et al. (2014) NICM represented 73 percent of the cohort.[60] Almost all studies ascertained exposure via medical record review. Overall, the risk of bias in the included cohort studies is moderate (Figure 11 and Table 14).

Given the heterogeneity of study designs, population characteristics, and followup times, we could not conduct meta-analyses.

Table 13. Summary of risk of bias for trials assessing harms of CRT-D

Author, year	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessors	Assessing blinding by outcome	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall quality
MADIT CRT									
Ouellet,2012[35] Moss,2009[6] Jamerson,2014[39] Ruwald,2014[40]	?	?	+	+	-	-	-	-	-
MIRACLE-ICD									
Young,2003[43]	-	-	-	-	-	-	-	-	-
MIRACLE-ICD II									
Abraham,2004[44]	?	-	-	-	-	-	-	-	-
RAFT Trial									
Gilis,2014[48]	?	-	-	-	-	-	-	-	-
Other trials									
Higgins,2003[54]	?	-	-	-	-	-	-	-	-
Pinter,2009[57]	?	-	-	-	-	-	-	-	-

+High
-Low
?Unclear

Figure 10. Summary of risk of bias for trials assessing harms of CRT-D

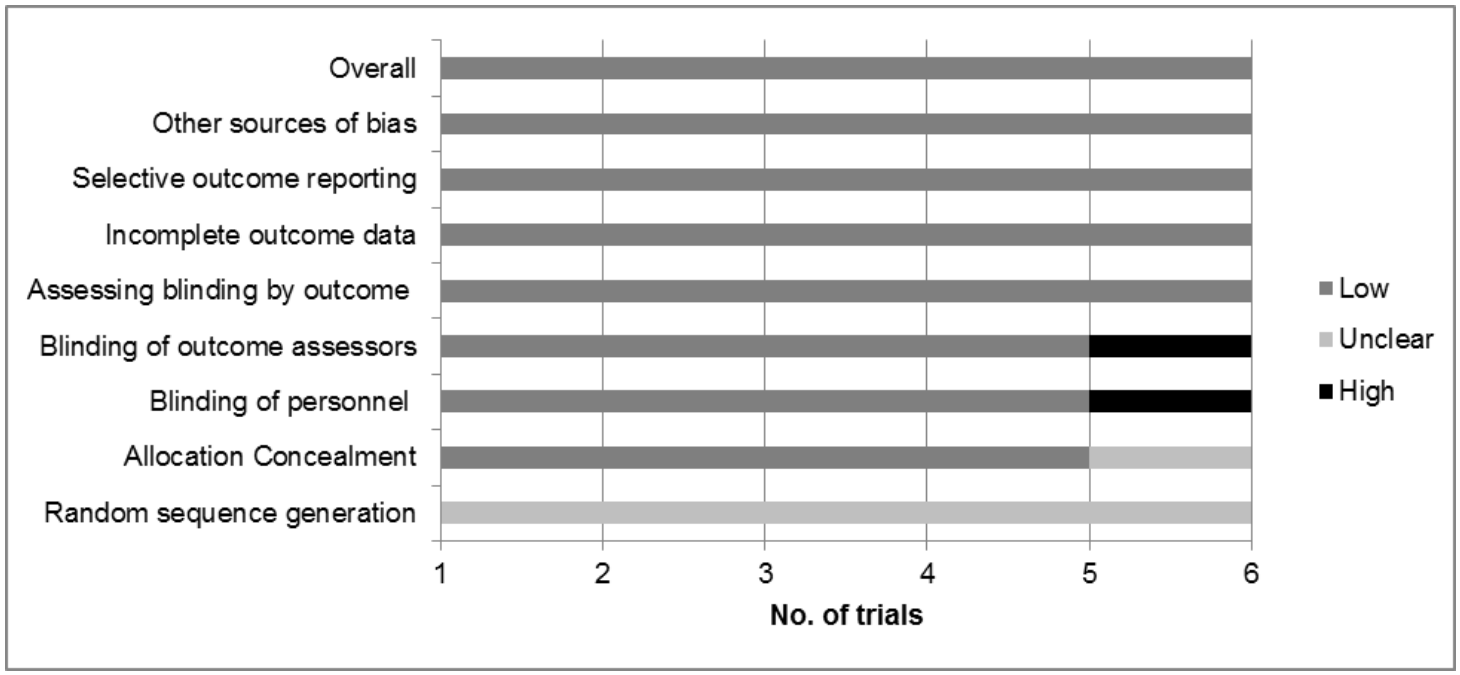


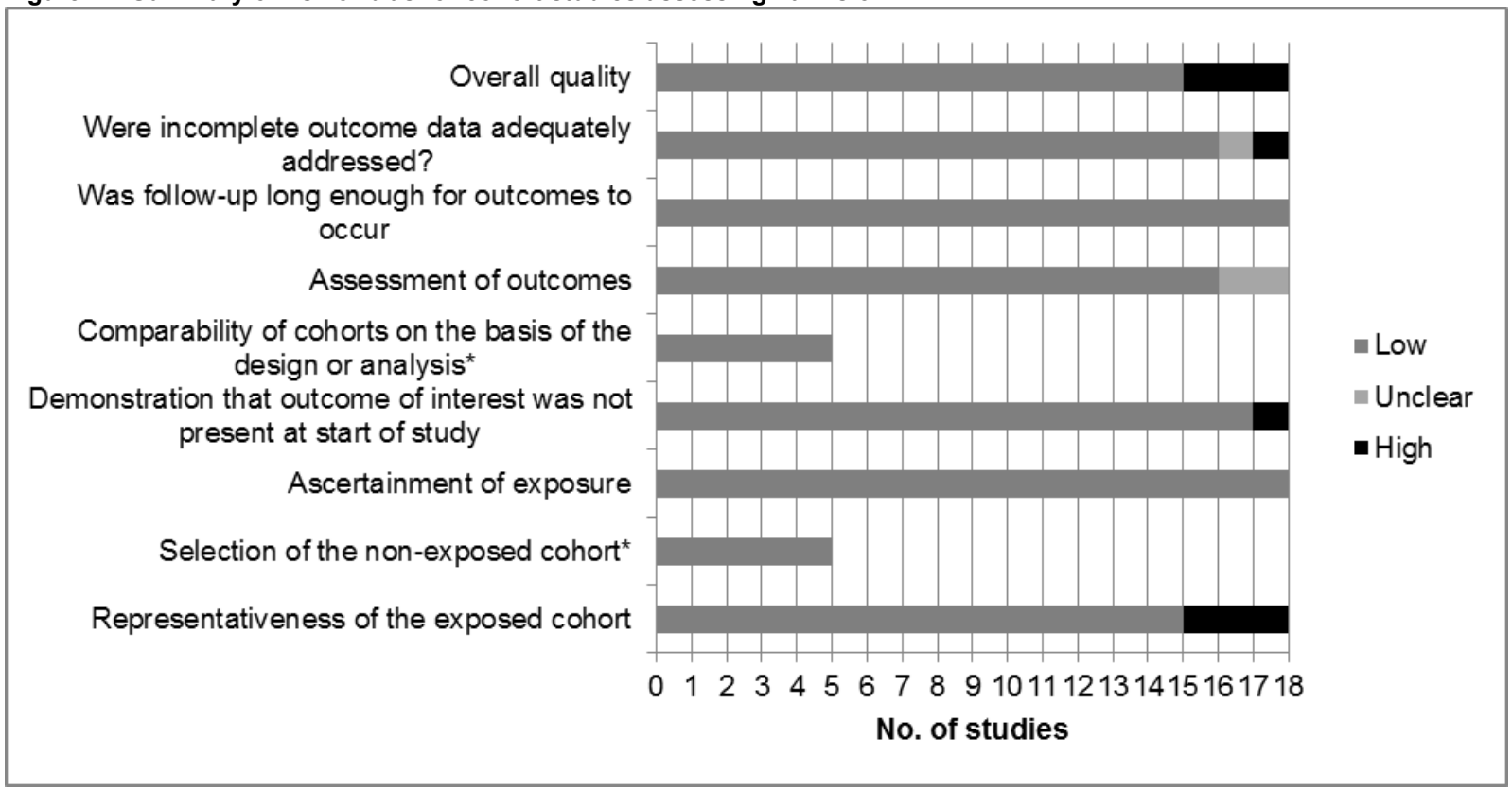
Table 14. Summary of risk of bias for cohort studies assessing harms of CRT-D

Author, year	Representativeness of the exposed cohort	Selection of the non-exposed cohort*	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis*	Assessment of outcomes	Was followup long enough for outcomes to occur	Were incomplete outcome data adequately addressed?	Overall quality
Auricchio,2014[59]	-		-	-		-	-	-	-
Bossard,2014[60]	+		-	-		-	-	-	+
Boven,2013[68]	-		-	-		-	-	-	-
Boven,2013[70]	-		-	-		-	-	-	-
Duray,2008[67]	-		-	-		-	-	-	-
Gasparini,2009[66]	-	-	-	-	-	?	-	-	-
Gopalamurugan, 2014[73]	-	-	-	-	-	-	-	-	-
Haugaa,2014[71]	-		-	-		?	-	-	-
Kuhlkamp, 2002[69]	-		-	+		-	-	+	-
Knight,2004[61]	-		-	-		-	-	-	-
Landolina,2011[62]	-		-	-		-	-	-	-
Masoudi,2014[72]	-	-	-	-	-	-	-	-	-
Nian-Sang,2010[63]	+		-	-		-	-	-	+
Ricci,2014[76]	-		-	-		-	-	-	-
Strimel, 2011[64]	+		-	-		-	-	-	+
Theuns,2005[65]	-		-	-		-	-	?	-
Vado,2013[74]	-		-	-		-	-	-	-
Wollmann,2014[75]	-	-	-	-	-	-	-	-	-

+ High, -Low, ?Unclear

*Only applicable to studies with control groups

Figure 11. Summary of risk of bias for cohort studies assessing harms of CRT-D



* Only applicable to studies with control groups.

Table 15. List of harms reported in studies assessing harms of CRT-D

Author, year	Procedure related complications (type not-specified)	Length of hospital stay	Pneumothorax	Pocket hematoma	Device Infection	Cardiac perforation/ tamponade	Lead dislodgement	Ventricular arrhythmias	Inappropriate ICD shocks (CRT-D only)	Death within a week
RCTs										
MADIT CRT										
Moss,2009[6]			X	X	X					
Ouellet,2012[35]								X		
Jamerson, 2014[39]			X	X	X	X	X	X		
Ruwald, 2014[40]								X	X	
MIRACLE-ICD										
Young, 2003[43]			X			X		X	X	
MIRACLE-ICD II										
Abraham,2004[44]						X	X	X	X	
RAFT										
Gilis,2014[48]	X	X		X	X	X			X	
Other trials										
Pinter,2009[57]								X		
Higgins,2003[54]								X		
Prospective cohorts										
Auricchio,2014[59]			X	X	X					
Wollman, 2014[75]	X		X		X	X	X			
Duray,2008[67]			X	X	X	X				X
Gasparini,2009[66]								X		
Knight,2004[61]					X					
Kuelkamp, 2002[69]			X	X	X	X	X			

Author, year	Procedure related complications (type not-specified)	Length of hospital stay	Pneumothorax	Pocket hematoma	Device Infection	Cardiac perforation/ tamponade	Lead dislodgement	Ventricular arrhythmias	Inappropriate ICD shocks (CRT-D only)	Death within a week
Landolina,2011[62]					X					
Theuns,2005[65]								X		
Retrospective cohorts										
Bossard,2014[60]							X	X		
Massoudi,2014[72]	X				X					
Gopalamuruga n,2014[73]								X		
Ricci, 2014[76]								X	X	
Haugaa,2014[71]								X		
Vado,2014[74]							X			
Nian-Sang,2010[63]								X		
Strimel, 2011[64]						X	X		X	X
Van Boven,2012[70]								X	X	
Van Boven,2013[68]									X	

Harms Outcomes

List of harms reported in the included studies is shown in Table 15.

Procedure-related Complications

Three studies reported on procedure-related harms in general[48 ,72 ,75] In the RAFT trial, 147 out of 904 (16.4 %) patients in the ICD group and 126 out of 894 (13.9 %) patients in the CRT-D group were hospitalized for "device-related events" over the course of the study (mean follow up in the ICD group was 39.2±19.4 months and mean follow up in the CRT-D group was 41.2±19.6 months, p=0.031).[48] This difference between the two groups was not statistically significant (p=0.148). In the study by Massoudi et al, mechanical complications occurred in 1.7 percent of ICD patients and 2.3 percent of CRT-D patients (p=0.049) at 3years of follow up.[72]In the study by Wollman et al. from the PainFree SmartShock™ Technology study, peri-procedural complications occurred in 13 of 114 (11.4%) patients in the ICD arm and 20 of 132 (15.2%) patients in the CRT-D arm at one month post implant.[75] In general, complications are slightly more common with a CRT-D device compared to an ICD alone.

Length of Hospital Stay

Only one study reported length of hospital stay.[48] Gillis et al. (2014) reported from the RAFT trial that the total number of days hospitalized was less in the group randomized to CRT-D as compared with the ICD-only group (12,783 vs. 14,896 days).[48] The average length of hospital stay (per stay) was significantly less in the CRT-D group versus the ICD-only group (8.83±13.30 vs. 9.59±14.40, p= 0.005).

Pneumothorax

Six studies in seven articles reported on the incidence of pneumothorax of which four reported on a cohort of CRT-D patients only, and two compared patients receiving a CRT-D device to an ICD alone (Table 7).[6 ,39 ,43 ,59 ,67 ,69 ,75]

The incidence of pneumothorax among patients receiving a CRT-D device ranged from 1.3-2.8 percent. In the large MADIT-CRT trial, pneumothorax was slightly more common in patients receiving a CRT-D device (1.7 %) compared to an ICD alone (0.85 %).[6] Men had a lower incidence of pnemo-or hemothorax compared with women(0.9% vs. 3.3%, p<0.001)[39] In the Wollman et al. study, there was one pneumothorax in each the CRT-D and ICD arms.[75] Lastly, the moderate-sized MIRACLE-ICD trial reported an incidence of pneumothorax or hemothorax of 0.8 percent but did not break down the incidence of pneumothorax further.

Pneumothorax is an uncommon complication of CRT-D device implant. The incidence of pneumothorax appears to be slightly more common in patients receiving a CRT-D device compared to an ICD alone although we need more data to confirm this finding (Table 16).

Table 16. Characteristics of studies of CRT-D reporting on the incidence of pneumothorax

Author, year	Arm name	N for analysis	Time Point (s)	N of patients with outcomes	% of patients with outcomes
Auricchio, 2014[59]	Overall	457	17.0+8.7 months (mean)	12.8	2.8
Duray, 2008[67]	Overall	79	6 months	1	1.3
Kuelkamp, 2002[69]	Overall	84	185 days (median)	2	2.4
Wollmann, 2014[75]	ICD	114	1 month	1	0.9%
Wollmann, 2014[75]	CRT-D	132	1 month	1	0.8%
Moss, 2009[6]	ICD	731	30 days	6	0.8
Moss, 2009[6]	CRT-D	1,089	30 days	19	1.7
Young, 2003[43] MIRACLE-ICD	Overall	369	6 months	3	0.8 (pneumothorax and hemothorax combined)

CRT=cardiac resynchronization therapy; ICD=implantable cardioverter defibrillator

Pocket Hematoma

Six articles from five studies reported on the incidence of pocket hematoma [6,39,48,59,67,69] (Table 6). Two studies reported a comparison of CRT-D with ICD alone[6,48] and three reported the incidence in cohorts of CRT-D only.[59,67,69] Overall, the incidence of pocket hematoma in patients receiving a CRT-D device ranged from 0.9 to 2.8 percent.

In the studies by Gills et al. (2014)[48] and Moss et al. (2009)[6], the incidence of pocket hematoma in CRT-D patients was slightly higher than in patients receiving an ICD alone (0.6-0.8 % higher). In the MADIT-CRT trial, there was no difference in the incidence of pocket hematoma between men and women receiving CRT-D devices (3.9% vs 3.6% p=0.75).

Pocket hematoma is an uncommon but well-reported complication of CRT-D device implantation. Compared to patients receiving an ICD alone, pocket hematoma appears to be slightly more common in patients receiving a CRT-D device (Table 17).

Table 17. Characteristics of studies of CRT-D reporting on the incidence of pocket hematoma

Author, year	Arm name	N for analysis	Time point (s)	N of patients with outcomes	% of patients with outcomes
Auricchio, 2014[59]	Overall	457	17.0+8.7 months (mean)	13	2.8
Duray, 2008[67]	Overall	79	6 months	1	1.3
Gillis, 2014[48]	ICD	904	30 days	3	0.3
Gillis, 2014[48]	CRT-D	894	30 days	8	0.9
Kuelkamp, 2002[69]	Overall	84	185 days (median)	3	3.6
Moss, 2009[6]	ICD	731	30 days	18	2.5
Moss, 2009[6]	CRT-D	1089	30 days	36	3.3

CRT=cardiac resynchronization therapy; ICD=implantable cardioverter defibrillator

Device Infection

Nine studies in 10 articles reported on the incidence of device infections.[6,39,48,59,61,62,67,69,72,75] Four studies in five articles compared infection rates between a CRT-D and an ICD alone arm.[6,39,39,48,72]

The other five studies were cohorts of CRT-D patients only. The range of CRT-D device infections ranged from 0.9 to 2.8 percent over a highly variable followup time. At 30 days, both the RAFT[48] and MADIT-CRT[6] trials showed a slightly higher incidence of device infection with CRT-D compared to an ICD alone (0.6 to 0.9 % higher). In the MADIT-CRT trial, the incidence of device infection amongst CRT-D devices was higher in women compared to men (2.0% vs. 0.8%, p=0.019).[39]In the study by Massoudi et al., there was a higher incidence of device infection in the CRT-D arm(1.9%) vs. the ICD arm (1.0%), p=0.002. In analysis from the Wollman et al. study, there were four infections in the ICD arm and 2 in the CRT-D arm at 1 month followup.[75]

Device infection is an uncommon complication of CRT-D device implant. The incidence of device infection is slightly more common in patients receiving a CRT-D device compared to an ICD alone (Table 18).

Table 18. Characteristics of studies of CRT-D reporting on the incidence of cardiac device infection

Author, year	Arm name	N for analysis	Time point (s)	N of patients with outcomes	% of patients with outcomes
Auricchio, 2014[59]	Overall	457	17.0+8.7 months (mean)	13	2.8
Duray, 2008[67]	Overall	79	6 months	1	1.3
Massoudi, 2014[72]	ICD	3545	3 years	32	1.0
Massoudi, 2014[72]	CRT-D	3545	3 years	62	1.9
Wollman,2014[75]	ICD	114	1 month	4	3.5
Wollman,2014[75]	CRT-D	132	1 month	2	1.5
Gillis, 2014[48]	ICD	904	30 days	20	2.2
Gillis, 2014[48]	CRT-D	894	30 days	25	2.8
Knight, 2004[61]	Overall	443	329 $\pm$ 180 days	5	1.1
Kuelkamp, 2002[69]	Overall	84	185 days (median)	2	2.4
Landolina, 2011[62]	Overall	3253	18 months (median)	30	0.92
Moss, 2009[6]	ICD	731	30 days	6	0.8
Moss, 2009[6]	CRT-D	1089	30 days	19	1.7

CRT=cardiac resynchronization therapy; ICD=implantable cardioverter defibrillator

Cardiac Perforation/Tamponade

Eight studies reported on cardiac perforation/tamponade (Table 5).[39,43,44,48,64,67,69,75] Four studies compared the incidence of cardiac perforation/tamponade in patients receiving CRT-D versus and ICD alone.[39,48,64,75]

In the study by Gillis et al. (2014), the incidence of cardiac perforation/tamponade was the same (0.1 %) regardless of receiving a CRT-D versus an ICD alone.[48] In the study by Strimel et al. (2011) one patient had perforation/tamponade in the CRT-D cohort compared to no patients in the ICD alone cohorts.[64] In the PainFree SST Study, there was one perforation in the CRT-D arm and none in the ICD arm. In subgroup analysis from MADIT-CRT, the incidence of tamponade between men and women receiving CRT_D devices were similar. The range of cardiac perforation/tamponade for patients receiving CRT-D across all reported cohorts was between 0.1-1.4 percent. The study by Kuelkamp et al. (2002) reported four cases of cardiac perforation or coronary sinus dissection but did not break the complication down any further.[69]

Cardiac perforation/tamponade existed in multiple trials but appears to be a rare event that does not appear to be more frequent in patients receiving a CRT-D device compared to an ICD alone (Table 19).

Table 19. Characteristics of studies of CR-D reporting on the incidence of cardiac perforation/tamponade

Author, year	Arm name	N for analysis	Time point (s)	N of patients with outcomes	% of patients with outcomes
Abraham, 2004[44] MIRACLE-ICD II	Overall	210	From time of implant to hospital discharge	3	1.4
Abraham, 2004[44] MIRACLE-ICD II	Overall	191	From hospital discharge to end of 6-month randomization period	1	0.5
Duray, 2008[67]	Overall	79	6 months	0	0
Wollman, 2014[75]	ICD	114	1 month	0	0
Wollman, 2014[75]	CRT-D	132	1 month	1	0.8
Gillis, 2014[48]	ICD	904	30 days	1	0.1
Gillis, 2014[48]	CRT-D	894	30 days	1	0.1
Kuelkamp, 2002[69]	Overall	84	185 days (median)	4 (cardiac perforation and CS dissection combined)	4.8
Strimel, 2011[64]	CRT-D	42	34 months (mean)	1	1.2
Strimel, 2011[64]	Dual-lead ICD	37	34 months (mean)	0	0
Strimel, 2011[64]	Single-lead ICD	5	34 months (mean)	0	0
Young, 2003[43] MIRACLE-ICD	Overall	369	6 months	4	1.1

CS=coronary sinus; CRT=cardiac resynchronization therapy; NYHA=New York Heart Association; CRT-D=cardiac resynchronization therapy with defibrillator

Lead Dislodgement

Eight studies reported on the incidence of lead dislodgement.[39,44,59,60,64,69,74,75] Two studies compared the incidence of lead dislodgement in CRT-D patients to patients with an ICD alone.[64,75] In the study by Strimel et al. (2011), one patient with CRT-D and one patient with a dual-lead ICD experienced a lead dislodgement over a mean followup of 34 months.[64] In the study by Wollman et al. (2014), there were 2 lead dislodgements in the ICD cohort and 5 in the CRT-D cohort. The remaining studies were cohorts containing patients with CRT-D devices only. The incidence of lead dislodgement ranged from 2.4 to 9.8 percent. Of note, from the MADIT-CRT trial there was no difference in the incidence of lead dislodgement between men and women receiving CRT (4.5% vs. 3.2%, p=0.23)

Lead dislodgement is the most common adverse event seen in the CRT-D population, experienced by up to 9.8 percent of participants in one relatively large prospective cohort, and in up to 5.8 percent of participants in the smaller, randomized MIRACLE-ICD II trial. The data are insufficient to determine whether there is a difference in lead dislodgement rates between patients receiving a CRT-D device versus an ICD alone (Table 20).

Table 20. Characteristics of studies of CRT-D reporting on the incidence of lead dislodgement

Author, year	Arm name	N for analysis	Time point (s)	N of patients with outcomes	% of patients with outcomes
Abraham, 2004[44] MIRACLE-ICD II	Overall	210	From time of implant to hospital discharge	5	2.4
Abraham, 2004[44] MIRACLE-ICD II	Overall	191	From hospital discharge to end of 6-month randomization period	11	5.8
Auricchio, 2014[59]	Overall	457	17.0+8.7 months (mean)	NR	9.8
Bossard, 2014[60]	Overall	49	84 + 18	4	8.2
Koehlkamp, 2002[69]	Overall	84	From time of implant to hospital discharge	1	1.2
Koehlkamp, 2002[69]	Overall	84	From hospital discharge to end of 6-month randomization period	2	2.4
Wollman,2014[75]	CRT-D	132	1 month	2	1.5
Wollman,2014[75]	ICD	114	1 month	5	4.4
Strimel, 2011[64]	CRT-D	42	34 months (mean)	1	2.4
Strimel, 2011[64]	Dual-lead ICD	37	34 months (mean)	1	2.7
Strimel, 2011[64]	Single-lead ICD	5	34 months (mean)	0	0
Vado,2014[74]	Overall	45	18.9 months	3	6.6

CRT-D=cardiac resynchronization therapy with defibrillator; ICD=implantable cardioverter defibrillator

Ventricular Arrhythmias

Thirteen studies from fifteen articles assessed ventricular arrhythmia (VA) outcomes in patients receiving CRT-D devices. [35,39,40,43,44,54,57,60,63,65,66,70,71,73,76] Five studies in seven articles compared VA between patients with a CRT-D device versus an ICD alone.[35,39,40,43,44,54,57] Ouellet analyzed data from 1,820 patients in the MADIT-CRT trial and found that 327 patients (18%) experienced at least one VA; of those, 148 (45 %) experienced at least one subsequent VA. In multivariate analysis, CRT-D conferred protection against first VA compared with ICD alone (HR: 0.71, 95% CI, 0.57 to 0.89). This effect was noted only amongst patients with an LBBB morphology with no difference seen between patients with a non-LBBB morphology with or without a CRT (RBBB or NSIVCD) (HR: 1.05, p=0.82). Once a patient

experienced an arrhythmic event, CRT-D was not protective against subsequent VA compared with ICD alone (HR: 1.58, 95% CI, 0.99 to 2.53).[35] In addition, acute procedure related VA's were similar among men and women receiving both CRT-D and ICD devices alone from this trial.[39] Ruwald et al. reported on the incidence of VAs based on EF response from MADIT-CRT 5 percent of patients in whom the LVEF improved to greater than 50 percent experienced a VA following CRT over a mean follow up of 2.2±0.8 years (following a 1 year post implant period) compared to 13 percent in the 36-50 percent LVEF group and 30 percent in the LVEF<35 percent group.[40]

Higgins et al. (2003) randomized 490 patients with symptomatic CHF and VA to have their CRT-D devices programmed with CRT-on versus off.[54] Of the 245 patients randomized to CRT-on, 36 (15%) received appropriate treatment of VA versus 16% with CRT-off.

In the study by Abraham et al. (2004) over a 6-month followup, 26 percent in the control group (ICD only) and 22 percent in the CRT group experienced ≥1 appropriately detected, spontaneous episode of ventricular tachycardia and ventricular fibrillation (p= 0.61).[44]

In the study by Young et al. (2003) 26 percent in the control group versus 22 percent in the CRT group experienced at least one VA (p=0.47).[43]

In the study by Pinter et al. (2009) over a 6-month followup, 19.4 percent of patients had a VA requiring therapy in the CRT-on arm versus 16.7 percent in the CRT-off arm, a difference that was non- significant.[57] In the study by Gopalamurugan et al., there was no difference in the incidence of VAs in patients receiving a CRT-D device compared to an ICD alone over a mean follow up of 23.9±9.8 months.[73] Theuns et al. (2005) compared CRT-D patients with primary or secondary ICD indications and found that VA occurred in only seven out of 38 patients with a primary prophylactic indication, compared with 29 out of 48 patients with a secondary prophylactic indication (p<0.001).[65]

Five studies reported the incidence of VA in a cohort of CRT-D patients alone.[60,63,66,71,76] The study by Gasparini et al. (2009) found that 126 patients had 621 appropriately detected VAs over a mean followup period of 14 months.[66] The study by Bossard et al. (2014) evaluated outcomes of 49 patients in a CRT-D registry who survived at least 5 years after implant.[60] Fourteen patients (28.6%) experienced VA.[60] Nian-sang et al. (2010) examined the potential pro-arrhythmic effect of CRT during the perioperative period in 54 patients newly implanted with CRT-D devices.[63] Except for one patient with a history of frequent premature ventricular contractions but without paroxysmal or sustained ventricular tachycardia before implantation, the others had no previous history of VA. In total, four patients (7.4%) experienced ventricular tachycardia/ventricular fibrillation within 3 days of implantation. They did not experience any additional VA over the 12 months of followup.[63] Ricci et al. followed 1,404 CRT-D patients over a median follow up of 31 months; 36 percent experienced a VA. Haugaa and colleagues followed 201 patients who had received a CRT-D device of whom 14 percent experienced a VA over a followup of 2 years.

van Boven et al. (2013) followed a cohort of patients primarily receiving CRT-D devices (96.5 %) and separated patients into responders and non-responders (response was defined as an LVEF≥35percent on followup echocardiogram).[70] Over a 3-year followup period, 12 percent of patients experienced ≥1 appropriate shock all of whom were deemed non-responders by echocardiography.

Overall, there is conflicting evidence as to whether CRT-D is protective from VAs compared to an ICD alone, with four trials showing no difference and one large trial showing CRT to be

protective from VAs. More data are needed to confirm this latter finding. The data, however, are consistent that CRT-D does not appear to increase the rate of VAs compared to an ICD alone.

Inappropriate Implantable Cardioverter Defibrillator Shocks

Eight studies reported on inappropriate ICD shocks.[40,43,44,48,64,68,70,76] Three studies compared the incidence of inappropriate shocks in patients receiving a CRT-D device versus an ICD alone. Abraham et al. (2004) found no difference in the rate of inappropriate shocks during the 6 month followup period in patients receiving a CRT-D device compared to those receiving an ICD alone [44]; however they did not report the numbers or percentages of participants experiencing inappropriate shocks (p=0.78).

In the RAFT trial, 2.2 percent of patients in the CRT-D group were hospitalized for inappropriate shocks versus 3.3 percent in the ICD-only group.[48] The trial did not report the incidence of inappropriate shocks not resulting in hospitalization.

In the study by Young et al. (2003) there was no difference in the incidence of inappropriate shocks between patients in the CRT group versus the control arm over a 6-month followup (4.2 vs. 7.2%, p=0.26). These data were not sufficient to serve as the basis for a meta-analysis because the duration of followup varied from 30 days to 3 years.

Strimel et al. (2011) reported that two (2.4%) of octogenarians with ICDs (with or without CRT) experienced inappropriate shocks over a mean followup of 34 months.[64]

In the retrospective cohort study by Van Boven et al. (2013), 33 participants (6.1 %) experienced an IS over a mean follow up time of 3.2 $\pm$ 1.8 years.[68] In a second study by van Boven et al. (2013)[70], the incidence of IS was 8.5 percent (Table 21). Ricci et al. reported an incidence of 7% of inappropriate shocks in a cohort of 1404 CRT-D patients over a median follow up of 31 months.[76] Ruwald et al, in analysis from MADIT-CRT, demonstrated no significant difference in inappropriate shocks amongst patients based on level of LVEF improvement. [40]

In conclusion, there is no apparent difference in the incidence of inappropriate ICD shocks in patients receiving a CRT-D device compared to an ICD alone.

Table 21. Characteristics of studies of CRT-D reporting inappropriate ICD shocks

Author, year	Arm name	N for analysis	Time point (s)	N of patients with outcomes	% of patients with outcomes
Gillis, 2014[48]	ICD	904	30 days	30	3.3
Gillis, 2014[48]	CRT-D	894	30 days	20	2.2
Strimel, 2011[64]	Overall	84	34 months (mean)	2	2.4
Ricci, 2014[76]	Overall	1404	31 months (median)	101	7
Van Boven, 2013[68]	CRT-D	543	3.2 $\pm$ 1.8 years (mean followup)	33	6.1

Author, year	Arm name	N for analysis	Time point (s)	N of patients with outcomes	% of patients with outcomes
Van Boven, 2013[70]	Overall	179	Median 3.0 years	12	8.5
Young, 2003[43]	CRT-on	180	6 months	8	4.2
Young, 2003[43] MIRACLE-ICD	CRT-off	189	6months	13	7.2

CRT=cardiac resynchronization therapy; CRT-D=cardiac resynchronization therapy with defibrillator; ICD=implantable cardioverter defibrillator

Death Within One Week

Only two studies reported on death within 1 week of implantation.[64,67] Both of these cohort studies reported zero deaths.

Effectiveness of Cardiac Resynchronization Therapy with Pacemaker (CRT-P)

Table 22. Evidence addressing effectiveness and harms of CRT-P

	CRT –P effectiveness	CRT–P Harms
Number of included studies	6 trials (reported in 16 articles)	11 studies (reported in 13 articles) Five were RCTs and the rest were prospective cohorts.
Patient characteristics	• The number of patients enrolled ranged from 56-1,520 • The percentage of women was between 9.1-33% • The mean age ranged from 63-73 years old • All trials reported NYHA class of the participants	• The number of patients enrolled ranged from 7-813 • The percentage of women in the studies ranged from 5-28.6% • The mean age ranged from 53-68 years old • Two studies reported the NYHA class of the participants.
Outcomes (number of included studies)	• All- cause mortality: 6 trials • Heart failure hospitalizations: 5 trials • Left ventricular end systolic • volume/volume index : 1 trial • Minnesota Living with Heart Failure Questionnaire: 5 trials • Left ventricular ejection fraction: 4 trials • Left ventricular end diastolic volume/volume index: 3trials • 6 minute hall walk distance: 5 trials	• Procedure related complications: 2 studies • Length of hospital stay: 2 studies • Pneumothorax: 2 studies • Pocket hematoma: 3 studies • Device Infection: 3 studies • Cardiac perforation/ tamponade: 3 studies • Lead dislodgement: 7 studies • Ventricular arrhythmias: 0 • Death (within a week): 3 studies
Key findings	There is moderate evidence that CRT-P, compared to optimal medical therapy, is effective in improving survival, reducing LESV, and reducing hospitalizations for heart failure in patients. We found insufficient evidence about the effect of CRT-P on quality of life as measured with the MLHFQ.	Harms associated with CRT-P were as follows: cardiac perforation/tamponade (0-1.6%), pocket hematoma (0.2-9.5%), pneumothorax (0.5-1.5%), device infection (0.7-4.8%), and lead dislodgement (1.7-17%). Death within one week of implantation was reported in only very small studies making the true incidence unclear.

Study Characteristics

Six trials[3-5,8,55,58] addressed the effectiveness of CRT-P (reported in 16 articles).[3-5,8,22-25,27-30,42,45,55,58] Six of the articles reported re-analyses from the CARE-HF clinical trial,[22-25,27,28] two reported secondary analyses of the COMPANION trial,[29,30] and one presented a secondary analysis of the MIRACLE trial.[42] Four trials were RCTs [3-5,58] and two were randomized crossover trials.[8,55] All six trials reported the device name (Table 20). The planned length of followup ranged from 3 to 18 months. One study did not report followup time.[23] One study also assessed effectiveness at the end of study (followup at 29 months) (Evidence Table 1).[25]

In general, the trials were heterogeneous in the optimal medical therapy used as the comparison group. Three trials compared CRT-P to medical therapy.[3-5] One trial compared CRT-P and coronary artery bypass grafting (CABG) to CABG alone.[58] One trial compared biventricular (BiV) pacing to no pacing, using a crossover design.[8] Another trial compared BiV pacing to right ventricular (RV) pacing alone, using a crossover model.[55] Three trials (published in 12 articles) were industry funded (Table 23).[3-5] One trial, published in two articles, was partially industry funded. [8,45]

Table 23. Study characteristics of trials assessing effectiveness of CRT

Author, year	Length of followup (months)	Study design	Number of patients	Comparison	Device model name	NYHA class	Funding source
CARE-HF							
Cleland, 2004[5]	18	RCT	809	CRT-P vs. OMT	InSync or InSync III, Medtronic	III-IV	Industry
Cleland, 2009[24]	18	RCT	809	CRT-P vs. OMT	InSync or InSync III, Medtronic	III-IV	Industry
Ghio, 2009[25]	18	RCT	735	CRT-P vs. OMT	InSync or InSync III, Medtronic	III-IV	Industry
Wikstrom,2009[27]	18	RCT	813	CRT-P vs. OMT	InSync or InSync III, Medtronic	III-IV	Industry
Cleland, 2006[22]	18	RCT	812	CRT-P vs. OMT	InSync or InSync III, Medtronic	III-IV	Industry
Cleland, 2012[28]	18	RCT	809 (309 with re-consent)	CRT-P vs. OMT	InSync or InSync III, Medtronic	III-IV	Industry
Cleland, 2007[23]	NR	Post Hoc Analysis	813	CRT-P vs. OMT	InSync or InSync III, Medtronic	I-IV	Industry
COMPANION							
Bristow, 2004[4]	Medical therapy arm: 14.8 months CRT-P arm 16.5 months	RCT	1,520	CRT-P vs. OMT	Contak TR 1241	III-IV	Industry
Carson 2005[30]	Mortality endpoint OMT arm: 14.8 months CRT-P arm 16.5 months	RCT	1,510	CRT-P vs. OMT	Contak TR 1241	III-IV	Industry
Anand 2009[29]	Hospitalization endpoint OPT arm:11.9 months CRT-P arm: 16.2 months	RCT	1,520	CRT-P vs. OMT	Contak TR 1241	III-IV	Industry
MIRACLE							
Abraham, 2002[3]	6	RCT	453	CRT-P vs. OMT	InSync 8040, Medtronic	III-IV	Industry

Author, year	Length of followup (months)	Study design	Number of patients	Comparison	Device model name	NYHA class	Funding source
St. John Sutton, 2003[42]	6	RCT	323	CRT-P vs. OMT	InSync 8040, Medtronic	III-IV	Industry
MUSTIC							
Cazeau, 2001[8]	6	RCT cross-over	67	CRT-P on vs. off	Chorum MSP 7336 and Insync 8040	III-IV	Industry; Swedish Heart and Lung Association; Swedish Medical Research Council
Leclercq,2002,[45]	6	RCT cross-over	45	CRT-P on vs. off	Chorum 7336 MSP, ELA Medical, Montrouge, France, and InSync 8040, Medtronic	III-IV	Industry
Other trials							
RD-CHF Leclercq, 2007[55]	6	RCT cross-over	56	CRT-P vs. RV pacing	Chorum MSP 7336, Ela Medical	III-IV	Not Reported
Pokushalov, 2010[58]	18	RCT	178	CABG vs. CABG+CRT-P	Insync III, Medtronic	III-IV	Not Reported

OMT=optimal medical therapy; RCT=randomized controlled trial; CRT-P=cardiac resynchronization therapy with pacemaker; CABG=coronary artery bypass grafting; RV=right ventricle; vs.=versus

Participant Characteristics

The number of patients in the trials ranged from 56 to 1,520. The percentage of women in the trials ranged from 9.1 percent in Leclerq et al. (2007)[55] (this study, the RD-CHF trial, included no women in one of its comparison arms) to 33 percent in the CRT-P arm of the COMPANION trial.[4] The mean age in the trials ranged from 63 to 73 years old. Two trials reported median rather than mean age (median ranging from 66-69 years old).[5,8] One study reported racial distribution of subjects (90 percent of the subjects were white).[3,42] The proportion of patients with ischemic cardiomyopathy (ICM) ranged from 32 to 59 percent. One trial did not report on the proportion of ICM.[42] Only one trial reported the prevalence of atrial fibrillation (AF) (21%).[55] Three trials excluded patients with any history of AF.[4,5,8] One trial excluded patients with a history of AF within 1 month[3] of enrollment, and another did not exclude patients with AF, but also did not report any history of AF.[58]

All six trials reported NYHA class of study participants, with five of six enrolling patients having class III-IV symptoms. Enrollment of class IV patients ranged from 6 percent in the CRT-P arm of CARE-HF[5] to 18 percent in the optimal medical therapy arm of the COMPANION trial.[4] Of note, in the large CARE-HF trial, 21.5 percent of patients assessed themselves to be class I-II (in contradiction to physician assessment).[23] The trial by Cazeau et al. (2001) only enrolled patients with class III symptoms.[8]

Four of the primary trials reported the mean left ventricle ejection fraction (LVEF),[3,8,55,58] ranging from 21.6 percent in the optimal medical therapy (OMT) arm of the MIRACLE trial[3] to 30 percent in the CABG alone arm in the trial by Pokushalov et al. (2010).[58] Two large trials reported median LVEF, ranging from 20 percent in the optimal medical therapy arm of the COMPANION trial[4] to 25 percent in both arms of the CARE-HF trial.[5]

Four of the primary trials reported the mean QRS duration,[3,8,55,58] ranging from 137ms in the CABG/CRT arm of the trial by Pokushalov et al. (2010)[58] to 20ms in the trial by Leclercq et al. (2007)[55] Of note, all patients had permanent RV pacing prior to CRT-P upgrade in this study.[55] Two large trials reported median QRS duration, ranging from 158ms in the OMT arm of the COMPANION trial[4] to 160ms in both arms of the CARE-HF trial.[5] Four of the primary trials reported the incidence of native left bundle branch block prior to CRT-P. The study by Leclercq et al. (2007)[55] enrolled only patients with permanent RV pacing and the MIRACLE[3] and CARE-HF[5] trials did not report on QRS morphology. The incidence of left bundle branch block ranged from 69 percent in the CRT-P arm of the COMPANION trial[4] to 87 percent in the MUSTIC trial.[8] Only the COMPANION trial reported the incidence of right bundle branch block[4] (9 percent in the optimal medical therapy arm and 12 percent in the CRT-P arm). No studies reported on patients with non-specific intraventricular conduction delay. The study by Leclercq et al. (2007) was the only trial to evaluate paced patients (100% in this trial).[55]

In general, these studies comprised homogeneous patient populations with regard to physiological criteria, such as NYHA class and QRS duration. The proportions of female patients varied between studies, and only one reported race; thus gender and racial makeup of these populations might not be generalizable (Evidence Table 2).

Risk of Bias

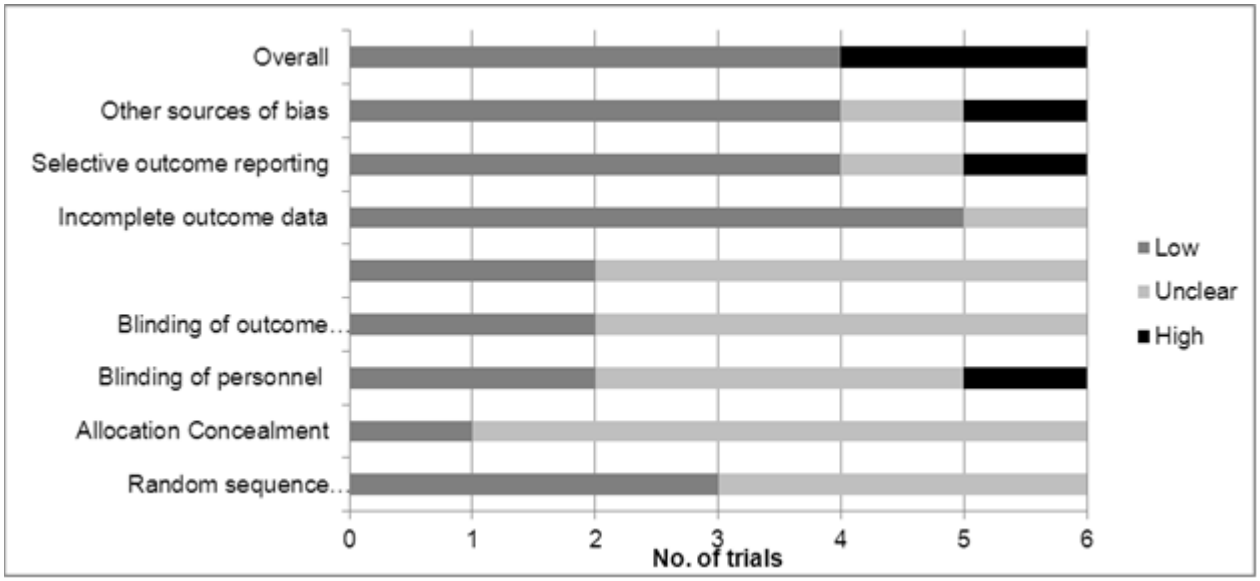
Several types of risk of bias were present in these studies. The most common potential cause of bias was lack of allocation concealment and blinding; details of allocation and blinding were not reported in the majority of studies. In the majority of studies, criteria or protocols for outcome assessment were also not assessed, making outcome reporting bias a potential concern (Table 24 and Figure 12).

Table 24. Summary of risk of bias for trials assessing effectiveness of CRT-P

Author, year	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessors	Assessing blinding by outcome	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall quality
CARE HF									
Cleland,2004[5] Cleland,2007[23] Cleland,2012[28] Cleland,2006[22] Cleland,2009[24] Wikstrom,2009[27] Ghio,2009[25]	-	?	?	?	?	-	+	?	+
COMPANION									
Bristow,2004[4] Anand, 2009[29] Carson,2005[30]	?	?	+	-	-	-	-	+	+
MIRACLE									
Abraham,2002[3] Sutton,2003[42]	-	-	-	-	-	-	-	-	-
MUSTIC									
Cazeau, 2001[8] Leclercq,2002,[45]	?	?	-	?	?	?	?	-	+
Other Trials									
Leclercq,2007[55]	-	?	?	?	?	-	-	-	-
Pokushalov,2010[58]	?	?	?	?	?	-	-	-	+

+=High
-=Low
?=Unclear

Figure 12. Summary of risk of bias for trials assessing effectiveness of CRT-P



Effectiveness Outcomes

The studies addressed various outcomes, the most common of which were all-cause mortality and changes in quality of life as measured by MLHFQ (in 8 studies) (Table 25). Five trials assessed changes in 6-minute hall walk distance and heart failure hospitalizations, four studies assessed changes in LVEF, left ventricle end systolic volume (LVESV), and left ventricle end diastolic volume (LVEDV). No studies assessed changes in clinical composite score. No study reported results for these outcomes by the pre-specified subgroups of interest.

Table 25. Outcomes reported in trials assessing effectiveness of CRT-P

Author, year	All-cause mortality	Heart failure hospitalizations	LVESV	LVEDV	MLHFQ score	Change in LVEF	Clinical composite score	6-MHWD
CARE-HF								
Cleland, 2004[5]	+	+			+			
Cleland, 2009[24]	+							
Ghio[25]			+	+				
Wikstrom[27]	+		+		+	+		
Cleland, 2006[22]								
Cleland, 2012[28]	+							
Cleland, 2007[23]	+				+			
COMPANION								
Bristow, 2004,[4]	+				+			+
Carson, 2005,[30]								
Anand, 2009,[29]		+						
MIRACLE								
Abraham, 2002[3]	0	+			+	+		+
St. John Sutton, 2003[42]			+	+		+		
MUSTIC								
Cazeau, 2001,[8]		+			+			+
Leclercq,2002,[45]		+			+			+
Other trials								
Leclercq, 2007,[55]		+			+			+
Pokushalov, 2010,[58]	+		0	0	+	+		+

Effectiveness outcomes for CRT-P by study: + = CRT-P effective over comparison group; - = CRT-P not effective compared to comparison group; 0 = no significant difference; LVEF=left ventricle ejection fraction; 6MHWD=6-minute hall walk distance; LVESV=left ventricle end systolic volume; LVEDV=left ventricle end diastolic volume; MLHFQ=Minnesota Living with Heart Failure Questionnaire

All-cause Mortality

Six trials (published in 10 articles) assessed all-cause mortality.[3-5 ,22-24 ,27 ,28 ,55 ,58]

Pokushalov et al. (2010) assessed the outcome at 6, 12, and 18 months, comparing those receiving CABG alone to those receiving CABG and CRT-P.[58] At 6 months of followup, 10 CABG patients (11.4%) and four CABG + CRT-P patients (4.4%) died. At 12 months of followup, eight CABG patients (9.1%) and three CABG + CRT-P patients (3.3%) died. At 18 months of followup, in the CABG group, 23 patients (26.4%) died, compared with nine (9.9%) in the CABG + CRT-P group (log-rank test, p=0.006). Fourteen of the observed deaths were due to sudden cardiac death, and 18 deaths were due to "pump failure".

In the study by Cleland et al. (2004) comparing CRT-P to medical therapy, 120 of 404 patients (30%) died of any cause in the medical therapy group, compared to 82 of 409 patients (20%) in the CRT-P group (HR: 0.64, 95% CI, 0.48 to 0.85, p<0.002).[5] Cleland et al. (2009) also reported these results.[24] In Cleland et al. (2006) after 1,600 days of followup (mean-followup of 36.4 months), the mortality was 154 of 404 (38%) in the medical therapy group, compared to 101 of 409 (25%), in the CRT-P group (HR: 0.6, 95% CI, 0.47 to 0.77, p<0.001).[22] Cleland et al. (2012)[28] also reported these results, as did Cleland et al. (2007).[23]

Abraham et al. (2002) compared a control group to a CRT-P group.[3] At 6 months, the number of patients who died from any cause was 16 of 225 (7.1%) in the control group, compared to 12 of 228 (5.3%) in the CRT-P group (HR: 0.73, 95% CI, 0.34 to 1.54, p=0.4).

Leclerq et al. (2007) assessed all-cause mortality at 6 months.[55] During the crossover phase, two patients died from sudden cardiac death during the biventricular phase and two patients died from CHF during the right ventricular phase. Two other patients died from a pulmonary embolism and respiratory failure while in the right ventricular phase. The overall mortality in the study was 13.5 percent at 6 months of followup. The study did not report analyses of comparisons of mortality between groups.

Wikstrom et al. (2009) compared all-cause mortality between CRT-P and medical therapy in two separate groups, those with and without ischaemic heart disease (IHD), at 18 months. CRT-P had a significant effect on all-cause mortality (HR: 0.60, 95% CI, 0.42 to 0.86 and HR: 0.59, 95% CI, 0.37 to 0.92 for IHD and no IHD, respectively).[27]

In the COMPANION trial, 77 of 308 patients in the optimal medical therapy group (25%) died during the entire study period, for a mortality rate of 19 percent. The mortality rate in the CRT-P group was 21 percent (131 of 617 patients) during the entire study period. The study reported an association between CRT-P implementation and a reduction in the risk of death from any cause (HR: 0.76, 95% CI, 0.58 to 1.01, p=0.059).[4 ,30] The study also reported that pump failure was the predominant mode of death and that it was reduced by CRT-P, but that cardiac death was not reduced by CRT-P compared to OMT.

Three trials with longer followup times (reported in 4 articles) showed statistically significant differences in mortality favoring CRT-P.[4 ,5 ,27 ,58] Two additional trials that reported on all-cause mortality had shorter followup times (3 or 6 months), which might partially explain the lack of statistically significant results showing difference between CRT-P and optimal medical therapy.[3 ,55]There is moderate strength of evidence favoring CRT-P versus optimal medical therapy in mortality (Table 27).

The results are derived from NYHA class III-IV patients and applicability to NYHA class I and II is unclear. Future studies should seek to reproduce this mortality finding in CRT-P with consistent comparators and methodology.

Heart Failure Hospitalizations

Five trials, reported in six articles, assessed heart failure hospitalization outcome.[3,5,8,29,45,55] Cleland et al., assessed hospitalizations for heart failure at 18 months.[5] Of the 404 patients in the medical therapy group, 184 (46%) had been hospitalized by the end of followup, compared to 125 (31%), of the 409 patients in the CRT-P group (HR: 0.61, 95% CI, 0.49 to 0.77, p<0.001).

Abraham et al. (2002) compared a control group, N=225, to a CRT-P group, N=228, at 6 months.[3] In the control group there were 34 hospitalizations (15.1%), and in the CRT-P group 18 hospitalizations (7.9%) (HR: 0.5, 95% CI, 0.28 to 0.88, p<0.02).

Leclerq et al. (2007) assessed heart failure hospitalization at 3 months in the crossover study.[55] At 3 months, there was one hospitalization in the BiV-first group versus nine hospitalizations in the RV first group. Compared to the RV first group, the BiV-first group had significantly fewer hospitalizations (p=0.01).

The MUSTIC trial[8] using a crossover model, randomized patients to active or inactive pacing first. Three hospitalizations for heart failure occurred during active pacing, and nine during inactive pacing (p<0.05). Among one of the subgroups specified for the current review, patients with atrial fibrillation, Leclercq et al. (2002) conducted a secondary analysis of the MUSTIC trial, finding a total of three hospitalizations during the first three-months of the crossover study (the number of hospitalizations in each group was not reported).[45] During the entire 6 months of this crossover study, 10 of 44 patients (23%) were hospitalized for heart failure during the univentricular period, for a total of 11 hospitalizations, compared to 3 (7%) during the biventricular period.

In a secondary analysis of the COMPANION trial, Anand et al. (2009) showed (after adjustment for length of followup) an association between CRT-P and a 44 percent reduction in heart failure hospital admissions per patient-year compared with the optimal medical therapy group (from 0.7 to 0.4, no p-value specified).[29]

In summary, the five trials addressing hospitalization outcome reported fewer hospitalizations in the CRT-P group compared to optimal medical therapy. One study found fewer hospitalizations in a subgroup of patients with AF.[45] There is moderate strength of evidence indicating fewer hospitalizations for CRT-P compared with optimal medical therapy (Table 27).

These results are derived from NYHA class III-IV patients and applicability to NYHA class I and II is unclear.

Left Ventricular End Systolic Volume

Four trials assessed LVESV in comparing CRT-P with optimal medical therapy.[25,27,42,58]

Pokushalov et al. (2010) assessed the outcome at 6, 12, and 18 months, comparing those receiving CABG alone to those receiving CABG and CRT-P.[58] At baseline, 6, 12, and 18 months, the difference in LVESV between CABG and CABG + CRT-P over time was not statistically significant (p=0.06). In addition, the differences intragroup and between groups at the individual time points were not statistically significant.

St John Sutton et al. (2003) compared CRT-P to control at 3 and 6 months and found a statistically significant decrease in LVESV in the CRT-P group but not in the control group.[42] In within-arm comparisons, the LVESV decreased a median of 21.8mL in the CRT-P group (95% CI, -29.7 to -13.9), compared to a median increase of 0.6mL in the control group (95% CI, -8.7 to 8.7, p<0.05). Similar changes were reported at 6 months, with the median decrease of 25.6mL in the intervention group (95% CI, -37.4 to -17.7, p<0.05).

Ghio et al. (2009) compared CRT-P to medical therapy in the CARE-HF trial.[25] The decrease in LVESV at 18 months from baseline was 55.1mL more, that is, a greater decrease, in the CRT-P group than in the medical therapy group (95% CI, -67.2 to -42.9. p<0.0001). Wikstrom et al. (2009) compared LVESV between CRT-P and medical therapy in two separate groups, those with and without ICM, at 3 months.[27] In those with ICM, the mean LVESV was 193.99cm^3 (SD 69.36) in the CRT-P group and 231.54cm^3 (SD 86.05) in the medical therapy group; in those without ICM, the mean LVESV was 194.01cm^3 (SD 104.74) in the CRT-P group and 233.18cm^3 (SD 98.36) in the medical therapy group (p=0.0354).

In summary, these trials provide moderate evidence that CRT-P improves LVESV (Table 27). These results are derived from NYHA class III-IV patients and applicability to NYHA class I and II is unclear.

Left Ventricular End Diastolic Volume

Three trials assessed LVEDV in comparing CRT-P with optimal medical therapy.[25,42,58]

Pokushalov et al. (2010) assessed the outcome at 6, 12, and 18 months, comparing those receiving CABG alone to those receiving CABG and CRT-P.[58] At baseline, 6, 12, and 18 months, the difference in LVEDV over time was not statistically significant (p=0.65). In addition, the differences intragroup and between groups at the individual time points were not statistically significant.

St John Sutton et al. (2003) compared CRT-P to control at 3 and 6 months and found a statistically significant decrease in LVEDV in the CRT-P group but not in the control group.[42] In within-arm comparisons, the LVEDV decreased a median of 22.6mL in the CRT-P group (95% CI, -33.3 to -5.8), compared to a median increase of 2.8mL in the control group (95% CI, -3.8 to 12.3, p<0.05). The study reported similar changes at 6 months, with a median decrease of 27.2mL in the intervention group (95% CI, -37.1 to -16.9, p<0.05

Ghio et al. (2009) compared CRT-P to medical therapy in the CARE-HF trial.[25] For LVEDV at 18 months, the change from baseline was greater in the CRT-P group than the medical therapy group, -57.6mL (95% CI, -71.8 to -43.4, p<0.0001).

The fact that only two of three studies showed statistically significant differences in LVEDV, can likely be explained by the difference in comparisons. St John Sutton et al. (2003) together with the CARE-HF trial (Ghio et al. (2009)) compared CRT-P to medical therapy[25,27,42] whereas Pokushalov et al. (2010)[58] compared CABG therapy alone to CABG + CRT-P.

In summary, it is unclear whether LVEDV is improved by CRT-P compared with optimal medical therapy (Table 27).

Minnesota Living with Heart Failure Questionnaire Score

Five trials (published in 8 articles) assessed quality of life using MLHFQ in comparing CRT-P with optimal medical therapy.[3-5,8,23,27,45,58]

Pokushalov et al. (2010) assessed the outcome at 6, 12, and 18 months, comparing those receiving CABG alone to those receiving CABG and CRT-P.[58] At baseline, 6, 12, and 18 months, the MLHFQ score in the CABG group versus the CABG + CRT-P group was 63.2+/-19 versus 64.9+/-20; 51.9+/-22 versus 39.8+/-16 (p<0.05 for difference between the two groups and p<0.01 for difference from baseline); 41.7+/-8 versus 32.9+/-7 (p<0.05 for difference between the two groups and p<0.01 for difference from baseline); and 46.4+/-11 versus 22.9+/- 5 (p<0.05 for difference between the two groups and p<0.01 for difference from baseline), respectively. The difference between CABG and CABG + CRT-P over time was statistically significant

(p<0.001). Of note, the MLHFQ score at 18 months decreased from 87 at baseline to 64 in the CABG-only group and from 91 at baseline to 82 in the CABG + CRT-P group.

Abraham et al. (2002) compared a control group to a CRT-P group.[3] At 6 months, the median change in the MLHFQ score from baseline was -9 in the control group (N=193, 95% CI, -12 to -5), and -18 in the CRT-P group (95% CI, -22 to -12). The difference between these intragroup changes was statistically significant (p=0.001).

Cleland et al. (2004) comparing CRT-P to medical therapy, found at 90 days that the mean difference between groups in MLHFQ score was -10 (95% CI, -8 to -12, p<0.001).[5] Wikstrom et al. (2009) also from the CARE-HF trial compared MLHFQ between CRT-P and medical therapy at 3 months in two separate groups, those with and without ICM.[27] CRT-P had no significant effect on MLHFQ. In those with ICM, the mean difference was 31.29 (SD 19.74) in the CRT-P group and 30.25 (SD 22.00) in the medical therapy group. In those without ICM, the mean difference was 41.50 (SD 20.49) in the CRT-P group and 35.56 (SD 21.68) in the medical therapy group, p=0.1542. Another report from the CARE-HF trial, Cleland et al. (2007) found that the proportion of subjects with an MLHFQ score <= 35 was 166 (41%) in the control group, compared to 213 (52%) in the CRT-P group (HR: 0.64, 95% CI, 0.48 to 0.86, p=0.002).[23]

Bristow et al. (2004) compared MLHFQ between CRT-P and optimal medical therapy groups. At 3 months, the change compared to baseline was -24+/-27 in the CRT-P group versus -9+/-21 in the OMT group (p<0.001). A similar, statistically significant difference existed at 6 months (p<0.001).[4]

In the MUSTIC trial those with active pacing had a MLHFQ score of 29.6+/-21.3, while those on inactive pacing had a score of 43.2+/22.8 (p<0.001).[8]

Among one of the subgroups specified for the current review, patients with atrial fibrillation, Leclercq et al. (2002) conducted a secondary analysis of the MUSTIC trial.[45] For the group receiving biventricular pacing first, the score was 40 (SD 23) at randomization. For the RV pacing first group, the score was 50 (SD 20) at randomization. At six months, the score was 38.5 (SD 21.4) in the univentricular group, and 34.1 (SD 20.6) in the biventricular group, showing no statistically significant difference.

These trials assessed this outcome at different endpoints and with different comparisons, which might explain the inconsistency in the results comparing CRT-P to other therapy. There was insufficient evidence to draw any conclusions about the effect of CRT-P on MLHFQ compared with optimal medical therapy (Table 27).

Left Ventricular Ejection Fraction

Four trials assessed the change in LVEF, including two reports of the MIRACLE trial.[3,27,42,55,58]

Pokushalov et al. (2010) assessed the outcome at baseline, 6, 12, and 18 months, comparing those receiving CABG alone to those receiving CABG and CRT-P.[58] At baseline, 6, 12, and 18 months, the LVEF in the CABG group versus the CABG + CRT-P group was 30+/-2.2 versus 28+/-2.7; 34+/-3.4 versus 39+/-3.7; 32+/-3.4 versus 41+/-2.5 (p<0.05 for difference between the two groups and p<0.01 for difference from baseline); 29+/-2.6 versus 42+/-1.4 (p<0.05 for difference between the two groups and p<0.01 for difference from baseline); and 28+/2.7 versus 42+/-1.9 (p<0.05 for difference between the two groups and p<0.01 for difference from baseline), respectively. The difference between CABG and CABG + CRT-P over time was significant (p<0.001). Of note, the number in the CABG-only group decreased over time from 87

at baseline to 64 at 18 months; and, in the CABG + CRT-P group, from 91 at baseline to 82 at 18 months.

St John Sutton et al. (2003) compared CRT-P to control at 3 and 6 months.[42] In within-arm comparisons, the LVEF increased a median of 0.6 in the CRT-P group (95% CI, -0.4 to 1.8), compared to a median increase of 2.3 in the control group (95% CI, 1.5to 3.2), which was significant ($p<0.05$). Similar changes were noticed at 6 months, with the median increase of 3.6 in the CRT-P group (95% CI, 2.5 to 5.8, $p<0.05$).

Abraham et al. (2002) compared a control group to a CRT-P group.[3] At 6 months, median change in the LVEF from baseline was -0.2 in the control group (95% CI, -1 to 1.5), and in the CRT-P group, 4.6 (95% CI, -3.2 to 6.4). This difference was statistically significant ($p<0.001$).

It should be noted that St. John Sutton et al. (2003)[42] and Abraham et al. (2002)[3] represent two reports of LVEF from the same trial, MIRACLE, with differing results.

In Leclerq et al. (2007) for all patients, the LVEF was 29.5 (SD 11) at baseline and 29 (SD 11) at 3 months.[55] For the group receiving biventricular pacing first, the LVEF was 32 (SD 11) at baseline and 34 (SD 12) at 3 months; for the group receiving right ventricular pacing first the LVEF was 32 (SD 13) at baseline and 37 (SD 11) at 3 months. The difference in the right ventricular- first group was not statistically significant from that of the biventricular-first group ($p=0.1$). Leclerq et al. (2007) conducted their crossover study differently from the other trials making it difficult to compare.

Wikstrom et al. (2009) compared LVEF between CRT-P and medical therapy in two separate groups, those with and without ICM, at 3 months and found no significant difference between CRT-P and medical therapy.[27] In those with ICM, the mean LVEF at 3 months was 29.08 (SD 6.90) in the CRT-P group and 26.31 (SD 6.50) in the medical therapy group; in those without ICM, the LVEF was 30.59 (SD 8.19) in the CRT-P group and 26.56 (SD 6.92) in the medical therapy group ($p=0.3550$).

In summary, three of these four trials showed improved LVEF with CRT-P compared to optimal medical therapy, though comparisons were different between trials, as was length of followup. Thus, the absolute difference in LVEF is not comparable from study to study.

6-Minute Hall Walk Distance

Five trials assessed 6-minute hall walk distance (6MHWD) in comparing CRT-P with optimal medical therapy. Pokushalov et al. (2010) assessed the outcome at 6, 12, and 18 months, comparing those receiving CABG alone to those receiving CABG and CRT-P.[58] At baseline, 6, 12, and 18 months, the distance walked by the CABG group versus the CABG + CRT-P group was: 265+/-32m versus 248+/-51m, 379+/-127m versus 432+/-129m ($p<0.05$ for difference between the two groups and $p<0.01$ for difference from baseline), 317+/- 67m versus 448 +/- 79m ($p<0.05$ for difference between the two groups and $p<0.01$ for difference from baseline), and 289+/-72m versus 452+/- 65m ($p<0.05$ for difference between the two groups and $p<0.01$ for difference from baseline).

Abraham et al. (2002) compared a control group to a CRT-P group.[3] At 6 months, the median change of walk distance from baseline was +10m in the control group (N=198, 95% CI, 0 to +25), and +39m in the CRT-P group (95% CI, +26 to +54). The difference between these groups was statistically significant ($p=0.005$).

Leclerq et al. (2007) assessed 6MHWD at baseline and 3 months in three groups: patients receiving biventricular pacing first, patients receiving right ventricular pacing first, and all patients.[55] For the group receiving biventricular pacing first, the walk distance was 316m (SD

25) at baseline and 358m (SD 88) at 3 months. For the right ventricular pacing first group, the distance was 332m (SD 173) at baseline and 414m (SD 110) at 3 months. For all patients, the distance was 324m (SD 149) at baseline and 386m (SD 99) at 3 months. The difference between the right ventricular-first group and the biventricular-first group was statistically significant ($p=0.002$).

Bristow et al. (2004) compared optimal medical therapy with CRT-P.[4] At 3 months, the change in 6MHWD was 33±99m in the pacemaker group, compared to 9±84m in the optimal medical therapy group ($p<0.001$). Results were similar at 6 months.

In the MUSTIC trial the mean distance walked was 375±83m during the inactive period, compared to 424±83m during the active period ($p<0.004$). [8]

Among one of the subgroups specified for the current review, patients with atrial fibrillation, Leclercq et al. (2002) conducted a secondary analysis of the MUSTIC trial.[45] For the group receiving biventricular pacing first, the walk distance was 338m (SD 95) at randomization. For the RV pacing first group, the distance was 317m (SD 71) at randomization. At six months, the walk distance was 341m (SD 100) in the univentricular group, and 359 (SD 121) in the biventricular group, which was not statistically significantly different.

In summary, though these five trials considered different comparisons, they all showed effectiveness in improving 6MHWD in comparing CRT-P to another treatment.

These results are derived from NYHA class III-IV patients and applicability to NYHA class I and II is unclear. One study showed no difference in the AF subgroup of the MUSTIC trial.[45] It is unclear whether the improvements in 6MHWD translate to differences that are significant for patients or clinically.

Table 26. Summary of CRT-P effectiveness outcomes reported by subgroup

Female (no. of trial)	LBBB (no. of trial)	QRS duration >150ms (no. of trial)	Non ischemic cardiac conditions (no. of trial)	Atrial fibrillation (no. of trial)
All-cause mortality				
1 trial Beneficial in women	NR	NR	NR	NR
Heart failure hospitalizations				
NR	NR	NR	NR	1 trials Beneficial in patients with AF
Minnesota Living with Heart Failure Questionnaire				
NR	NR	NR	NR	NR
6-minute hall walk distance				
NR	NR	NR	NR	1 trial No difference in outcome
Left ventricular end systolic volume/volume index				
NR	NR	NR	NR	NR
Left ventricular ejection fraction				
NR	NR	NR	1 trial No difference in outcome	NR
Left ventricular end diastolic volume/volume index				
NR	NR	NR	NR	NR

Table 27. Strength of evidence for key effectiveness outcomes of CRT-P

Key Outcomes	No. Studies (number of patients)	Study limitation	Directness	Consistency	Precision	Reporting bias	Strength of evidence Finding
All- cause mortality	6 (2,635)	Low	Direct	Inconsistent	Precise	Undetected	Moderate Studies showed statistically significant differences in mortality favoring CRT-P
Hospitalizations for heart failure	5 (1,666)	Low	Direct	Consistent	Precise	Undetected	High Studies showed fewer hospitalizations in the CRT-P group
Left ventricular end systolic volume (LVESV)	3 (1,236)	Low	Direct	Consistent	Precise	Undetected	Moderate CRT-P significantly reduced LESV compared with optimal medical therapy
Minnesota Living with Heart Failure Questionnaire (MLHFQ)	5 (2,445)	Low	Direct	Inconsistent	Precise	NA	Insufficient These studies assessed this outcome at different endpoints and with different comparisons, which might explain the inconsistency in the results comparing CRT-P to other therapy

CRT-P=cardiac resynchronization therapy with pacemaker; 6MHWD=6-minute hall walk distance; NA=not applicable

Harms of Cardiac Resynchronization Therapy with Pacemaker (CRT-P)

Study Characteristics

Eleven studies (reported in 13 articles) assessed harms associated with CRT-P.[4,5,8,24,26,53,58,77-82] Five were RCTs [4,5,24,26,53,58], three were secondary analyses of CARE-HF trial[5,24,26] one was a crossover study,[8] and the rest were prospective cohort studies. Followup ranged from 185 days to 36 months.

The studies used various devices. Three studies reported the use of only a single type of CRT-P device.[58,77,79] Three studies used the InSync model 8040,[77,78,81] three studies used the InSync III,[58,79,81] one study used the InSync 7272,[78] and four studies used other devices.[78,80-82] Two studies did not report the device type they used.[5,53]

Two studies explicitly reported funding from industry.[5,77] One study had non-profit organization funding.[78] The other studies did not report their sources of support (Evidence Table 1).

Participant Characteristics

The number of participants in the trials at baseline ranged from seven to 813. The percentage of women among participants ranged from 5[80] to 28.6 percent.[82] One study did not report the mean age.[5] Mean age in other studies ranged from 53 to 68 years old. No studies assessing harms reported the racial makeup of their participants.

The proportion of patients with ICM ranged from 36 to 48 percent. Three studies did not report on the proportion of ICM.[58,81,82] Two studies reported the prevalence of AF among their participants, which ranged from 6 to 33 percent[78,80] Two studies reported the NYHA class of the participants[78,79] and included participants in all NYHA classes.

Three studies did not report either the mean or the median LVEF.[53,81,82] Of those studies reporting this characteristic, the mean LVEF ranged from 19 to 30 percent.

In general, these studies were heterogeneous in patient population, and frequently did not report proportions of female patients or racial categories of participants (Evidence Table 3).

Risk of Bias

There were limitations in the reporting of harms in the studies. The studies did not report at what time point the harms were assessed, making it impossible to calculate an incidence for these harms. In addition, the studies did not report confidence intervals for the proportions of patients with these harms. For these reasons (implying statistical imprecision), as well as other issues reflecting possible bias (including lack of clarity regarding outcome reporting and outcome assessment) the risk of bias was generally high (Table 28 and 29) (Figure 13 and 14).

Table 28. Summary of risk of bias for trials assessing harms of CRT-P

Author, year	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessors	Assessing blinding by outcome	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall quality
COMPANION									
Bristow,2004[4]	?	?	+	-	-	-	-	+	+
CARE HF									
Cleland,2009[24] Gras,2007[26] Cleland,2004[5]	-	?	?	?	?	-	+	?	+
MUSTIC TRIAL									
Cazeau,2001[8]	?	?	-	?	?	?	?	-	+
Other trials									
Pokushalov,2010[58]	?	?	?	?	?	-	-	-	+
Garikipati,2014[53]	-	?	+	-	-	?	?	?	-

+High
-Low
?Unclear

Figure 13. Summary of risk of bias for trials assessing harms of CRT-P

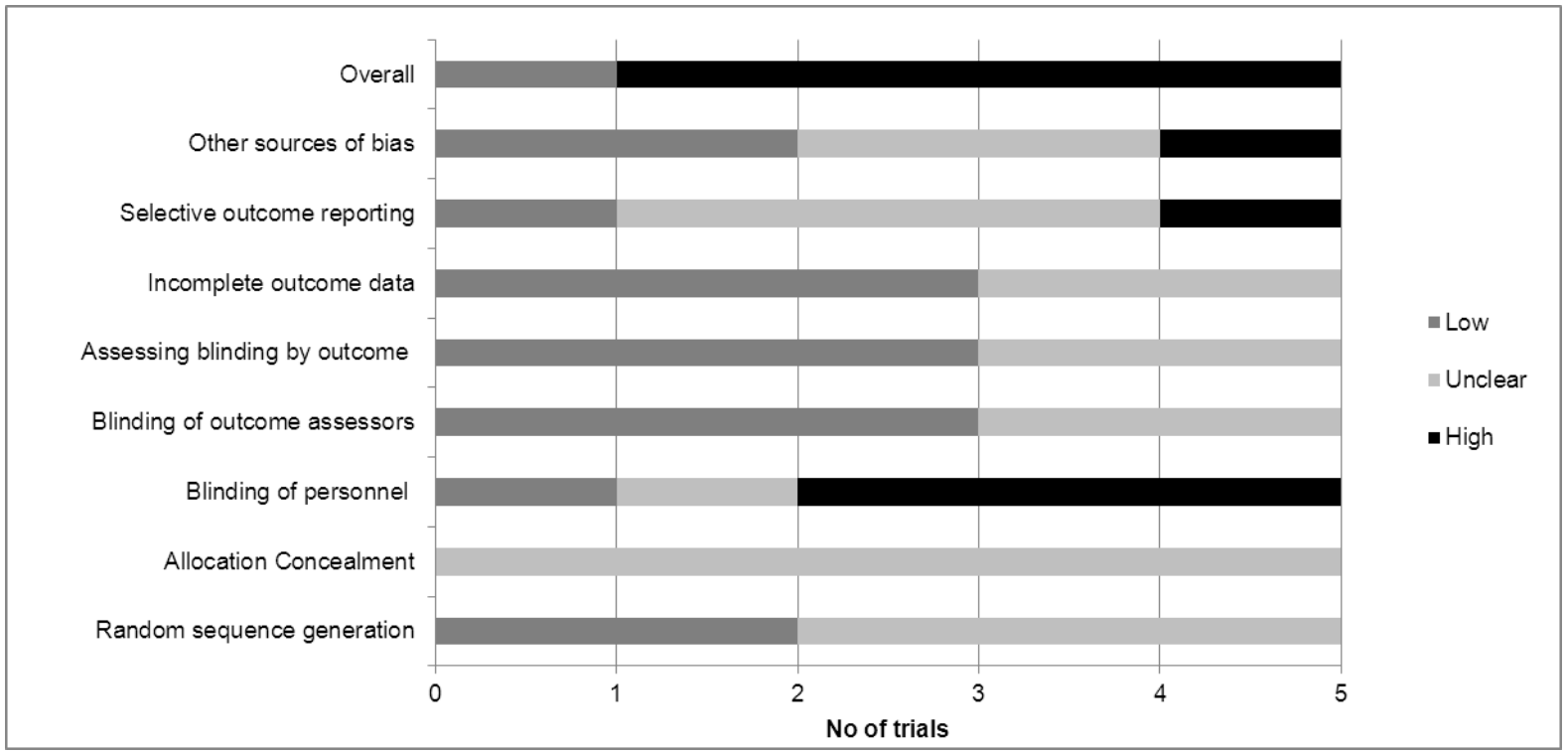
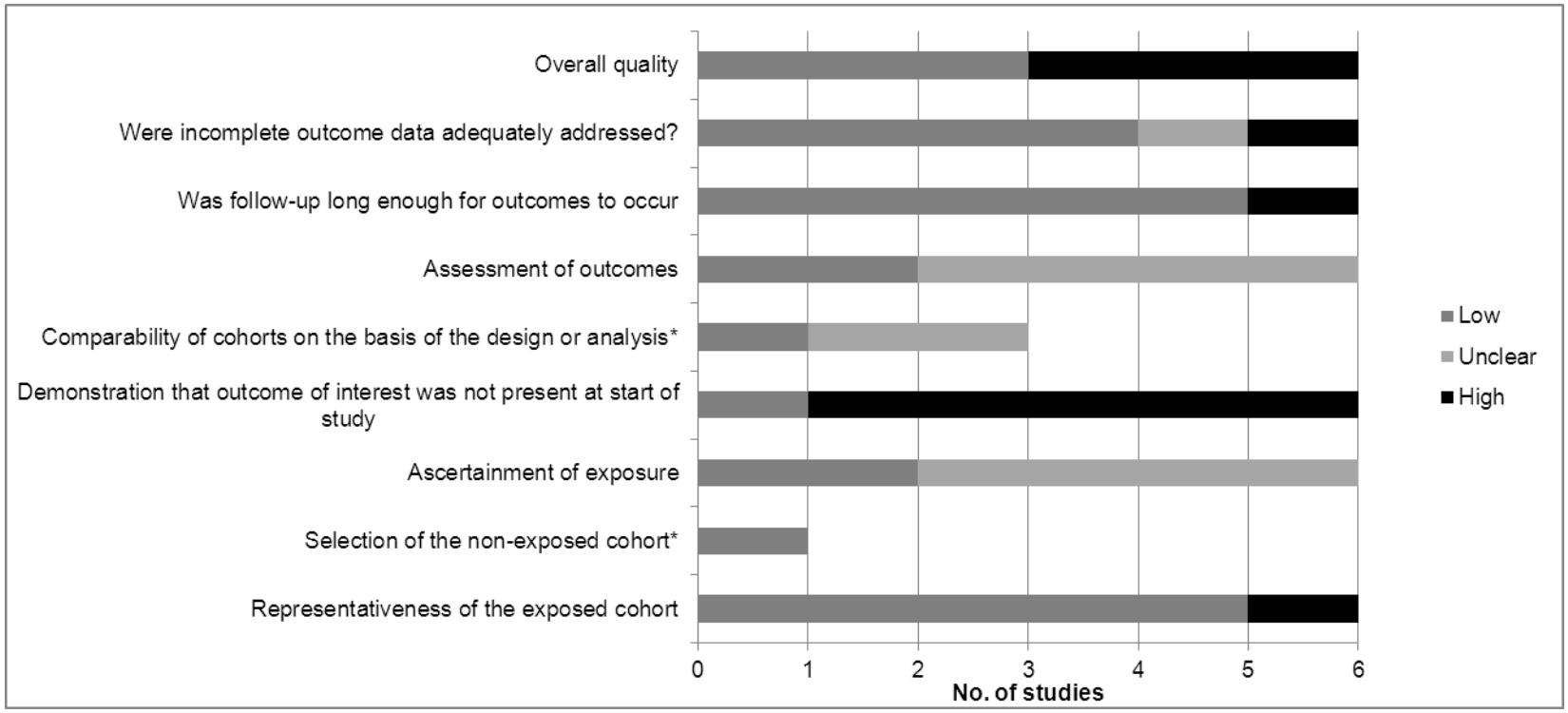


Table 29. Summary of risk of bias for cohort studies assessing harms of CRT-P

Author, year	Representativeness of the exposed cohort	Selection of the non-exposed cohort*	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis*	Assessment of outcomes	Was followup long enough for outcomes to occur	Were incomplete outcome data adequately addressed?	Overall quality
Krahn,2002[78]	+		?	-	?	?	-	?	+
Hong-xia,2006[81]	-		?	+	?	?	+	+	+
Gras,2002[77]	-	-	?	+	-	?	-	-	+
Mortensen,2004[79]	-		-	+		-	-	-	-
Stahlberg,2005[80]	-		-	+		-	-	-	-
Cock,2003[82]	-		?	+		?	-	-	-

+High
-Low
?Unclear
*Only applicable to studies with control groups

Figure 14. Summary of risk of bias for cohort studies assessing harms of CRT-P



*= Only applicable to studies with control groups.

Table 30. List of harms reported in the studies assessing harms of CRT-P

Author, year	Study design	Procedure related complications	Length of hospital stay	Pneumothorax	Pocket hematoma	Device Infection	Cardiac perforation/ tamponade	Lead dislodge-ment	Death within a week
COMPANION									
Bristow, 2004,[4]	RCT						X		
CARE-HF									
Cleland, 2004[5]	RCT			X		X		X	
Cleland, 2009 [24]	RCT		X						
Gras, 2007[26]	RCT			X	X	X		X	
MUSTIC									
Cazeau,2001 [8]	Randomized crossover								X
Other trials									
Garikipati, 2014[53]	RCT	X	X		X	X			
Pokushalov ,2010[58]	RCT								X
Cock, 2003[82]	Prospective cohort						X		
Gras, 2002[77]	Prospective cohort					X	X	X	
Hong-xia, 2006[81]	Prospective cohort							X	
Krahn, 2002[78]	Prospective cohort	X						X	X
Mortensen, 2004[79]	Prospective cohort				X			X	
Stahlberg, 2005[80]	Prospective cohort							X	

RCT=randomized controlled trail

Harms Outcomes

Procedure-related Complications

Two studies reported miscellaneous procedure-related complications, both reporting a 33.3 percent proportion of patients with this outcome (Table 31). The small sample sizes and the small number of studies make it difficult to draw a conclusion other than that more data are needed.

Table 31. Characteristics of studies of CRT-P reporting on the procedure-related complications

Author, year	N for analysis	N of patients with outcomes	% of patients with outcomes
Garikipati, 2014[53]	21	4	33.3
Krahn, 2002[78]	45	15	33.3

Length of Hospital Stay

Garikipati et al. (2014) reported that among 21 patients, the patients undergoing transvenous placement of the CRT-P (N=12) had a shorter hospital stay than those in the epicardial arm (N=9), though the difference was not statistically significant (3.4 +/-2.6 vs. 5.4 +/- 4.6 days, p=0.22).[53]

Cleland et al. (2009) reported from the CARE-HF trial that as a result of the implantation procedure, patients receiving CRT-P initially spent more days in the hospital by 3 months followup (mean 7.5 days, median 4, IQR 2-8), versus 3.4 days (median 0, IQR 0-1).[24] Afterwards, patients with CRT-P spent fewer days in the hospital (384 in the control group versus 222 in the CRT-P group). The overall number of days spent in the hospital per patient was similar in the CRT-P and control groups (20.7, median 9, IQR 4-26, compared to 22.4, median 9, IQR 0-31, respectively).

These two studies indicate that length of hospital stay might not be significantly different in those receiving CRT-P. However, as with other harms, few studies, with small sample sizes, address this harm.

Pneumothorax

The CARE-HF trial (reported in two articles) assessed pneumothorax.[5,26] At 24 hours, the proportion of pneumothorax was higher in the medical therapy group than in the CRT-P group. At 18 months, only the proportion on the CRT-P group was reported (Table 32).[5] As is the case with other harms, it is difficult to draw a conclusion based on limited data.

Table 32. Characteristics of studies of CRT-P reporting on the incidence of pneumothorax

Author, year	Arm name	N for analysis	Time Point (s)	N of patients with outcomes	% of patients with outcomes
Cleland, 2004[5]	CRT-P	409	18 month	6	1.5
Gras, 2007[26]	CRT-P	404	24 hrs.	2	0.5

CRT-P=cardiac resynchronization therapy with pacemaker

Pocket Hematoma

Three studies assessed pocket hematoma. The percentage of patients with this outcome was different in all three studies, likely due to the difference in sample size. Given the small number of studies that assessed this harm, we could not draw conclusions (Table 33).

Table 33. Characteristics of studies of CRT-P reporting on the incidence of pocket hematoma

Author, year	N for Analysis	Time Point (s)	N of Patients with Outcomes	% of Patients with Outcomes
Garikipati, 2014[53]	21	12 months	2	9.5
Mortensen, 2004[79]	189	6 months	2	1.1
Gras, 2007[26]	404	30 day	0	0

Device Infection

Three studies (reported in 4 articles), assessed device infection, with heterogeneous population sizes and followup.[5,26,53,77] Followup time in these studies ranged from 30 days to 18 months, and the proportion of device infection ranged from 0.7 to 4.8 percent (Table 34). The percentage of patients with this outcome varied by approximately an order of magnitude, and the heterogeneity of these studies make it difficult to draw clear conclusions.

Table 34. Characteristics of studies of CRT-P reporting on the incidence of cardiac device infection

Author, year	Arm name	N for analysis	Time Point (s)	N of patients with outcomes	% of patients with outcomes
Cleland, 2004[5]	CRT-P	409	18 months	3	0.7
Garikipati, 2014[53]	Overall	21	12 months	1	4.8
Gras, 2002[77]	Overall	117	12 months	1	0.85
Gras, 2007[26]	CRT-P	404	30 days	3	0.74

CRT-P=cardiac resynchronization therapy with pacemaker

Cardiac Perforation/Tamponade

Three studies assessed cardiac perforation/tamponade,[4,77,82] assessing harm at varying time points, with the percentage ranging from 0 to 5 percent. However, the study reporting no cardiac perforation or tamponade had the smallest sample size of any study assessing harms. Given the lack of comparability in the sample sizes or followup times of these studies, we could not conduct a meta-analysis (Table 35). These studies seem to indicate that this risk is prevalent,

Table 35. Characteristics of studies of CRT-P reporting on the incidence of cardiac perforation/tamponade

Author, year	N for analysis	Time Point (s)	N of patients with outcomes	% of patients with outcomes
Bristow, 2004,[4]	617	During procedure	NR	1.6
Cock, 2003[82]	7	2-3 months	0	0
Gras, 2002[77]	117	During procedure	1	0.85

Lead Dislodgement

Seven studies assessed lead dislodgement[5,26,77-81]. The proportion of patients experiencing this harm ranged from 1.71 to 17 percent for those studies that assessed the proportion over the entire population, which comprised all except one study.[5] Two studies reported lead dislodgement rates for only part of their study population. Cleland et al. (2004)[5] reported the proportion of patients with lead dislodgement only in the CRT-P arm as 5.9 percent; and Gras et al. (2007) reported a proportion of patients with lead dislodgement in the CRT-P arm as 2.7 percent (Table 36).[26] It is difficult to interpret these results since the studies did not report the recorded time point of the dislodgement, and the studies followed their populations for different lengths of time.

Table 36. Characteristics of studies of CRT-P reporting on the incidence of lead dislodgement

Author, year	Arm	N for analysis	N of patients with outcomes	% of patients with outcomes
Cleland, 2004[5]	CRT-P	409	24	5.9
Gras, 2002[77]	Overall	117	16	13.7
Gras, 2007[26]	CRT-P	404	11	2.7
Hong-xia, 2006[81]	Overall	117	2	1.71
Krahn, 2002[78]	Overall	45	3	6.7
Mortensen, 2004[79]	Overall	189	12	6.4
Stahlberg, 2005[80]	Overall	35	6	17

CRT-P=cardiac resynchronization therapy with pacemaker

Death within One Week

Three studies assessed death within a week.[8,58,78] Krahn et al. (2002) found one death within 1 week, due to sequelae from stroke, among 45 patients, for a prevalence of 2.2 percent.[78] Pokushalov et al. (2010) assessed the harm in two arms, one of patients undergoing CABG (4 of 87 patients, or 4.6%), at 4 days, the other in patients undergoing CABG and CRT-P (1 of 91 patients, or 1.1%), at 4 days.[58] In the MUSTIC trial using a crossover design, one patient died from myocardial infarction a few hours after a premature switch from inactive to active pacing; another patient died suddenly two hours after switching from inactive to active pacing (Table 37).[8] As for the other harms, the studies are heterogeneous in their assessment time points and in

populations. The risk of death within one week with CRT-P is present, though exact estimations await further data.

Table 37. Characteristics of studies of CRT-P reporting on the death within one week

Author, year	Arm name	N for analysis	Time Point (s)	N of patients with outcomes	% of patients with outcomes
Cazeau, 2001[8]MUSTIC	Overall	67	NR	2	2.9
Krahn, 2002[78]	Overall	45	7 days	1	2.2
Pokushalov, 2010[58]	CABG	87	4 days	4	4.6
Pokushalov, 2010[58]	CABG+CRT-P	91	4 days	1	1.1

CRT-P=cardiac resynchronization therapy with pacemaker; CABG=coronary artery bypass grafting

Effectiveness of Cardiac Resynchronization Therapy with Pacemaker versus Defibrillator (CRT-P vs CRT-D)

Table 38. Evidence addressing effectiveness and harms of CRT–P vs CRT-D

	CRT–P vs CRT-D effectiveness	CRT–P vs CRT-D Harms
Number of included studies	1 trial (reported in 3 articles)	9 studies (reported in 11 articles) 2 were RCTs, 3 were prospective cohorts and four were retrospective cohorts.
Patient characteristics	• The percentage of women was between 33-31% • The median age ranged from 66-68 years old • The trial reported NYHA class of the participants • The median LVEF ranged from 20-22%	• The percentage of women in the studies ranged from 16-44% • The mean age ranged from 58-74 years old • Four studies reported the NYHA class of the participants. • The mean LVEF ranged from 20-31%
Outcomes (number of included studies)	• All- cause mortality: 1 trial (reported 2 articles) • Hospitalizations for heart failure: 1trial • Left ventricular end systolic • volume/volume index : 0 • Minnesota Living with Heart Failure Questionnaire: 1 trial • Left ventricular ejection fraction: 0 study • Left ventricular end diastolic volume/volume index: 0 study • 6 minute hall walk distance: 1trial	• Procedure related complications: 2 studies • Length of hospital stay: 2 studies • Pneumothorax: 4 studies • Pocket hematoma: 2 studies • Device Infection: 5 studies • Cardiac perforation/ tamponade: 4 studies • Lead dislodgement: 4 studies • Ventricular arrhythmias: 1 study • Inappropriate shocks: 2 studies • Death (within a week): 2 studies
Key findings	There was insufficient evidence to determine the effectiveness of CRT-D vs. CRT-P	Compared to CRT-P, device infection was slightly more common in patients receiving CRT-D. There was insufficient evidence to draw conclusions on any other harms comparing the two devices

Study Characteristics

One RCT (reported in three articles) compared the effectiveness of CRT-P versus CRT-D.[4,29,30] The COMPANION trial reported initial results in 2004,[4] with subsequent additional analyses for mortality[30] and hospitalizations.[29] The trial included 1,520 subjects with NYHA Class III or IV heart failure and ICM or dilated cardiomyopathy with a QRS duration of greater than 120ms, randomized in a 1:2:2 ratio to optimized pharmacological therapy alone, or in combination with CRT-P (Contak TR model 1241, Guidant) or CRT-D (Contak CD model 1823, Guidant). The planned length of followup was 12 months. The study was industry sponsored (Guidant) (Table 39).

Participant Characteristics

The COMPANION trial included 308 participants in the optimal pharmacologic therapy (OPT) alone arm, 617 in the CRT-P plus OPT arm and 595 in the CRT-D plus OPT arm.[4] The median age of participants in the trial arm ranged from 66-68 years old, and the majority of participants were male (67-69%). Most participants were NYHA class III (67-68%), had ICM (54-59%), and a median left ventricle ejection fraction ranging from 20-22 percent. Median QRS duration was 160ms in the CRT-P and CRT-D arms, and 158ms in the OPT arm. Over two-thirds of participants had a left bundle branch block (range 69-73%). None of the articles reported racial distribution, history of atrial disease, or glomerular filtration rates of the participants (Evidence Table 6).

Table 39. Study characteristics of trials assessing effectiveness of CRT-P vs CRT-D

Author, year	Number of patients	Length of followup	Device manufacturer name/ device model	Comparison	Funding source
COMPANION Bristow,2004[4] Anand, 2009[29] Carson,2005[30]	OMPT : 308 CRT-P: 617 CRT-D: 595	12 months	CRT-P (Contak TR model 1241, Guidant) or CRT-D (Contak CD model 1823, Guidant)	OPT CRT-P CRT-D	Industry

Risk of bias

The primary endpoint of the COMPANION trial was a composite of all-cause mortality and hospitalization, with a secondary endpoint of all-cause mortality. Additional outcomes assessed included the 6-minute hall walk distance and MLHFQ. However, while the study masked the steering and endpoints committee to treatment assignment, it did not mask physicians, patients, and members of the data management and analysis team, raising concerns for potential bias. Similarly, the randomization technique and allocation concealment are unclear. Despite having both CRT-P and CRT-D arms, direct comparisons between the two arms were lacking (Table 40).

Table 40. Summary of risk of bias for trials assessing effectiveness of CRT-P vs CRT-D

Author, year	Random sequence generation	Allocation Concealment	Blinding of personnel	Blinding of outcome assessors	Assessing blinding by outcome	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall quality
COMPANION-Bristow,2004[4] Anand, 2009[29] Carson,2005[30]	?	?	+	-	-	-	-	+	+

+=High
-=Low
?=Unclear

Effectiveness Outcomes

The COMPANION trial did not report change in left ventricle ejection fraction, left ventricle end systolic volume, left ventricle end diastolic volume, or clinical composite score (Packer score). The trial reported composite outcomes of hospitalization with death and separate outcomes by cardiovascular diagnoses. Subgroup analyses were presented for the hazards of all-cause mortality for CRT-D.

All-cause Mortality

Two articles reported all-cause mortality from the COMPANION trial.[4,30] Carson et al. (2005) examined the time to cause-specific death, including sudden cardiac death and "pump failure" (progressive heart failure).[30] The study did not specify followup time, but provided 3 years of data. Overall, 313 patients died, 78 percent from a cardiac cause, of which pump failure (44.4%) and sudden cardiac death (26.5%) were most common. Only CRT-D resulted in statistically significant fewer cardiac deaths (p=0.006). In regards to non-cardiac mortality, there was no significant difference between the treatment groups. The all-cause mortality for the OPT, CRT-P, and CRT-D arms were 25, 21.2, and 17.6 percent, respectively, suggesting the benefit in mortality is from CRT-D in attenuating death from cardiac causes. Compared to OPT, CRT-D reduced cardiac deaths by 38 percent (p=0.006) whereas CRT-P reduced cardiac deaths by only 14.5 percent (p=0.33).

Bristow et al. (2004) reported the secondary outcome from COMPANION, mortality at 12 months, classified according to cardiac and non-cardiac causes.[4] The 1-year mortality rate in the OPT group was 19 percent. Compared to OPT, CRT-P resulted in a mortality reduction of 24 percent (HR: 0.76, 95% CI, 0.58 to 1.01, p=0.059) whereas CRT-D resulted in a 36 percent reduction (HR: 0.64, 95% CI, 0.48 to 0.86, p=0.003). For CRT-D, subgroup analyses for all-cause mortality showed that subjects with non-ischemic cardiomyopathy (NICM) had a greater reduction in mortality (HR: 0.50, 95% CI, 0.29 to 0.88; p=0.015). The study reported no significant reduction in mortality for CRT-D for participants with ICM (HR: 0.73, 95% CI, 0.52 to 1.04, p=0.082). The trial found a reverse trend for CRT-P. Compared to OPT, subjects with NICM had a 9 percent reduction in mortality with CRT-P (HR: 0.91, 95% CI, 0.55 to 1.49, p=0.70) in contrast to 28 percent for those with ICM (HR: 0.72, 95% CI, 0.51 to 1.01, p=0.058). The study, however, reported no direct comparisons of CRT-P versus CRT-D.

In conclusion, the trial reported that CRT-D significantly decreased all-cause mortality by 36 percent (p=0.003) (likely driven by cardiac causes). The reduction in mortality by CRT-P was more moderate (24%; p=0.059). Primarily due to high risk of bias, and lack of direct comparisons, there is insufficient strength of evidence for this outcome (Table 42). Interestingly, subgroup analyses suggest that those with NICM benefit more with CRT-D whereas those with ICM benefit more from CRT-P.

Hospitalization for Heart Failure

One article reported the impact of CRT-P and CRT-D on hospitalization from the COMPANION trial.[29] Median followup ranged from 11.9 to 16.2 months. Overall, of the 1,520 patients, 959 were hospitalized at least once. Of the total 2,428 hospitalizations, 1,596 (66%) were for cardiac causes. OPT, CRT-P, and CRT-D arms accounted for 388, 628, and 580 cardiac hospitalizations respectively. CRT therapy resulted in a lower number of cardiac hospital admissions per patient-year: 1.2 for OPT, 0.8 for CRT-P, 0.8 for CRT-D. Also, almost half as many subjects with CRT had greater than two cardiac hospital admissions per patient-year, 27

percent for the OPT arm versus 16 percent for the CRT-P and CRT-D arms. Hospital admissions specific to heart failure were also higher in the OPT arm (46%) than either the CRT-P (33%) or CRT-D (36%) arms. The study found a 44 percent and 41 percent reduction in heart failure hospital admissions per patient-year for CRT-P and CRT-D, respectively, compared to the OPT arm (OPT: 0.7 admissions per patient-year; CRT-P: 0.4; CRT-D: 0.4, no p-value specified).

In summary, the study found that when compared with OPT, CRT-P and CRT-D resulted in a 44 and 41 percent reduction, respectively, in heart failure hospitalizations. No statistically significant differences were found when CRT-P was directly compared to CRT-D for the hospitalization endpoints. We graded this finding as low strength of evidence primarily due to the high risk of bias (Table 42).

Left Ventricular End Systolic Volume and Left Ventricular End Diastolic Volume

The COMPANION trial did not report on change in left ventricular end systolic volume and left ventricular end diastolic volume. There is insufficient evidence to draw conclusions about CRT-D versus CRT-P for this outcome.

Minnesota Living with Heart Failure Questionnaire

One article reported the change MLHFQ score for CRT-P and CRT-D at 3 and 6 months with the OPT arm as reference.[4] For the OPT arm, the MLHFQ median score decreased by -9±21 and -12±23 at 3 and 6 months respectively. In contrast, compared to OPT, the MLHFQ score decreased by over 2-fold for both the CRT-P and CRT-D arms: -24±27 and -25±26 versus -24±28 and -26±28 at 3 and 6 months for CRT-P versus CRT-D arms respectively ($p < 0.001$). The study made no direct comparison between the CRT-P versus CRT-D groups, but the results appear similar. Because of this indirect comparison of CRT-P and CRT-D and the high risk of bias, there is insufficient evidence to draw conclusions about CRT-D versus CRT-P for MLHFQ (Table 42).

Change in Left Ventricular Ejection Fraction

The COMPANION trial did not report on change in left ventricular ejection fraction.

6-minute Hall Walk Distance

One article reported 6-minute hall walk distance outcome for the COMPANION trial.[4] At baseline, there was no statistically significant difference in median distance walked between the OPT, CRT-P, and CRT-D arms (244m, 274m, 258m, respectively). The outcome was assessed at 3 and 6 months post-intervention with the OPT arm as reference. For the OPT arm, the distance walked increased by 9±84m and 1±93m at 3 and 6 months respectively. In contrast, compared to OPT, the median distance walked significantly increased: 33±99m and 40±96m versus 44±109m and 46±98m at 3 and 6 months for CRT-P versus CRT-D ($p<0.001$). The study made no direct comparison between the CRT-P versus CRT-D arms, but the results appear similar.

Table 41. Summary of effectiveness outcomes reported in the trial of CRT-P versus CRT-D, by subgroup

Female	LBBB	QRS duration >150ms	Non ischemic cardiac conditions	Atrial fibrillation
No Sub group analysis done				

LBBB-Left bundle branch block

Table 42. Strength of evidence for key effectiveness outcomes of CRT-P vs CRT-D

Key outcomes	No. Studies (number of patients)	Risk of bias	Directness	Consistency	Precision	Reporting bias	Strength of evidence Finding
All- cause mortality	1 (1520)	High	Indirect	Unknown (Single study)	Precise	NA	Insufficient
Hospitalizations for heart failure	1 (1,520)	High	Direct	Unknown (Single study)	Precise	Undetected	Low Compared with optimal medical therapy, CRT-P and CRT-D were associated with 44% and 41% reduction in heart failure hospitalizations (not significantly different).
Left ventricular end systolic volume	0	NA	NA	NA	NA	NA	Insufficient
Minnesota Living with Heart Failure Score	1 (1,520)	High	Direct	Unknown (Single study)	Imprecise	NA	Insufficient

NA = not applicable

Harms of Cardiac Resynchronization Therapy with Pacemaker versus Defibrillator (CRT-P vs CRT-D)

Study Characteristics

Nine studies (reported in eleven articles) assessed harms comparing CRT-P with CRT-D, including two RCTs.[4,29,30,46,83-89] The Management of Atrial Fibrillation Suppression in Atrial Fibrillation-Heart Failure Comorbidity Therapy (MASCOT) trial was a multicenter, single-blinded, randomized parallel trial that examined the safety and efficacy of an atrial overdrive pacing algorithm in CRT patients.[46] However, treating clinicians determined the selection of CRT-P versus CRT-D and the harms assessment was a post-hoc analysis (Evidence Table 1).

The second RCT, COMPANION, was a single-blinded trial that assigned patients in a 1:2:2 ratio to treatment with protocol-mandated optimal pharmacologic therapy alone, optimal pharmacologic therapy plus CRT-P, or optimal pharmacologic therapy plus CRT-D.[4,29,30]The primary outcome was a composite of all-cause mortality and all-cause hospitalization, and the secondary endpoint was all-cause mortality. The other included studies were cohort studies.

Of the non-randomized studies, three were prospective[84,87,89] and four were retrospective.[83,85,86,88] Followup ranged from approximately 6 months[84] to 5 years.[86] Only three studies specified the device names.[4,29,30]

Three studies (reported in five articles) reported funding.[4,29,30,46,88] The two RCTs were industry funded.[4,29,30,46] Two studies explicitly specified no funding.[85,87]

Population Characteristics

The number of participants in the studies ranged from 40[84] to 26,887.[88] The percentage of women among participants in the study arms ranged from 16[85] to 44 percent.[85] Only one study reported the racial makeup of its participants.[88] Mean age in the study arms ranged from 58 to 74 years old.

Seven studies (reported in nine articles) reported the percentage of participants with ICM,[4,29,30,84-89] ranging from 19[84] to 70 percent[86] per study arm. All but two studies reported mean ejection fraction.[85,88] ranging from 20 to 31 percent.[87] All but two studies reported history of atrial fibrillation,[4,29,30,88] ranging from 11 to 41 percent per study arm.[85]

Mean QRS duration ranged from 147ms to 185ms but four studies did not report it.[83-85,88] Only two studies specified QRS morphology, with the predominance being left bundle branch block, ranging from 69 to 84 percent per arm. Only four studies (reported in six articles) specified NYHA classification,[4,29,30,46,83,87] with the majority of participants being Class III, ranging from 54 to 87 percent. Four studies reported baseline renal function.[85-87,89] Two studies reported eGFR,[85,87] with a mean range of 52 to 72ml/min/1.73m^2 per arm.[87] Two studies reported creatinine, ranging from a median of 1.2 mg/dL[89] to a mean level of 1.6mg/dL.[86]

No studies reported baseline left atrial volume. However, four studies reported left atrial diameter,[46,85-87] ranging from a mean of 4.2cm[85,87] to 6.2cm.[86] Only one study reported baseline left ventricular end diastolic volume, the mean volume ranging from 236ml to 251ml per arm.[84] Five additional studies reported baseline left ventricular end diastolic diameter,[4,46,85-87] ranging from a mean diameter of 6.1cm to 7.1cm. Only one study reported body mass index, ranging from 27 kg/m^2 to 28kg/m^2 in the study arms (Evidence Table 7).[85]

Risk of Bias

The COMPANION trial had high risk of bias as it did not mask patients, physicians, independent statisticians, and members of the data-management group and the data safety and monitoring board to the treatment assignments (although the steering committee, the end-points committee, and the sponsor were unaware of the treatment assignments). Similarly, a very high percentage (26%) of participants changed from medical therapy to receive implants. Random sequence generation and allocation concealment for the trial were also unclear. Finally, reporting bias is suggested, as articles rarely reported direct comparisons of CRT-P versus CRT-D. The MASCOT trial was also at high risk of bias as device type was not randomized but determined by the treating clinicians. The harms assessment in this trial was a post-hoc analysis. Risk of bias was introduced in this analysis, as the randomization no longer preserved the distribution of measured and unmeasured confounders. The authors noted that compared to CRT-P participants, CRT-D recipients were more likely to be male ($p < 0.0001$), have ICM ($p < 0.001$) and shorter QRS duration ($p < 0.0005$), and less likely to receive spironolactone ($p < 0.0001$) and anti-arrhythmic medications ($p < 0.0222$). The study made no adjustment for these factors.

With respect to the cohort studies[83-89], the main concerns for bias included unclear description of the cohort,[83] self-reported outcomes in the main study,[87] and no standardized followup time.[88] However, ascertainment of exposure, pre-specified outcomes, and followup were adequate. Four of the seven studies had low risk of bias (Table 43 and 44) (Figure 15).

Table 43. Summary of risk of bias for trials assessing harms of CRT-P vs CRT-D

Author, year	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessors	Assessing blinding by outcome	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall quality
COMPANION-Bristow,2004[4] Companion Sub Study Anand, 2009[29] Carson,2005[30]	?	?	+	-	-	-	-	+	+
Schuchert,2013[46]	-	?	?	?	?	-	-	-	+

+=High
-=Low
?=Unclear

Table 44. Summary of risk of bias for cohort studies assessing harms of CRT-P vs CRT-D

Author, year	Representativeness of the exposed cohort	Selection of the non-exposed cohort*	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis*	Assessment of outcomes	Was followup long enough for outcomes to occur	Were incomplete outcome data adequately addressed?	Overall quality
Azizi, 2006[83]	?		-	-		-	-	-	-
Killu,20113[86]	-		-	-		-	-	-	-
Romeyer-Bouchard,2010[89]	-		-	-		-	-	-	-
Swindle,2010[88]	?		-	-		-	+	-	+
Takaya, 2013[84]	?		-	-		-	-	?	+
Verbrugge,2013[85]	-		-	-		-	-	-	-
Verbrugge,2013[87]	-		-	-		+	-	-	+

+=High
-=Low
?=Unclear
*=Only applicable to studies with control groups

Figure 15. Summary of risk of bias for cohort studies assessing harms of CRT-P vs CRT-D

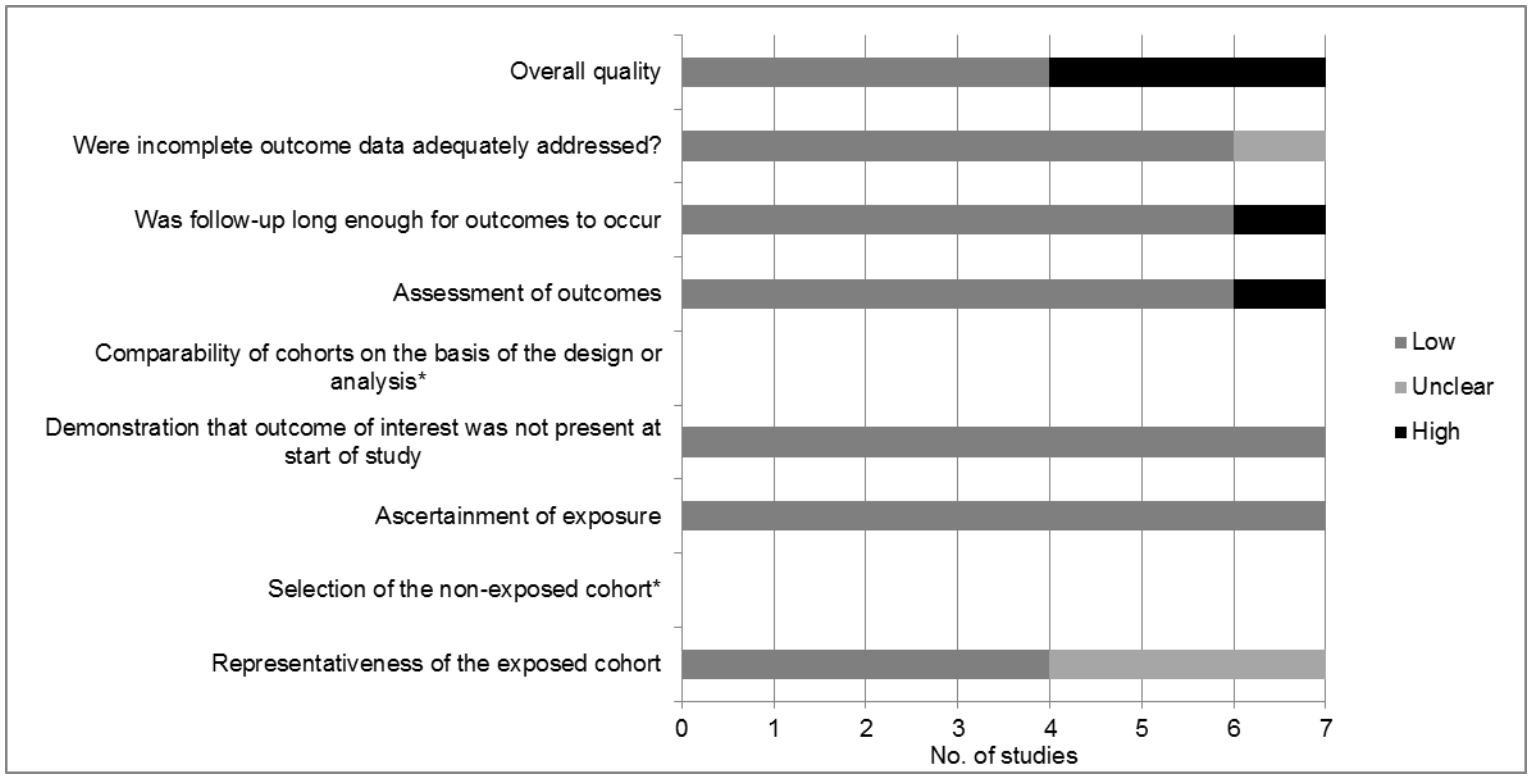


Table 45. List of harms reported in the studies assessing harms of CRT-P vs CRT-D

Author, year	Procedure related complications	Length of hospital stay	Pneumothorax	Pocket hematoma	Cardiac perforation/ tamponade	Device infection	Lead dislodgement	Death within 1 week	Ventricular arrhythmia	Inappropriate shocks (CRT-D Only)
RCTs										
COMPANION Anand,2009[29]		X[1]								
MASCOT Schuchert,2010[46]*						X				
Bristow, 2004[4]	X				X					
Carson,2005[30]								X[5]		
Prospective Cohorts										
Romeyer-Boucherd, 2007[89]			X	X		X	X			
Takaya, 2010[84]								X		
Verbrugge, 2011[87]		X	X		X	X[2]	X			
Verbrugge, 2011[85]										X
Retrospective Studies										
Azizi, 2005[83]			X		X	X	X	X	X	
Killu, 2008[86]			X	X	X	X	X	X[4]		X
Swindle, 2005[88]	X	X						X[3]		

*Post-hoc analysis

1. Index hospitalization of the device implantation was excluded from length of stay analyses for the COMPANION Trial.
2. Device infections were classified as "long term complications."
3. Mortality was reported as in-hospital mortality for patients undergoing device procedures.
4. 30-Day Mortality was reported.
5. Exact timing of death was not specified.

CRT-D=cardiac resynchronization therapy with defibrillator

Harms Outcomes

Harms most commonly reported were pneumothorax[83,86,87,89] and device infections.[46,83,86,87,89] Studies rarely reported pocket hematoma, ventricular arrhythmia, or inappropriate shocks (Table 45). For most adverse events, the studies did not report the exact timing and did not specify the differential experience amongst CRT-P and CRT-D participants. Instead, the studies often reported events for the entire CRT cohort.

Procedure-related Complications

Two studies reported procedure-related complications.[4,88] Swindle et al. (2005) utilized a definition of complications which included, but was not limited to, pneumothorax, cardiac perforation with pericardial effusion or tamponade, mechanical complications of the device, implant infection, hemorrhage, and acute renal failure requiring dialysis.[88]

For CRT-P compared to CRT-D, 94.2 versus 95.0 percent of participants had no complications, 5.2 versus 4.6 percent had one complication, and 0.6 versus 0.4 percent had greater than one complication.

In comparing CRT-P, CRT-D, and ICD, the study found no difference in frequency of complications by device type (p=0.29), although it was lower for younger patients, under the age of 80 years old (p=0.03). The second study, COMPANION, reported 10 percent of CRT-P and 8 percent of CRT-D patients experienced moderate or severe adverse events related to the implantation procedure.[4] There was no statistically significant difference in complications between CRT-P and CRT-D (p=0.42), consistent with the first study.

Length of Hospital Stay

Two studies reported the length of hospital stay,[87,88] finding that the presence of a device complication or an elevated comorbidity score resulted in increased length of stay and total cost of hospitalization.[88]

Swindle et al. (2005) showed that advanced age was associated with increased length of stay and total cost of hospitalization, but this was only consistent among patients undergoing a CRT-D procedure. The study found an association between elective admission coding or by implantation of the device on day 1 or 2, and shorter lengths of stay (median 2.0 vs. 6.0 days) and lower mortality (by 80.0%) (The study defined elective procedures as those that used the Uniform/Universal Billing Form 92 Managed Care, the official Centers for Medicare and Medicaid Services form used by hospitals when submitting bills for reimbursement).

The study also compared the length of stay within the three device groups (CRT-P, CRT-D, and ICD) across the number of device complications and participant comorbidity scores, but made no direct comparisons between the CRT-P and CRT-D groups. Verbrugge et al. (2011) reported an overall median length of stay of 3 days (IQR: 3, 5) for CRT for all age groups but did not specify length of stay by CRT type [87].

The COMPANION trial excluded initial implantation and elective implantation of CRT-P and CRT-D devices from its hospitalization and length of stay analyses.[29]

No studies provided direct comparison of CRT-P and CRT-D for length of hospital stay for the initial device implantation.

Pneumothorax

Four studies reported on pneumothorax.[83,86,87,89] These studies reported a pneumothorax prevalence of 0.3, 0.6, 1, and 1.4 percent, respectively.[83,86,87,89] One study also noted no difference by age, comparing participants age ≤80 (1.3%) versus >80 years old (2.2%) (p=0.36).[86] No study directly compared pneumothorax by CRT type.

Pocket Hematoma

Two studies reported on pocket hematoma,[86,89] each with a clear definition of the event.

Killu et al. (2008) defined a pocket hematoma as "clotted blood in the device pocket" with a severe classification when it "resulted in refractory pain, threatened the integrity of the incision, or required pocket evacuation or transfusion".[86] Among those participants age ≤80 versus >80 years old, 0.5 and 1.1 percent, respectively, experienced a hematoma requiring intervention (p=0.41). The study did not report CRT type.[86]

The other study, by Romeyer-Bouchard et al. (2007),[89] defined a pocket hematoma as requiring two investigators to agree on a "palpable mass that protruded 2cm anterior to the pulse generator and lead (s)".[89] Twenty-nine patients (9.5%) experienced a large hematoma, with five (1.66%) requiring re-intervention due to the size of the hematoma. The presence of hematoma was significantly correlated with re-intervention (r=0.2; p<0.001). As in the prior study by Killu et al. (2008) this study did not report the CRT type, although it did suggest larger pockets from the larger leads, connectors, and size of the CRT-D devices as a predisposing factor for hematoma.[89]

Device Infection

Five studies reported on device infection.[46,83,86,87,89].

Killu et al. (2008) reported a prevalence of 0.3 percent, with no statistically significant difference among participants above versus below the age of 80 years (p >0.99).[86] Verbrugge et al. (2011) report a prevalence of 0.5 percent secondary to infection.[87] Azizi et al. (2005) reported infection and prevalence in only two of 244 participants (0.8%).[83] However, none of these three studies distinguished infection by CRT type or provide specific definitions of or timing criteria for infections.

In contrast, Schuchert et al. (2010) did report a CRT-specific rate of infection: 1.7 percent for CRT-P and 2.1 percent for CRT-D (p=0.88).[46] However, only one study clearly defined infection and adjusted for device type.[89] Romeyer-Bouchard et al. (2007) defined device-related infection (DRI) as "local signs of inflammation at the generator pocket (e.g. erythema, warmth, fluctuance, wound dehiscence, tenderness, purulent drainage, or frank erosion by generator or lead puncturing the skin)".[89] This was further categorized as "early", "late", or "delayed" when occurring within 30 days, after 30 but less than 365 days, and over 364 days, respectively. The overall prevalence of DRI was 4.3 percent (1.7 percent incidence per year; 7 early and 6 late infections of 303 participants with a mean followup of 31 months). With respect to devices, 1.6 percent of CRT-P and 8.6 percent of CRT-D participants experienced a DRI. Infections were predominantly among participants with CRT-D (77%), followed by CRT-P (15.4%) and a device upgrade (7.6%). After adjusting for procedure time, dialysis, and re-intervention, a CRT-D device had a hazard ratio of 10.45 (95% CI, 1.75 to 62.45, p=0.01) for a DRI compared to CRT-P. Procedure time, dialysis, re-intervention, and a CRT-D device were independent predictors of DRI. This study would suggest that CRT-D is associated with higher risk of device infections.

The authors point out that technical factor, such as larger leads, connectors, size, and pocket size may predispose to infection and stretch the skin relatively thinner. Similarly, lead materials and size may affect bacterial adhesion.

Cardiac Perforation/Tamponade

Four studies reported on cardiac perforation (including coronary sinus perforation) or cardiac tamponade.[4,83,86,87] In the COMPANION trial, coronary venous perforation and tamponade were 1.1 and 0.5 percent respectively for the CRT-P and 0.8 and 0.3 percent respectively for the CRT-D groups (no p-value specified).[4] Azizi et al. (2005) only reported one coronary sinus perforation for 244 participants (0.4%).[83] Verbrugge et al. (2011) reported cardiac tamponade in only one case of 220 participants (0.5%), occurring in the 70-79 year old cohort.[87] Killu et al. (2008) compared coronary sinus perforation among those participants age ≤80 (0.2%) versus >80 years old (0%) and found no significant difference ($p > 0.99$) [86]; however, all three studies did not report which CRT type experienced the event.[83,86,87] No direct comparison of cardiac perforation/tamponade was made for CRT-P versus CRT-D.

Lead Dislodgement

Four studies reported on lead dislodgement.[83,86,87,89] However, only one study explicitly defined lead dislodgement as: "a radiographic finding of lead dislocation", "a significant increase in capture threshold or loss of capture", "inadequate lead sensing necessitating a lead revision", or a combination of these.[86] Verbrugge et al. (2011) reported multiple reasons for lead replacement (5.4%), including dislocation, microperforation, and diaphragmatic stimulation.[87] However, the study reported this complication by age category and not separated by device type. Similarly, Romeyer-Bouchard et al. (2007) reported dislodgement in 6.9 percent of cases but did not specify by device type.[89] The study also correlated lead dislodgement with re-intervention ($r = 0.8$; $p < 0.001$).[89] Azizi et al. (2005) reported seven of 244 cases with dislodged leads (2.9%)[83] and Kilu et al. (2008) reported a lead revision rate of 7.1 percent,[86] but neither study specified dislodgement by device type. Consequently, lead dislodgement could not be compared for CRT-P versus CRT-D. Interestingly, two studies found no difference in the prevalence of lead replacement with increasing age (age ≤80 vs. >80 years old; 7.3% vs. 5.6%, $p = 0.66$)[86] or dislodgment (age <70, 70-79 and ≥80 years old; 3% vs. 1% vs. 2% respectively; no p-value).[87]

Ventricular Arrhythmia

Only one study reported on ventricular arrhythmia perioperatively.[83] In the study by Azizi et al. (2005) ventricular tachyarrhythmia's requiring defibrillation occurred in four of 285 procedures (1.3%).[83] However, the study did not specify the prevalence for CRT-P versus CRT-D procedures. No direct comparison of ventricular arrhythmia was made for CRT-P versus CRT-D.

Inappropriate Shocks Cardiac Resynchronization Therapy with Defibrillator Only

Two studies reported inappropriate shocks.[85,86] Killu et al. (2008) reported 31 of 728 (4.3%) participants received inappropriate shocks over the duration of the study (median 3.1 years).[86] Younger participants (age ≤80 years old) received a higher percentage of inappropriate therapy (5.1%) as compared to those over the age of 80 years old (1.4%) (no p-value specified).

However, time to first inappropriate shock did not significantly vary by age group (p=0.21). Verbrugge et al. (2011) reported three inappropriate shocks in their study but did not specify among how many participants the events occurred.[85] The variation in followup and reporting of number of inappropriate shocks versus number of participants with inappropriate shocks limits the interpretation of this data.

Death Within a Week

Two studies reported death within 1 week.[83,84] In the study by Takaya et al. (2010) no events occurred during the 6 month followup for either the five CRT-P or 35 CRT-D participants.[84] Similarly, the study by Azizi et al. (2005) reported no peri-operative mortality.[83] The study by Killu et al. (2008) specified a 30-day mortality, with six deaths among those participants age ≤80 (1.0%) versus zero among those >80 years old (0%) (p >0.99).[86] The study did not report mortality by CRT type, however. Although Swindle et al. (2005) did report odds of in-hospital mortality by device type (CRT-D, CRT-P, ICD), they did not make any direct comparisons.[88] The authors did find that among patients undergoing CRT-D placement, the odds of death were over 30-fold greater for those using ionotrope and at least one complication versus those with none (OR: 35.51, 95% CI, 14.44 to 87.32, p<0.001).[88] However, the study made no direct CRT comparisons. The COMPANION trial did not specify the timing of deaths in its study nor directly compare mortality between CRT-P and CRT-D.[30] Consequently, although five studies reported on mortality, the studies rarely specified the exact timing of death, and they used Kaplan-Meyer survival curves for mortality.[30,86] These included studies are not comparable in their followup and definition of mortality, and no definitive conclusion can be made.

Table 46. Summary of effectiveness outcomes by comparator

Outcomes	CRT-D vs. Implantable Cardioverter Defibrillator (ICD) (no. of studies and result)	CRT-P vs Optimal medical therapy (no. of studies and result)	CRT D vs. CRT P (no. of studies and result)
All- cause mortality	7 trials (reported in 14 articles) The data offer modest corroboration that CRT-D improves mortality in patients with minimally symptomatic CHF. Data are inconclusive as to the effect on this outcome in patients with NYHA class III-IV	6 trials (reported in 10 articles) The data offer moderate support favoring CRT-P versus OMT in reducing mortality.	1 trial (reported in 2 articles) Data are inconclusive as to the effect on this outcome
Heart failure hospitalizations	6trials (reported in 11 articles) The data strongly favor CRT-D over an ICD alone in terms of reduced hospitalizations	5 trials, (reported in 6 articles) The data moderately support fewer hospitalizations for CRT-P compared with OMT	1 trial (reported in one article) Data are inconclusive as to the effect on this outcome
Left ventricular end systolic volume/volume index	5 trials (reported in 8 articles) The data strongly favors CRT-D over an ICD alone in terms of LVESV reduction	3 trials The data from the studies suggest that CRT-P significantly improves LVESV	NR
Minnesota Living with Heart Failure Questionnaire	5 trials (reported in 6 articles) The current data suggest that CRT-D does not improve QOL in minimally symptomatic patients compared to an ICD alone. The data do suggest a significant improvement in QOL in patients with NYHA class III-IV CHF	5 trials (reported in 8 articles) Data are inconclusive as to the effect on this outcome	1 trial (reported in one article) Data are inconclusive as to the effect on this outcome
Left ventricular ejection fraction	6 trials (reported in 9 articles) The majority of studies were consistent in demonstrating an improvement in LVEF with CRT compared to ICD alone	4 trials Three of these four showed improved LVEF with CRT-P, though comparisons were different between studies, as was length of followup. Thus, the absolute difference in LVEF is not comparable from study to study.	NR
Left ventricular end diastolic volume/volume index	4 trials (reported in 7 articles) The trials were consistent in demonstrating a reduction in LVEDV with CRT-D compared to an ICD alone	3 trials It is unclear whether LVEDV is improved by CRT-P	NR

Outcomes	CRT-D vs. Implantable Cardioverter Defibrillator (ICD) (no. of studies and result)	CRT-P vs Optimal medical therapy (no. of studies and result)	CRT D vs. CRT P (no. of studies and result)
Clinical composite score	2 trials The current data suggest that CRT-D likely results in greater improvement in clinical composite score compared with an ICD alone	NR	NR
6-Minute Hall Walk Distance	4 trials (reported in 5 articles) Data suggest that CRT-D is effective in improving 6MHWD in patients with minimally symptomatic CHF compared to those receiving an ICD alone. It is unclear for patients with advanced CHF	5 trials All showed effectiveness in improving 6MHWD in comparing CRT-P to another treatment	1 trial (reported in one article) The study made no direct comparison between the CRT-P versus CRT-D arms, but the results appear similar.

Table 47. Summary of harms by comparator

Harms	CRT-D vs. Implantable Cardioverter Defibrillator (no. of studies and result)	CRT-P vs Optimal medical therapy (no. of studies and result)	CRT D vs. CRT P (no. of studies and result)
Procedure-related complications	1 study No statistically significant difference between the two groups	2 studies The small sample sizes and the small number of studies make it difficult to draw a conclusion other than that more data are needed	2 studies There was no statistically significant difference in complications between CRT-P and CRT-D
Length of hospital stay	1 study The average length of hospital stay (per stay) was significantly less in the CRT-D group vs. the ICD-only group	2 studies These two studies indicate that length of hospital stay might not be significantly different in those receiving CRT-P. However, as with other harms, few studies, with small sample sizes, address this harm	2 studies No studies provided direct comparison of CRT-P and CRT-D for length of hospital stay for the initial device implantation
Pneumothorax	5 studies The incidence of pneumothorax appears to be slightly more common in patients receiving a CRT-D device compared to an ICD	1 study It is difficult to summarize a conclusion based on limited data.	4 studies No study directly compared pneumothorax by CRT type
Pocket hematoma	5 studies Compared to patients receiving an ICD alone, pocket hematoma appears to be slightly more common in patients receiving a CRT-D device	3 studies The heterogeneity of these studies make it difficult to draw clear conclusions	2 studies Studies did not report incidence of pocket hematoma by CRT type
Device infection	7 studies The incidence of device infection is slightly more common in patients receiving a CRT-D device compared to an ICD alone	3 studies The heterogeneity of these studies make it difficult to draw clear conclusions	5 studies Only one study clearly defined infection and adjusted for device type. As such, the conclusion is unclear.
Cardiac perforation/tamponade	3 studies Cardiac Perforation/Tamponade appears to be a rare event that does not appear to be more frequent in patients receiving a CRT-D device compared to an ICD	3 studies These studies seem to indicate that the risk of this outcome is prevalent.	4 studies All three studies did not report which CRT type experienced the outcome
Lead dislodgement	5 studies The data are insufficient to determine whether there is a difference in lead dislodgement rates between patients receiving a CRT-D device versus an ICD	7 studies It is difficult to interpret these results since the studies did not report the recorded time point of the dislodgement, and the studies	4 studies No study specified dislodgement by device type

Harms	CRT-D vs. Implantable Cardioverter Defibrillator (no. of studies and result)	CRT-P vs Optimal medical therapy (no. of studies and result)	CRT D vs. CRT P (no. of studies and result)
	alone	followed their populations for different lengths	
Ventricular arrhythmias	10 studies There is conflicting evidence as to whether CRT-D is protective from VAs compared to an ICD alone. . The data, however, are consistent that CRT-D does not appear to increase the rate of VAs compared to an ICD alone	NR	1 study The study did not specify the prevalence for CRT-P versus CRT-D
Inappropriate implantable cardioverter defibrillator shocks	6 studies There is no apparent difference in the incidence of inappropriate ICD shocks in patients receiving a CRT-D device compared to an ICD alone	NA	2 studies The variation in followup and reporting of number of inappropriate shocks versus number of participants with inappropriate shocks limits the interpretation of this data
Death within one week	2 studies Both of these cohort studies reported zero deaths	3 studies The risk of death within one week with CRT-P is present, though exact estimations await further data	2 studies The studies rarely specified the exact timing of death and are not comparable in their followup and definition of mortality

Predictors of Response to Cardiac Resynchronization Therapy with Defibrillator (CRT-D)

Study Characteristics

We identified secondary analyses from two RCTs: three were from the MADIT-CRT trial[33,34,36] and two from the SMART-AV trial.[50,51] We also identified a study analyzing the Medicare Implantable Cardioverter-Defibrillator Registry [90] and eight cohort studies. Of the cohort studies, one included multiple centers[91], five included single centers[92-96], and two didn't specify the number of centers.[97,98]

Five studies (reported in 8 articles) used CRT-D devices only,[33,34,36,50,51,90,92,97] and six used a mixed CRT-D and cardiac resynchronization therapy with pacemaker (CRT-P) population where the CRT-D cohort represented ≥90 percent of the total cohort.[91,93-96,98] Only three studies (reported in 4 articles) identified the specific device name.[50,51,95,98]

Two such studies were secondary analyses from the SMART-AV trial, which used Boston Scientific CRT-D models (including H220, H225, H227, H229, N119, and N118).[50,51] One cohort study used the following devices: Boston Scientific Contak Renewal 4RF, TR, or CD; Medtronic InSync Sentry or III; and Biotronik Lumax 340 HF-T.[98] In the trial by Leong et al. (2013), implanted devices included the Guidant Contak Renewal, Contak TR or CD, Medtronic Insync III or Sentry, Insync Protecta, St. Jude Atlas HF, and Biotronik Lumax.[95] The MADIT-CRT and SMART-AV trials were both industry funded (Evidence Table 1).

Population Characteristics

The average patient was in their 60s and the percentage of women in the cohorts ranged from 21.4 percent in the study by Shen et al. (2009b)[92] to 57.1 percent in the study by Niebauer et al.[96]Ischemic cardiomyopathy (ICM) was slightly more common than non-ischemic cardiomyopathy (NICM) in the majority of studies, ranging from 38 percent in the less than 65-year-old arm from the analysis by Penn et al.[36] to 77.8 percent in the right bundle branch block (RBBB) cohort from the study by Bilchick et al. (2010)[90] History of atrial fibrillation ranged from 8 percent in the analysis of the MADIT-CRT trial by Penn et al. (2010)[36] to 70.5 percent in the study by Rickard et al.[94] The MADIT-CRT trial excluded patients with any form of AF present less than 1 month prior to enrollment.[33,34,36]

Bundle branch block morphology and pacing varied amongst the studies. The studies by Mascioli et al. (2012)[91] and Niebauer et al. included only patients with native LBBB.[91,96] In the study by Shen at al. (2009b), one arm contained only patients with a native LBBB, and the other arm contained only patients with a paced LBBB pattern.[92] The incidence of native LBBB in the remaining studies ranged from 67.7 to 76.9 percent. Three articles reported on the incidence of RBBB (range 6.7 to 13 %).[34,51,98] Three articles also reported on the incidence of non-specific intraventricular conduction delay (NSIVCD) (range 12 to 23.6%).[51,90,98] Two studies reported data on patients with paced-LBBB morphology.[91,95] In the study by Leong et al. (2013), the incidence of a paced rhythm prior to CRT was 5 percent.[95] The study by Mascioli et al. (2012)[91] contained one arm that was 100 percent patients with paced RBBB. One study included only patients with near 100 percent right ventricle pacing, although it did not report the exact number of patients or from where they were recruited (Evidence Table 9).[94]

The studies were heterogeneous in their inclusion of varied NYHA class patients. Analyses using the MADIT-CRT trial contained only patients with NYHA class I-II CHF.[33,34,36] The two secondary studies from the SMART-AV trial contained primarily NYHA class III-IV patients.[50,51] Four cohort studies included only patients with NYHA class III-IV symptoms[91,93,96,97] while two others included patients with NYHA class II, III, and IV symptoms.[92,95] The inclusion criteria were not clear in one study that reported 6.2 percent NYHA class IV patients out of a baseline of 581 patients.[98]

The studies were homogenous in terms of study design and many key variables including baseline ejection fraction, age, cardiomyopathy subtype, QRS duration, incidence of native LBBB, and gender. However, there were several important heterogeneities. NYHA class varied significantly with some studies including only NYHA class I-II patients, some including only class III and IV patients, and others including class II, III, and IV patients. Only a minority of studies reported the incidence of a RBBB, NSIVCD, and paced QRS pattern prior to CRT, and it varied modestly. The six studies that reported renal function did so in three different ways (baseline creatinine, glomerular filtration rate, creatinine clearance), making a general comparison across studies difficult. Only one analysis reported the race of the included patients (Table 48).

Table 48. Study characteristics of studies assessing predictors of response to CRT-D

Author, year	CRT-D (%)	Funder	Total number of patients	Age (mean, years)	Female gender (%)	NYHA class	Race
Analyses of RCTs							
MADIT-CRT							
Goldenberg,2011[33]	100%	Industry	718 (derivation)	NR	NR	I-II*	NR
Hsu,2012[34]	100%	Industry	Hypo: 190	63.6	33	I-II*	88% Caucasian/9% AA
			Resp: 371	64.9	77	I-II*	92% Caucasian/6% AA
			Super Resp: 191	64.2	75	I-II*	93%Caucasian/ 5%AA
Penn, 2010[36]	100%	Industry	Arm 1 (Age<60):548	53	24	I-II*	NR
			Arm 2 (Age 60-74):941	67	27	I-II*	NR
			Arm 3 (Age >75):331	78	22	I-II*	NR
SMART-AV							
Cheng, 2012[50]	100%	Industry	846	Female:65.2 Male:66.5	32.7	III-IV*	NR
Gold,2011[51]	100%	Industry	426	66	34	III-IV*	NR
Cohort Studies							
Bilchick ,2010[90]	100%	Institutional grand	14946	73.02	27.3	I:1.21% II:10.99% III:74.07% IV:13.73%	NR
Niebauer, 2014[96]	98.8%	NR	170	Responders:64.4 Non-responders:53.8	Responders:52.1 Non-responders:31.6	III-IV	NR
Leong,2013[95]	92%	NR	848	67	22	II:23%	NR

Author, year	CRT-D (%)	Funder	Total number of patients	Age (mean, years)	Female gender (%)	NYHA class	Race
						III:68% IV:9%	
Mascioli,2012[91]	90.1%	NR	Arm 1 (Group 1):61	68	30	III-IV*	NR
			Arm 2 (Group 2):50	70	34	III-IV*	NR
Rickard,2013[94]	93.8%	NR	112	69.3	29.5	III-IV*	NR
Shen,2009a[97]	100%	NR	108	NR	NR	NR	NR
Shen,2009b[92]	100%	NR	Arm 1 (I-LBBB (CRT-D):67	70	31.3	III-IV*	NR
			Arm 2 (RV-LBBB (CRT-D)):28	70	21.4	III-IV*	NR
Shanks,2011[98]	97.1%	NR	581	66.4	22.4	Mean 2.8	NR
Shen,2011[93]	99%	NR	Arm 1 (Group A):100	70	27	III-IV*	NR
			Arm 2 (Group B):36	71	31	III-IV*	NR

NR=not reported hypo=hypo responder AA=African American resp=responder; I-LBBB=intrinsic left bundle branch block; RV-LBBB=right ventricular paced left bundle branch block

*NYHA class reported in participant characteristics but actual number of patients in each class not reported.

Risk of Bias

Given a strong predilection towards the publishing of positive results, the findings from this section must be qualified by the high likelihood of reporting bias. The studies, including analyses from the RCTs, had several potential sources of bias as assessed using QUIPS: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis. In terms of study participation, the majority of studies were adequate in their description of the source population, recruitment period and place, and exclusion/inclusion criteria. We assessed two studies as having potential for bias from poor description of study participation.[97,98] Three studies had very specific populations. One study included only patients with near 100 percent right ventricular pacing[94], and the other two had only patients with either a native or paced LBBB.[92,96] These factors limit the generalizability of these three studies.

In terms of attrition rates, the majority of studies did not report dropout rates or reasons for dropout, making the risk of bias from this unclear. The measurement of the prognostic indicators and outcomes across the studies was, in general, adequate. In terms of confounding, for inclusion we required all studies to control for at least gender and either QRS duration or morphology. A significant limitation of the modeling for many studies was not including *a priori* known clinically significant factors for adjustment, but rather relying solely on statistical criteria for model building. Otherwise, statistical analysis across the studies was generally of adequate quality. Overall, the risk of bias was high due to the high likelihood of reporting bias (Table 49 and Figure 16).

Table 49. Summary of risk of bias for studies assessing predictor of response to CRT-D

Author, year	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall quality
MADIT CRT Goldenberg,2011[33] Penn, 2010[36] Hsu,2012[34]	-	-	-	-	-	-	-
SMART AV Cheng, 2012[50] Gold,2011[51] Sub Study	-	+	-	-	-	-	-
Bilchick,2010[90]	-	-	-	-	-	-	+
Niebauer, 2014[96]	-	-	-	-	-	-	-
Leong,2013[95]	-	-	-	-	-	-	-
Mascioli,2012[91]	-	-	+	-	+	+	+
Rickard,2013[94]	-	-	-	-	-	-	+
Shen,2009a[97]	++	+	+	-	-	-	+
Shen,2000b[92]	-	-	-	-	-	-	-
Shen,2011[93]	-	-	-	-	-	-	-
Shanks,2011[98]	++	+	-	-	-	-	+

-=Low
++=High
+=Moderate

Figure 16. Summary of risk of bias for studies assessing predictor of response to CRT-D

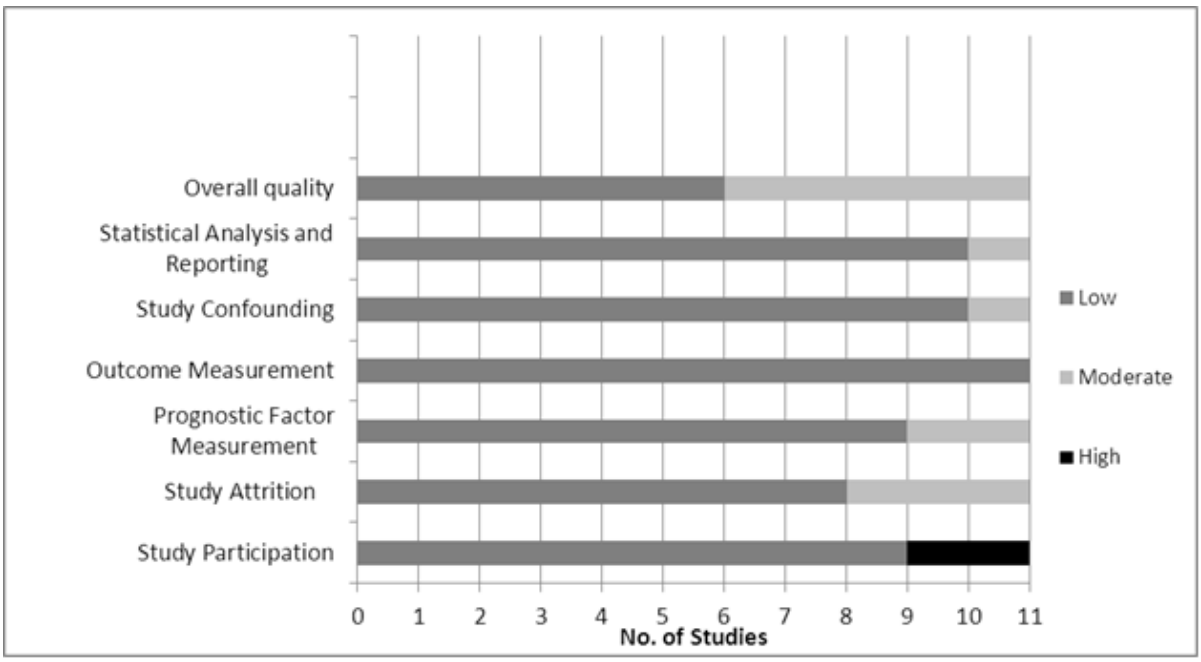


Table 50. Included predictors of response for CRT-D

Author, year	Age	Gender	CM type	AF	QRSd	QRS morphology	CKD	LA volume	LVEF	BMI	LVEDV
MADIT-CRT											
Goldenberg,2011[33]		X	X		X	X		X			X
Hsu,2012[34]		X	X		X	X		X		X	
Penn, 2010[36]	X	Y	Y	Y	Y	Y	Y		Y		
SMART-AV											
Cheng, 2012[50]	X	X	X	X	X	X	X		X		
Gold,2011[51]	X	X	X		X	X			X		
Niebauer, 2014[96]		X	X		X	Z			X		
Bilchick ,2010[90]	X	X	X	X	X	X			X		
Leong,2013[95]	X	X	X	X	X		X		X		
Mascioli,2012[91]		Y				X	X				
Rickard,2013[94]	Y	Y	Y			Y			Y		
Shanks,2011[98]		X	X		X			X			
Shen,2009a[97]	X	X			X	X			X		
Shen,2009b[92]	X	X			X	X		X	X		
Shen,2011[93]	X	X	X		X	X		X	X		

X= controlled for and effect size reported
Y=controlled for but effect size not reported
Z=included only patients with LBBB
CM=cardiomyopathy; AF=atrial fibrillation; QRSd=QRS duration; CKD=chronic kidney disease; LA=left atrial; LVEF=left ventricular ejection fraction BMI=body mass index; LVESV=left ventricular end systolic volume

Table 51. Definitions of response for CRT-D predictors

Author, year	All-cause mortality	Cardiovascular mortality	Combined endpoint	HF	LVEF	LVESV continuous	LVESV ≥10%	LVEDV continuous	LVEDV ≥10%	Quality of life score (MLHFQ)	6 Minute Hall Walk Distance	Clinical composite score
MADIT-CRT												
Goldenberg,2011[33]							X		X			
Hsu,2012[34]					X							
Penn, 2010[36]	X		X (Death or CHF)	X								
SMART-AV												
Cheng, 2012[50]						X (LVESVi)						
Gold,2011[51]							X			X		
Niebauer, 2014[96]							X					
Bilchick,2010[90]	X		X (death or CHF)									
Leong,2013[95]	X											
Mascioli,2012[91]			X (death or CHF)									
Rickard,2013[94]							X					
Shanks,2011[98]			X (nonresponse: lack of improvement in NYHA class, death from CHF, heart transplant, and lack of reduction in LVESVi≥15%)									
Shen,2009a[97]							X					
Shen,2009b[92]							X					
Shen,2011[93]			X (LVESV ≥15% and survival free of CHF)									

HF: heart failure hospitalization; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; LVESVi: left ventricular end-systolic volume index; LVEDV left ventricular end diastolic volume; NYHA: New York Heart Association; MLHFQ: Minnesota Living with Heart failure Questionnaire

Clinical Predictors

Table 52. Evidence addressing predictors of response to CRT-D, by predictor

Predictor	Outcome (Number of studies)	Author, year	Model	Key findings
Age	Mortality (3)	Penn, 2010[36] Bilchick,2010[90] Leong,2013[95]	Multivariate Cox regression	Data are conflicted as to the association of age with all-cause mortality in patients undergoing CRT. Heterogeneity in NYHA functional class amongst the studies may have a role in this discrepancy in that age may be a stronger predictor of time-to-death in patients with more advanced CHF symptoms
	Heart failure hospitalization (4)	Penn, 2010[36a] Bilchick,2010[90a] Shen,2011[93c] Shanks,2011[98a]	Multivariate Cox regression	Unclear
	LVEF (0)	NA	NA	Unclear
	LVESV (5)	Cheng, 2012[50]	Multivariate linear regression	The preponderance of data suggest that age is not an important predictor of changes in LVESV
		Gold,2011[51] Shen,2009a[97] Shen,2009b[99] Rickard,2013[94]	Multivariate logistic regression	
	LVEDV (0)	NA	NA	Unclear
	MLHFQ (1)	Gold,2011[51]	Multivariate logistic regression	Data suggest that age is not an important predictor of changes in QOL
	Clinical Composite Score (0)	NA	NA	Unclear
	SF-36 (0)	NA	NA	
	6MHWD (0)	NA	NA	
Gender	Mortality (2)	Bilchick,2010[90] Leong,2013[95]	Multivariate Cox regression	Data suggest that female gender is predictive of improved survival following CRT-D implant at 3 years. The association of female gender and survival at shorter followup times is less certain
	Heart failure hospitalization (3)	Bilchick,2010[90a]	Multivariate Cox regression	Unclear
		Shen,2011[93c] Shanks,2011[98b]	Multivariate logistic regression	
	LVEF (1)	Hsu,2012[34]	Multivariate linear regression	Data suggest that female gender is a strong positive predictor of reverse ventricular remodeling endpoint
	LVESV (5 studies reported in 6 articles)	Goldenberg,2011[33] Gold,2011[51] Shen,2009a[97] Shen,2009b[99]	Multivariate logistic regression	The preponderance of data suggest that female gender is a strong positive predictor of reverse ventricular remodeling endpoint

Predictor	Outcome (Number of studies)	Author, year	Model	Key findings
		Rickard,2013[94]		
		Cheng, 2012[50]	Multivariate linear regression	
	LVEDV (1)	Goldenberg,2011[33]	Multivariate logistic regression	Data suggest that female gender is a strong positive predictor of reverse ventricular remodeling endpoint
	MLHFQ (1)	Gold,2011[51]	Multivariate logistic regression	Female gender may be predictive of improved MLHFQ scores but we need more data to confirm this finding
	Clinical Composite Score (0)	NA	NA	Unclear
	SF-36 (0)	NA	NA	
	6MHWD (0)	NA	NA	
Cardiomyopathy subtype	Mortality (2)	Bilchick,2010[90] Leong,2013[95]	Multivariate Cox regression	NICM is predictive of improved survival at early, 1-year, and 3-year followup after CRT-D implantation
	Heart failure hospitalization (3)	Bilchick,2010[90a]	Multivariate Cox regression	Unclear
		Shen,2011[93c] Shanks,2011[98b]	Multivariate logistic regression	
	LVEF (1)	Hsu,2012[34]	Multivariate linear regression	Data suggest that NICM is a strong positive predictor of reverse ventricular remodeling endpoint
	LVESV (4 studies in 5 articles)	Goldenberg,2011[33] Cheng, 2012[50] Gold,2011[51] Rickard,2013[94] Niebauer, 2014[96]	Multivariate logistic regression	The preponderance of data suggest that NICM is a strong positive predictor of reverse ventricular remodeling endpoints
	LVEDV (1)	Goldenberg,2011[33]	Multivariate logistic regression	Data suggest that NICM is a strong positive predictor of reverse ventricular remodeling endpoints
	MLHFQ (1)	Gold,2011[51]	Multivariate logistic regression	Cardiomyopathy subtype is not predictive of improved QOL scores, although we need more data to confirm this finding
	Clinical Composite Score (0)	NA	NA	Unclear
	SF-36 (0)	NA	NA	Unclear
	6MHWD (0)	NA	NA	Unclear
Atrial fibrillation	Mortality (2)	Bilchick,2010[90] Leong,2013[95]	Multivariate Cox regression	Data suggest that a history of AF is predictive of increased all-cause mortality at early, 1-year, and 3-year followup after CRT-D
	Heart failure hospitalization (1)	Bilchick,2010[90a]	Multivariate Cox regression	Unclear
	LVEF (0)	NA	NA	
	LVESV (1)	Cheng, 2012[50]	Multivariate linear regression	

Predictor	Outcome (Number of studies)	Author, year	Model	Key findings
	LVEDV (0)	NA	NA	
	MLHFQ (0)	NA	NA	
	Clinical Composite Score (0)	NA	NA	
	SF-36 (0)	NA	NA	
	6MHWD (0)	NA	NA	
QRS duration	Mortality (2)	Bilchick,2010[90] Leong,2013[95]	Multivariate Cox regression	The data are conflicted with regard to the association of QRS duration and mortality
	Heart failure hospitalization (3)	Bilchick,2010[90a]	Multivariate Cox regression	Unclear
		Shanks,2011[98b] Shen,2011[93c]	Multivariate logistic regression	
	LVEF (1)	Hsu,2012[34]	Multivariate logistic regression	Data suggest that QRS duration is directly associated with improved rates of reverse ventricular remodeling
	LVESV (6 studies reported in 7 articles)	Goldenberg,2011[33] Gold,2011[51] Shen,2009a[97] Shen,2009b[99] Rickard,2013[94] Niebauer, 2014[96]	Multivariate logistic regression	The preponderance of data suggest that QRS duration is directly associated with improved rates of reverse ventricular remodeling
		Cheng, 2012[50]	Multivariate linear regression	
	LVEDV (1)	Goldenberg,2011[33]	Multivariate logistic regression	Data suggest that QRS duration is directly associated with improved rates of reverse ventricular remodeling
	MLHFQ (1)	Gold,2011[51]	Multivariate logistic regression	Unclear Unclear
	Clinical Composite Score (0)	NA	NA	
	SF-36 (0)	NA	NA	
	6MHWD (0)	NA	NA	
QRS morphology	Mortality (1)	Bilchick,2010[90]	Multivariate Cox regression	Data suggest that a native LBBB is predictive of improved survival early, one year, and three year followup after CRT-D, compared to an RBBB or NSIVCD pattern
	Heart failure hospitalization (3)	Bilchick,2010[90a] Mascioli,2012[91a]	Multivariate Cox regression	Unclear
		Shen,2011[93c]	Multivariate logistic regression	
	LVEF (1)	Hsu,2012[34]	Multivariate logistic regression	Data suggest that a LBBB morphology is a strong positive predictor of reverse ventricular remodeling
	LVESV (4 studies reported in 5 articles)	Goldenberg,2011[33] Gold,2011[51] Shen,2009a[97]	Multivariate logistic regression	The preponderance of data suggest that a LBBB morphology is a strong positive predictor of reverse ventricular remodeling

Predictor	Outcome (Number of studies)	Author, year	Model	Key findings
		Shen,2009b[99]		
		Cheng, 2012[50]	Multivariate linear regression	
	LVEDV (0)	NA	NA	Unclear
	MLHFQ (1)	Gold,2011[51]	Multivariate logistic regression	QRS morphology was not associated with change in QOL
	Clinical Composite Score (0)	NA	NA	Unclear
	SF-36 (0)	NA	NA	
	6MHWD (0)	NA	NA	
Chronic kidney disease	Mortality (1)	Leong,2013[95]	Multivariate Cox regression	Unclear
	Heart failure hospitalization (1)	Mascioli,2012[91a]	Multivariate Cox regression	
	LVEF (0)	NA	NA	
	LVESV (1)	Cheng, 2012[50]	Multivariate linear regression	
	LVEDV (0)	NA	NA	
	MLHFQ (0)	NA	NA	
	Clinical Composite Score (0)	NA	NA	
	SF-36 (0)	NA	NA	
	6MHWD (0)	NA	NA	
Left atrial volume	Mortality (1)	Shanks,2011[98b]	Multivariate logistic regression	Unclear
	Heart failure hospitalization (1)	Shen,2011[93c]	Multivariate logistic regression	Unclear
	LVEF (1)	Hsu,2012[34]	Multivariate logistic regression	Data suggest that LVEF a predictor in minimally symptomatic CHF population (NYHA class I-II)
	LVESV (3)	Shen,2011[93c] Goldenberg,2011[33] Shen,2009b[99]	Multivariate logistic regression	Data suggest that LVESV a predictor in minimally symptomatic CHF population (NYHA class I-II)
	LVEDV (1)	Goldenberg,2011[33]	Multivariate logistic regression	Data suggest that LVEDV is a predictor in minimally symptomatic CHF population (NYHA class I-II)
	MLHFQ (0)	NA	NA	Unclear
	Clinical Composite Score (0)	NA	NA	
	SF-36 (0)	NA	NA	
	6MHWD (0)	NA	NA	
Left ventricular ejection fraction	Mortality (2)	Bilchick,2010[90] Leong,2013[95]	Multivariate Cox regression	Current data suggest an association between increasing baseline LVEF and improved survival out to three years in patients receiving CRT-D devices
	Heart failure hospitalization (1)	Bilchick,2010[90a]	Multivariate Cox regression	Unclear
	LVEF (1)	Hsu,2012[34]	Multivariate logistic regression	Baseline LVEF is a poor predictor of reverse ventricular remodeling

Predictor	Outcome (Number of studies)	Author, year	Model	Key findings
	LVESV (5 studies reported in 6 articles)	Shen,2009a[97] Shen,2009b[99] Gold,2011[51] Rickard,2013[94] Niebauer, 2014[96]	Multivariate logistic regression	The data is conflicted as to whether baseline LVEF is predictive of reverse remodeling
		Cheng, 2012[50]	Multivariate linear regression	
	LVEDV (0)	NA	NA	Unclear
	MLHFQ (1)	Gold,2011[51]	Multivariate logistic regression	Baseline LVEF is a poor predictor of changes in QOL scores
	Clinical Composite Score (0)	NA	NA	Unclear
	SF-36 (0)	NA	NA	
	6MHWD (0)	NA	NA	
Body mass index	Mortality (0)	NA	NA	Unclear
	Heart failure hospitalization (0)	NA	NA	
	LVEF (1)	Hsu,2012[34]	Multivariate logistic regression	
	LVESV (0)	NA	NA	
	LVEDV (0)	NA	NA	
	MLHFQ (0)	NA	NA	
	Clinical Composite Score (0)	NA	NA	
	SF-36 (0)	NA	NA	
	6MHWD (0)	NA	NA	
Left ventricular end-diastolic volume	Mortality (0)	NA	NA	Unclear
	Heart failure hospitalization (0)	NA	NA	
	LVEF (0)	NA	NA	
	LVESV (1)	Goldenberg,2011[33]	Multivariate logistic regression	
	LVEDV (0)	NA	NA	
	MLHFQ (0)	NA	NA	
	Clinical Composite Score (0)	NA	NA	
	SF-36 (0)	NA	NA	
	6MHWD (0)	NA	NA	

LVESV-Left Ventricular End Systolic Volume, LVEDV- Left Ventricular End Diastolic Volume, LVEF-Left Ventricular Ejection Fraction, QOL-Quality of Life, 6MHWD-6 Minute Hall Walk Distance, MLHFQ-Minnesota Living with Heart failure Questionnaire NA-Not applicable

a- Combined endpoint of Death or CHF, b- Combined endpoint of lack of improvement in NYHA class, death from HF, heart transplant, and lack of reduction in LVESVi≥15%), c- Combined endpoint of LVESV ≥15% and survival free of HF

Age

Age as a potential predictor of response in examining the effects of CRT-D was assessed in eight analyses.[36,50,51,90,92-95,97] Three studies evaluated age as a predictor of mortality alone following CRT-D.[36,90,95] In the analysis by Penn et al. (2010),[36] of data from MADIT-CRT (a population of NYHA class I and II patients), age was not a predictor of mortality at 3-year followup. (≥75 years old group compared to all others (HR: 1.14, 95% CI, 0.55-2.33, p=0.728)

In the very large Medicare registry study by Bilchick et al. (2010), patients 70-79 years old had higher 3-year mortality rates compared to patients 50-59 years old (HR: 1.75, 95% CI, 1.51 to 2.04).[90] In the study by Leong et al. (2013), age was not a predictor of worsened survival at a median of 44 months followup (HR: 0.991, 95% CI, 0.973 to 1.01, p=0.3).[95]

Four analyses evaluated age as a predictor of heart failure hospitalizations, one looked at HF hospitalization alone[36] and the others combined it with another endpoint.[36,90,93,98] In the MADIT-CRT analysis by Penn et al. (2010) age (broken into 3 groups: ≥75, 60-74, and <60 years old) was a predictor of CHF admissions at 3-year followup (the oldest group derived the most benefit) (HR: 0.46, 95%CI,0.29 to 0.74, p=0.001).[36] Two studies combined time-to-death or first hospitalization into a single endpoint.[36,90] Also in this analysis, age was a predictor of survival without CHF admissions in patients 60-74 and ≥75 but not in patients <60 years old. In contrast, the study by Bilchick et al. (2010) reported an association between age and the composite outcome of survival without CHF admissions at 3 years in patients ≥80 compared to patients 50-59 years old (HR:1.24, 95% CI, 1.10 to 1.38). Patients in the 60-69 year old cohort in this study had improved survival without CHF admissions compared to the 50-59 year old reference group (HR:0.84, 95% CI, 0.75 to 0.94).

One study used combined endpoints incorporating both CHF admissions and evidence of change in left ventricular end-systolic volume (LVESV) from baseline.[93] Shen et al. (2011) reported no statistically significant association between age and response (defined as a reduction in LVESV >15 percent and survival without CHF admissions) (OR 0.97 (0.88-1.08), p=0.60).[93] No studies evaluate age as a predictor of change in LVEF. Five studies assessed age as a predictor of changes in LVESV from baseline following CRT.[50,51,92,94,97] Cheng et al. (2012), in analysis of data from the SMART-AV trial, reported that increasing age was associated with a greater reduction in LVESV.[50] Gold and colleagues, using data from the same trial but using a dichotomous definition of response (reduction in LVESV ≥15%), found no association between age and response (OR: 1.00, 95% CI, 0.98 to 1.02, p=0.801).[51] The other three studies (two by Shen, and one by Rickard), did not report an association between age and changes in left LVESV.[92,94,97] No studies looked at age as a predictor of changes in LVEDV. Only one study looked at age as a predictor of change in quality of life (QOL) (as assessed by the MLHFQ. Gold et al. (2011) found that age was not associated with changes in QOL score (OR: 0.99, 95% CI, 0.97 to 1.01, p=0.209).[51] No studies examined age as a predictor of changes in clinical composite score, SF-36, or 6-minute hall walk distance (6MHWD).

To summarize, the data are conflicted as to the association of age with all-cause mortality in patients undergoing CRT. Heterogeneity in NYHA functional class amongst the studies may have a role in this discrepancy in that age may be a stronger predictor of time-to-death in patients with more advanced CHF symptoms. Given a paucity of data on CHF admissions alone, it's unclear whether age is predictive of CHF admissions. The preponderance of data suggests that age is not an important predictor of changes in LVESV and changes in QOL scores following CRT (Table 50 and 51).

Gender

Ten (reported in 12 articles) included gender as a potential predictor of response.[33,34,50,51,90,92-98] Two studies evaluated gender as a predictor of mortality alone following CRT.[90,95] The study by Bilchick et al. (2010)[90], associated female gender with improved mortality at 3 years (HR:0.87, 95% CI, 0.81to 0.94, p <0.001) but not at 1 year (HR:0.92, 95% CI, 0.82 to 1.02,

p=0.155). In the study by Leong et al. (2013) gender was not a significant predictor of survival at a median of 44 months followup (HR: 0.991, 95% CI, 0.973 to 1.01, p=0.3).[95]

Three studies addressed gender in terms of predicting CHF admissions: all utilized CHF as part of a combined endpoint.[90,93,98] The study by Bilchick et al. (2010) reported non-statistically significant association of female gender with the endpoint of survival without CHF admissions at 1 year (1.08 95% CI, 1 to 1.16, p=0.065) or at 3 years (1.00 95% CI, 0.94-1.05, p=0.872).[90] In the study by Shanks et al. (2011), gender was not a predictor of non-response defined as lack of improvement in NYHA class ≥1, death from worsening CHF, heart transplant, or lack of reduction in LVESV indexed to body surface areas (LVESV index >15 %) (OR: 1.504 [male gender], 95% CI, 0.814 to 2.777, p=0.192).[98] Shen et al. (2011) reported a non-statistically significant association between gender and response (defined as a reduction in LVESV >15 percent and survival without CHF admissions).[93] Only one study reported the association of gender and change in ejection fraction. This analysis of MADIT-CRT trial by Hsu et al. (2012), reported an association between female gender and an improvement in LVEF (≥14.5 percent from baseline) (OR: 1.96,95% CI, 1.32 to 2.90, p<0.001).[34]

Six studies (reported in 7 articles) assessed the relationship between gender and changes in LVESV from baseline following CRT.[33,50,51,92,94,96,97] In an analysis from MADIT-CRT, Goldenberg et al. (2011) reported an association between female gender and improved rates of rates of reduction in LVESV ≥15 percent from baseline.[33] Cheng et al. (2012) reported a positive association between male gender and an increase in LVESV index from baseline with data from the SMART-AV trial.[50] Gold and colleagues reported a negative association between male gender and reduction in LVESV ≥15 percent from baseline (OR: 0.53, 95% CI, 0.33 to 0.85, p=0.008) also from the SMART-AV trial.[51] The study by Shen et al. (2009a) reported no association between gender with response (OR: 0.51, 95% CI, 0.11 to 2.34, p=0.38).[97] Three studies reported no association between gender and change in LVESV.[94,96,97] These studies included highly specialized populations. Rickard et al. (2013) was a cohort of patients with paced rhythms undergoing upgrade to CRT and Shen et al. (2009b) and Niebauer et al. [96] included populations of patients all with native or paced LBBB.

One study reported an association between female gender and improved rates of reduction in LVEDV ≥10 percent from baseline.[33] Only one study reported gender as a predictor of change in QOL. This analysis from the SMART-AV trial reported that male gender was significantly associated with inferior MLHFQ scores following CRT-D (OR: 0.56, 95% CI, 0.34 to 0.91, p=0.018).[51] No studies examined gender as a predictor of changes in clinical composite score, SF-36, or 6MHWD.

Overall, the data suggest that female gender is predictive of improved survival following CRT-D implant at 3 years. The association of female gender and survival at shorter followup times is less certain. Given the lack of data on CHF admissions alone, it is unclear whether gender is predictive of CHF admissions. The preponderance of data suggest that female gender is a strong positive predictor of reverse ventricular remodeling endpoint (changes in LVEF, LVESV indexed to body surface areas [LVESVi] , and LVEDV indexed to body surface areas [LVEDVi]) following CRT. The studies that failed to show this association were limited by substantial heterogeneities in the population studied. Female gender may be predictive of improved MLHFQ scores but we need more data to confirm this finding (Table 50 and 51).

Cardiomyopathy Subtype

Eight studies (reported in 9 articles) included cardiomyopathy subtype as a potential predictor of response in examining the effects of CRT-D.[33,34,50,51,90,93-96,98] Two CRT-D studies evaluated cardiomyopathy subtype as a predictor of mortality alone following CRT.[90,95] The study by Bilchick et al. (2010), reported an association between ICM and impaired survival at 1 year (HR: 1.39, 95% CI, 1.21 to 1.59, p<0.001) and 3 years (HR: 1.44, 95% CI, 1.33 to 1.57, p<0.001) compared to NICM.[90] The study by Leong et al. (2013) found an association between NICM and improved survival at a median of 44 months followup (HR: 0.730, 95% CI, 0.535-0.996, p=0.047) compared to ICM.[95] Three studies assessed cardiomyopathy subtype as a predictor of CHF admissions, all of which utilized CHF as part of a combined endpoint.[90,93,98] The study by Bilchick et al. (2010) reported an association between ICM and impaired survival without CHF admissions both at 1 year (HR: 1.24, 95% CI, 1.13 to 1.35, p =<0.001) and at 3 years (HR: 1.32, 95% CI, 1.22-1.40, p<0.001). In the study by Shanks et al. (2011), ICM was predictive of non-response (defined as lack of improvement in NYHA class ≥1, death from worsening CHF, heart transplant, or lack of reduction in LSESV index >15 %) (OR: 2.264, 95% CI, 1.272 to 4.031, p=0.005). The study by Shen et al. (2011) did not report an association between ICM and response (OR: 0.74, 95% CI, 0.04 to 12.87, p=0.84) (defined as a reduction in LVESV >15 percent and survival without CHF admissions).[93]

Only one study examined the association of cardiomyopathy subtype and change in LVEF. In an analysis of MADIT-CRT trial data, Hsu et al. (2012) reported a strong association between NICM and a large improvement in LVEF (≥14.5% from baseline) (OR: 1.80, 95% CI, 1.20 to 2.71, p=0.005).[34] Four studies (reported in 5 articles) examined whether cardiomyopathy subtype would predict changes in LVESV from baseline following CRT.[33,50,51,94,96] In an analysis from MADIT-CRT, Goldenberg et al. (2011) reported an association between NICM and improved rates of reduction in LVESV ≥15 percent from baseline.[33] Cheng et al. (2012) reported a positive association between ICM and increase in LVESV index from baseline from the SMART-AV trial.[50] Gold et al. (2011) reported a negative association between ICM and reduction in LVESV ≥15 percent from baseline (OR: 0.58, 95% CI, 0.37 to 0.91, p=0.019) also from the SMART-AV trial.[51] The study by Niebauer et al. reported no association between cardiomyopathy subtype and response in a highly selected population of patients with LBBB.[96] Similarly, the study by Rickard et al. (2013) reported no association between cardiomyopathy subtype and response in a highly selected population of patients with frequent right ventricular pacing.[94]

One study examined the association of cardiomyopathy type and change in left ventricular end diastolic volume (LVEDV). In an analysis from MADIT-CRT, Goldenberg et al. (2011) reported an association between NICM and improved rates of rates of reduction in LVEDV ≥10 percent from baseline.[33] Only one study assessed cardiomyopathy subtype as a predictor of change in quality of life. In an analysis from SMART-AV, Gold et al. (2011) found that cardiomyopathy subtype was not associated with change in quality of life following CRT.[51] There were no studies that examined cardiomyopathy subtype as a predictor of changes in clinical composite score, SF-36, or 6MHWD.

To summarize, our findings suggest that NICM is predictive of improved survival at early, 1-year, and 3-year followup after CRT-D implantation. Given the lack of data on CHF admissions alone, it's unclear whether cardiomyopathy subtype is predictive of CHF admissions. The preponderance of data suggests that NICM is a strong positive predictor of reverse ventricular remodeling (changes in LVEF, LVESVi, and LVEDVi following CRT. Cardiomyopathy subtype

is not predictive of improved quality of life scores, although we need more data to confirm this finding (Table 50 and 51).

Atrial Fibrillation

Three studies examining the effects of CRT-D included a history of AF as a potential predictor of response.[50,90,95] Two studies evaluated a history of AF as a predictor of mortality alone following CRT-D.[90,95] The study by Bilchick et al. (2010) reported an association between a history of AF and impaired survival at 1 year (HR:1.27, 95% CI, 1.14 to 1.41, p <0.001) and 3 years (HR:1.21, 95% CI, 1.14 to 1.30, p<0.001).[90] The study by Leong et al. (2013) reported an association between a history of AF and worsened survival at a median of 44 months followup (HR:1.4, 95% CI, 1.0 to 2.0, p=0.045).[95] No study assessed AF as a predictor of CHF admissions alone. One study assessed history of AF in terms of predicting a combined endpoint of CHF admissions and death.[90] This study reported an association between a history of AF and impaired survival without CHF admissions both at 1 year (HR:1.27, 95% CI, 1.18 to 1.37, p=<0.001) and at 3 years (HR:1.22, 95% CI, 1.15 to 1.28, *p* <0.001). No studies reported the history of AF and change in ejection fraction or LVEDV. In an analysis from SMART-AV, Cheng et al. (2012) did not report an association between a history of AF and a change in LVESV index (p=0.945).[50] No studies examined a history of AF as a predictor of changes in QOL score, clinical composite score, or 6MHWD.

Overall the data suggest that a history of AF is predictive of increased all-cause mortality at early, 1-year, and 3-year followup after CRT-D. Given the lack of data on CHF admissions alone, it's unclear whether a history of AF is predictive of CHF admissions. Similarly there are not sufficient data to determine the predictive value of AF in terms of remodeling endpoints, changes in quality of life, and 6MHWD (Table 50 and 51).

QRS Duration

Nine studies (reported in 11 articles) included QRS duration as a potential predictor of response in examining the effects of CRT-D.[33,34,50,51,90,92,93,95-98] Two studies evaluated QRS duration as a predictor of mortality alone.[90,95]

The study by Bilchick et al. (2010) reported an association between a QRS duration ≥150ms and improved survival at one year (HR: 0.77, 95% CI, 0.70 to 0.84, p <0.001) and three years (HR: 0.86, 95% CI, 0.81 to 0.91, p <0.001) compared to a QRS duration of 120-149ms.[90] The study by Leong et al. (2013) reported a non-statistically significant association of QRS duration with survival (HR: 0.997, 95% CI, 0.991 to 1.00, p=0.4).[95] Three studies assessed the QRS duration in terms of predicting CHF admissions, all of which utilized CHF as part of a combined endpoint.[90,93,98]

The study by Bilchick et al. (2010) reported an association between a QRS duration ≥150ms and improved survival without CHF admissions at one year (HR:0.78, 95% CI, 0.73 to 0.83, p<0.001) and three years (HR:0.83, 95% CI, 0.79 to 0.87, p<0.001), compared to a QRS duration 120-149ms.[90] The study by Shanks et al. (2011) reported that QRS duration was not predictive of non-response (defined as lack of improvement in NYHA class ≥1, death from worsening CHF, heart transplant, or lack of reduction in LVESV index >15 %) (OR: 0.994, 95% CI, 0.986 to 1.002, p=0.119).[98] The study by Shen et al. (2011) reported no association between QRS duration and response (OR: 1.03, 95% CI, 0.995 to 1.07, p=0.09) (defined as a reduction in LVESV >15 percent and survival without CHF admissions).[93]

An analysis from MADIT-CRT, Hsu et al. (2012), reported a strong association between a QRS duration >150ms and a large improvement in LVEF (≥14.5% from baseline) (OR: 1.79, 95% CI, 1.17 to 2.73, p=0.007).[34]

Five studies (reported in 6 articles) assessed association of QRS duration subtype with changes in LVESV from baseline following CRT.[33,50,51,92,94,97] In an analysis from MADIT-CRT, Goldenberg et al. (2011) reported an association between QRS duration ≥150ms and improved rates of rates of reduction in LVESV ≥15 percent from baseline.[33] In analysis from SMART-AV Cheng et al. (2012) reported an association between increasing QRS duration and reduction in LVESV index from baseline.[50] In another analysis from SMART-AV Gold et al. (2011) did not report an association between QRS duration and reduction in LVESV ≥15 percent from baseline.[51] The study by Shen et al. did not associate increasing QRS duration with increased rates of response (OR: 1.02, 95% CI, 1.00 to 1.04, p<0.13).[97]The study by Niebauer found no association with QRS duration and reduction in LVESV≥15% in a highly selected population all with native LBBB. [96]Finally two other studies reported no association between QRS duration and response.[94,99]

In an analysis from MADIT-CRT, Goldenberg et al. (2011) reported an association between QRS duration ≥150ms and improved rates of rates of reduction in LVEDV ≥10 percent from baseline.[33] In an analysis from SMART-AV, Gold et al. (2011) reported no association between QRS duration and change in QOL following CRT.[51] No studies examined QRS duration as a predictor of changes in clinical composite score or 6MHWD.

To summarize QRS duration is intimately linked with QRS morphology and the relative contribution of each in predicting outcomes is unclear. The data are conflicted with regard to the association of QRS duration and mortality in patients undergoing CRT-D implantation. Given the lack of data on CHF admissions, it is unclear whether QRS duration is predictive of CHF admissions. The preponderance of data suggests that QRS duration is directly associated with improved rates of reverse ventricular remodeling (changes in LVEF, LVESVi, and LVEDVi) following CRT (Table 50 and 51).

QRS Morphology

Seven studies (reported in 9 articles) included QRS morphology as a potential predictor of response in examining the effects of CRT-D [33,34,50,51,90-93,97] One study assessed QRS morphology as a predictor of mortality.[90] This study reported an association between an RBBB pattern and worsened survival at both 1 year (HR:1.44, 95% CI, 1.26 to 1.65, p<0.001) and 3 years (HR:1.37, 95% CI, 1.26 to 1.49, p<0.001), compared to patients with a LBBB morphology.[90] In addition, it reported an association between an NSIVCD pattern and worsened survival at 1 year (HR: 1.18, 95% CI, 1.05 to 1.32, p<0.001) and 3 years (HR: 1.08, 95% CI, 1.00 to 1.16, p<0.001), compared to patients with a LBBB morphology.

Three studies assessed QRS morphology as a predictor of CHF admissions as part of a composite endpoint.[90,91,93] The study by Bilchick et al. (2010) reported an association between an RBBB and worsened survival without CHF admissions at one year (HR:1.32, 95% CI, 1.20 to 1.45, p<0.001) and three years (HR:1.28,95% CI, 1.20 to 1.38, p<0.001) compared to patients with a LBBB morphology.[90] In addition, it reported an association between an NSIVCD pattern and worsened survival without CHF admissions at one year (HR:1.08, 95% CI, 1.00 to 1.17, p<0.001) and three years (HR:1.05, 95% CI, 0.99 to 1.12, p<0.001), compared to patients with a LBBB morphology. The study by Shen et al. (2011) reported an association between right ventricle paced LBBB pattern and response (OR: 6.83, 95% CI, 1.11 to 42.12, p=0.04) (defined

as a reduction in LVESV >15 percent and freedom from CHF admissions).[93] The study by Mascioli et al. (2012) reported an association between the presence of a "false" LBBB pattern and worsened survival free of CHF admissions, compared to patients with a "true" LBBB (defined as a QRS morphology in V1-V2, duration ≥140ms for men and ≥130ms for women and mid-QRS notching or slurring in ≥2 leads among I, AVL, V1,V2,V5, and V6) (OR: 3.98, 95% CI, 1.51to 10.48, p=0.005).[91]

One study assessed the association of QRS morphology and change in LVEF.[34] This study reported a strong association between a LBBB pattern and a large improvement in LVEF (≥14.5%from baseline) (OR: 2.05, 95% CI, 1.24 to 3.40, p=0.006). Four studies (reported in 5 articles) assessed whether QRS morphology would predict changes in LVESV from baseline following CRT.[33,50,51,92,97] In an analysis from MADIT-CRT, Goldenberg et al. (2011) reported an association between a LBBB pattern and improved rates of reduction in LVESV ≥15 percent from baseline.[33] In an analysis from SMART-AV, Cheng et al. (2012) reported a strong association between LBBB and reduction in LVESV index from baseline.[50] In another analysis from SMART-AV, Gold et al. (2011) reported no association between QRS morphology and reduction in LVESV ≥15 percent from baseline.[51] The study by Shen et al. (2009a) found no association between a QRS morphology and increased rates of response (OR: 0.53, 95% CI 0.06 to 4.89, p<0.58).[97] Another study by Shen et al. (2009b) (including only patients with native or pacing induced LBBB morphologies) reported an association between an right ventricle paced LBBB pattern and response (OR: not reported, , 95% CI, 2.00 to 111.85, p<0.008).[92]

In an analysis from MADIT-CRT, Goldenberg et al. (2011) reported an association between a LBBB pattern and improved rates of rates of reduction in LVESV ≥10 percent from baseline.[33] One study examined QRS morphology subtype as a predictor of change in quality of life. Gold et al. (2011) found that QRS morphology was not associated with change in quality of life following CRT.[51] No studies examined QRS morphology as a predictor of changes in clinical composite score or 6MHWD.

Overall, QRS morphology is intimately linked with QRS duration, and the relative contribution of each in predicting outcomes is unclear. Our analysis suggests that a native LBBB is predictive of improved survival early, one year, and three year followup after CRT-D, compared to an RBBB or NSIVCD pattern. Given the lack of data on CHF admissions alone, it's unclear whether QRS morphology is predictive of CHF admissions. The preponderance of data suggest that a LBBB morphology is a strong positive predictor of reverse ventricular remodeling (changes in LVEF, LVESVi, and LVEDVi) following CRT, compared with RBBB or NSIVCD. Due to a paucity of data, the association of paced ventricular rhythms and response is unclear (Table 50 and 51).

Chronic Kidney Disease

Three studies included chronic kidney disease (CKD) as a potential predictor of response in patients receiving a CRT-D device.[50,91,95] Leong et al. (2013) reported a direct association between improving renal function (measured via GFR) and improved all-cause mortality (HR (per 10ml/min increase in GFR): 0.83, 95% CI, 0.77 to 0.89, p<0.001).[95] Mascioli et al. (2012) reported no significant association between the presence of class IV CKD and survival free of CHF admissions.[91] Cheng et al. (2012) reported no statistically significant association between CKD and change in LVESV index.[50] Overall, there are not sufficient data to determine the predictive nature of CKD in patients receiving CRT-D devices (Table 50 and 51).

Left Atrial Volume

Four studies (reported in 5 articles) included left atrial volume (LAV) alone or indexed to body surface area (LAVi) as a potential predictor of response in patients receiving a CRT-D device.[33,34,92,93,98] In the study by Shanks et al. (2011) there was a non-statistically significant association of a greater LAVi and non-response to CRT (defined as lack of improvement in NYHA class ≥1, death from worsening CHF, heart transplant, or lack of reduction in LVESV index >15 %) (OR: 1.013, 95% CI, 1.000 to 1.026, p =0.058).[98] A study by Shen et al. (2011) did not find an association between LAVi and response (defined as a reduction in LVESV ≥15 percent from baseline and freedom from CHF admissions over the duration of followup).[93] In an analysis from MADIT-CRT, Goldenberg et al. (2011) reported an association between baseline LAV <40ml/m^2 and a higher rate of reduction in LVESV ≥15 percent from baseline.[33] Another study by Shen et al. (2009b) (in a highly selected population containing only patients with native or paced LBBB patterns) reported no association between LAV and response defined as a ≥15% reduction in LVESV from baseline (OR: not reported, , 95% CI, 0.99 to 1.02, p=NS).[92] Hsu et al. (2012), analyzing data from MADIT-CRT, reported LAVi as a predictor of a dramatic improvement in LVEF (≥14.5 percent from baseline) (OR: 1.47, 95% CI, 1.21 to 1.79, p<0.001). In another analysis from MADIT-CRT, Goldenberg et al. (2011) reported an association between a baseline LAV <40ml/m^2 and improved rates of rates of reduction in LVEDV ≥10 percent from baseline.[33]

To summarize there are insufficient data to determine the predictive nature of LAV in terms of mortality, CHF hospitalizations, quality of life, 6MHWD, or change in clinical composite score for patients undergoing CRT-D implantation. LAV at baseline does seem to be a predictor of reverse remodeling endpoints (changes in LVEF, LVESVi, and LVEDVi) in a minimally symptomatic CHF population (NYHA class I-II). There is not sufficient evidence to conclude that LAV is a predictor of reverse ventricular remodeling in patients with NYHA class III and IV CHF (Table 50 and 51).

Left Ventricular Ejection Fraction

Seven studies (reported in 8 articles) included baseline LVEF as a potential predictor of response in examining the effects of CRT-D.[50,51,90,92,94-97] Two studies evaluated LVEF as a predictor of mortality alone following CRT-D.[90,95] The study by Bilchick et al. (2010), reported an association between an increased LVEF and improved survival at both one year (HR: 0.97, 95% CI, 0.96 to 0.98, p<0.001) and three years (HR: 0.98, 95% CI, 0.98 to 0.99, p<0.001).[90] The smaller study by Leong et al. (2013) reported no association between LVEF and improved survival (HR: 0.95, 95% CI, 0.84 to 1.1, p=0.4). [95] One study assessed LVEF as a predictor of a composite endpoint including CHF admissions.[90]

The study by Bilchick et al. (2010) reported an association between a higher baseline LVEF and improved survival without CHF admissions at one year (HR: 0.97, 95% CI, 0.96 to 0.98, p<0.001) and three years (HR:0.98, 95% CI, 0.98 to 0.99, p<0.001).[90] Five studies (reported in 6 articles) assessed baseline LVEF as a predictor of changes in LVESV from baseline following CRT [50,51,92,94,96,97] The study by Niebauer and colleague was the only study to demonstrate an association between baseline LVEF and reduction in LVESV from baseline (OR 1.08 (1.03-1.14), p=<0.005).[96]

Cheng et al. (2012) reported no association between baseline LVEF and change in LVESV index from baseline in the SMART AV trial.[50] Similarly Gold et al. (2011) reported no

association between baseline LVEF and reduction in LVESV ≥15 percent from baseline also from the SMART-AV trial.[51] In the study by Shen et al. (2009a) baseline LVEF was not predictive of improved rates of response (≥15% reduction in LVESV).[97] Two studies reported that there was no association between baseline LVEF and response.[92,94] No studies assessed baseline LVEF and change in LVEDV.

One study assessed baseline LVEF and change in quality of life. In an analysis from SMART-AV, Gold et al. (2011) found that baseline LVEF was not associated with change in quality of life following CRT.[51] No studies examined baseline LVEF as a predictor of changes in clinical composite score or 6MHWD.

In summary, the current data suggest an association between increasing baseline LVEF and improved survival out to three years in patients receiving CRT-D devices. Baseline LVEF is a poor predictor of reverse ventricular remodeling and changes in QOL scores following CRT-D. There are not sufficient data, however, to determine the predictive nature of baseline LVEF in terms of CHF hospitalizations, 6MHWD, or change in clinical composite score (Table 50 and 51).

Body Mass Index

In an analysis from MADIT-CRT, Hsu et al. (2012) included body mass index (BMI) as a potential predictor of response to CRT-D.[34] This study reported a direct association between a BMI <30 kg/m^2 and a dramatic improvement in LVEF (≥14.5% from baseline) following CRT (OR: 1.51, 95% CI, 1.03 to 2.20, p<0.035). Overall, there are not sufficient data to determine the predictive nature of BMI and response to CRT-D (Table 50 and 51).

Left Ventricular End-diastolic Volume

In an analysis from MADIT-CRT, Goldenberg et al. (2011) assessed the LVEDV at baseline as a potential predictor of response to CRT-D.[33] This study reported an association between baseline LVEDV ≥125ml/m^2 and improved rates of reduction in LVESV from baseline ≥15 percent and baseline ≥10 percent. Overall, there are insufficient data to determine the predictive nature of LVEDV and response to CRT-D (Table 50 and 51).

Table 53. Summary of findings of predictors of response to CRT-D, by outcome

Outcome	Predictor (number of studies)	Key findings
Mortality	Age (3)	Data are conflicted as to the association of age with all-cause mortality in patients undergoing CRT. Heterogeneity in NYHA functional class amongst the studies may have a role in this discrepancy in that age may be a stronger predictor of time-to-death in patients with more advanced CHF symptoms
	Gender (2)	Data suggest that female gender is predictive of improved survival following CRT-D implant at 3 years. The association of female gender and survival at shorter followup times is less certain
	Cardiomyopathy Subtype (2)	NICM is predictive of improved survival at early, 1-year, and 3-year followup after CRT-D implantation
	Atrial Fibrillation (2)	Data suggest that a history of AF is predictive of increased all-cause mortality at early, 1-year, and 3-year followup after CRT-D
	QRS Duration (2)	The data are conflicted with regard to the association of QRS duration and mortality
	QRS Morphology (1)	Analysis suggests that a native LBBB is predictive of improved survival early, one year, and three year followup after CRT-D, compared to an RBBB or NSIVCD pattern
	Chronic Kidney Disease (1)	Unclear
	Left Atrial Volume (1)	Unclear
	Left Ventricular Ejection Fraction (2)	Current data suggest an association between increasing baseline LVEF and improved survival out to three years in patients receiving CRT-D devices
	Body Mass Index (0)	Unclear
	Left Ventricular End-Diastolic Volume (0)	Unclear
Heart failure hospitalizations	Age (4)	Unclear
	Gender (3)	
	Cardiomyopathy Subtype (3)	
	Atrial Fibrillation (1)	
	QRS Duration (3)	
	QRS Morphology (3)	
	Chronic Kidney Disease (1)	
	Left Atrial Volume (4)	
	Left Ventricular Ejection Fraction (1)	
	Body Mass Index (0)	
	Left Ventricular End-Diastolic Volume (0)	
LVEF	Age (0)	Unclear
	Gender (1)	Data suggest that female gender is a strong positive predictor of reverse ventricular remodeling endpoint
	Cardiomyopathy Subtype (1)	Data suggest that NICM is a strong positive predictor of reverse ventricular remodeling endpoint
	Atrial Fibrillation (1)	Unclear

Outcome	Predictor (number of studies)	Key findings
	QRS Duration (1)	Data suggest that QRS duration is directly associated with improved rates of reverse ventricular remodeling
	QRS Morphology (1)	Data suggest that a LBBB morphology is a strong positive predictor of reverse ventricular remodeling
	Chronic Kidney Disease (0)	Unclear
	Left Atrial Volume (1)	Data suggest that left atrial volume is a predictor in minimally symptomatic CHF population (NYHA class I-II)
	Left Ventricular Ejection Fraction (1)	Baseline LVEF is a poor predictor of reverse ventricular remodeling
	Body Mass Index (1)	Unclear
	Left Ventricular End-Diastolic Volume (0)	Unclear
LVESV	Age (5)	The preponderance of data suggests that age is not an important predictor of changes in LVESV
	Gender (6 studies reported in 7 articles)	The preponderance of data suggest that female gender is a strong positive predictor of reverse ventricular remodeling endpoints
	Cardiomyopathy subtype (5 studies in 5 articles)	The preponderance of data suggest that NICM is a strong positive predictor of reverse ventricular remodeling endpoints
	Atrial Fibrillation (1)	Unclear
	QRS Duration (6 studies reported in 7 articles)	The preponderance of data suggest that QRS duration is directly associated with improved rates of reverse ventricular remodeling
	QRS Morphology (4 studies reported in 5 articles)	The preponderance of data suggest that a LBBB morphology is a strong positive predictor of reverse ventricular remodeling
	Chronic Kidney Disease (1)	Unclear
	Left Atrial Volume (3)	Data suggest that left atrial volume is a predictor in minimally symptomatic CHF population (NYHA class I-II)
	Left Ventricular Ejection Fraction (5 studies reported in 6 articles)	The data are conflicted as to the association between baseline LVEF and reverse ventricular remodeling
	Body Mass Index (0)	Unclear
	Left Ventricular End-Diastolic Volume (1)	Unclear
LVEDV	Age (0)	Unclear
	Gender (1)	The preponderance of data suggest that female gender is a strong positive predictor of reverse ventricular remodeling endpoint
	Cardiomyopathy Subtype (1)	The preponderance of data suggest that NICM is a strong positive predictor of reverse ventricular remodeling endpoint
	Atrial Fibrillation (0)	Unclear
	QRS Duration (1)	The preponderance of data suggest that QRS duration is directly associated with improved rates of reverse ventricular remodeling
	QRS Morphology (0)	Unclear
	Chronic Kidney Disease (0)	Unclear
	Left Atrial Volume (1)	Seem to be a predictor in minimally symptomatic CHF population (NYHA class I-II)
	Left Ventricular Ejection Fraction (0)	Unclear

Outcome	Predictor (number of studies)	Key findings
	Body Mass Index (0)	Unclear
	Left Ventricular End-Diastolic Volume (0)	Unclear
Minnesota Living with Heart failure Questionnaire	Age (1)	Data suggest that age is not an important predictor of changes in QOL
	Gender (1)	Female gender may be predictive of improved MLHFQ scores but we need more data to confirm this finding
	Cardiomyopathy Subtype (1)	Cardiomyopathy subtype is not predictive of improved QOL scores, although we need more data to confirm this finding
	Atrial Fibrillation (0)	Unclear
	QRS Duration (1)	Unclear
	QRS Morphology (1)	QRS morphology was not associated with change in QOL
	Chronic Kidney Disease (0)	Unclear
	Left Atrial Volume (1)	Unclear
	Left Ventricular Ejection Fraction (1)	Baseline LVEF is a poor predictor of changes in QOL scores
	Body Mass Index (0)	Unclear
	Left Ventricular End-Diastolic Volume (0)	Unclear
Clinical composite score	Age (0)	Unclear
	Gender (0)	
	Cardiomyopathy Subtype (0)	
	Atrial Fibrillation (0)	
	QRS Duration (0)	
	QRS Morphology (0)	
	Chronic Kidney Disease (0)	
	Left Atrial Volume (0)	
	Left Ventricular Ejection Fraction (0)	
	Body Mass Index (0)	
	Left Ventricular End-Diastolic Volume (0)	
SF-36	Age (0)	Unclear
	Gender (0)	
	Cardiomyopathy Subtype (0)	
	Atrial Fibrillation (0)	
	QRS Duration (0)	
	QRS Morphology (0)	
	Chronic Kidney Disease (0)	
	Left Atrial Volume (0)	

Outcome	Predictor (number of studies)	Key findings
	Left Ventricular Ejection Fraction (0)	
	Body Mass Index (0)	
	Left Ventricular End-Diastolic Volume (0)	
6MHWD	Age (0)	Unclear
	Gender (0)	
	Cardiomyopathy Subtype (0)	
	Atrial Fibrillation (0)	
	QRS Duration (0)	
	QRS Morphology (0)	
	Chronic Kidney Disease (0)	
	Left Atrial Volume (0)	
	Left Ventricular Ejection Fraction (0)	
	Body Mass Index (0)	
	Left Ventricular End-Diastolic Volume (0)	

LVESV-Left Ventricular End Systolic Volume, LVEDV- Left Ventricular End Diastolic Volume, LVEF-Left Ventricular Ejection Fraction, QOL-Quality of Life, 6MHWD-6 Minute Hall Walk Distance

Predictors of Response to Cardiac Resynchronization Therapy with Pacemaker (CRT-P)

Study Characteristics

Two studies evaluated predictors of response in patients undergoing CRT-P implantation (Table 54).[100,101] Both studies were multiple-center cohort studies and included a mixed CRT-D and CRT-P population. The studies used a multivariate model that controlled the presence of a concomitant defibrillator (CRT-D implanted) with CRT-P as the reference group. One of the studies reported the specific names of the devices implanted (Boston Scientific TR/TR2, Contak CD or Renewal I/II, and Medtronic Insync I/III).[100] None of these studies reported the source of funding (Evidence Table 1).

Population Characteristics

The percentage of women in the included studies ranged from 23 to 24 percent. The mean age of participants ranged from 65 to 69.3 years old. No studies reported the race of participants. Only one study reported incidence of AF.[100] In this study, 22 percent of the participants had a history of AF. Only one study reported the mean QRS duration (148.5ms).[101] None of the studies reported the incidences of any type of QRS morphology. Both studies included data on NYHA class. The study by Stabile et al. (2009) included patients with NYHA II, III, and IV CHF, of whom class III represented 69 percent.[100] The study by Zhang et al. (2009) included patients with NYHA class III-IV CHF, of whom 87 percent were NYHA class III.[101] Both studies reported baseline LVEF, which ranged from 24.5 percent in the study by Zhang et al. (2009)[101] to 28.2 percent in the CRT-P arm in the study by Stabile et al. (2009)[100] Neither study reported data on renal function. Both studies were homogenous in terms of baseline patient population (Table 54).

Table 54. Study characteristics of studies assessing predictor of response to CRT-P

Author, year	CRT-P (%)	Funder	Total number of patients	Age (mean, years)	Female gender (%)	NYHA class	Race	Ischemic cardiomyopathy (%)
Stabile, 2009[100]	50.2%	NR	233	68.8	23	III-IV	NR	49
Zhang, 2009[101]	49%	NR	Survivors: 175	65	25	III-IV	NR	50
			Non-survivors:64	68	19	III-IV	NR	67

NR = not reported

Risk of Bias

As for the predictor studies of CRT-P, the findings here must be qualified by the high likelihood of reporting bias. One study was assessed as high risk of bias for poor description of study participation, as assessed with QUIPS.[100] Overall, the risk of bias was high (Table 55).

Table 55. Summary of risk of bias for studies assessing predictor of response to CRT-P

Author, year	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall quality
Stabile, 2009[100]	++	-	+	-	-	+	++
Zhang,2009[101]	+	-	-	-	-	-	+

-=Low
+=Moderate
++=High

Table 56. Included predictors of response for CRT-P

Author, year	Age	Gender	CM type	AF	QRSd	QRS morphology	CKD	LA volume	LVEF	BMI	LVEDV
Stabile, 2009[100]	X	X	X	X	X						
Zhang, 2009[101]	X	X	X		X				X		

X= controlled for and effect size reported
Y=controlled for but effect size not reported
CM=cardiomyopathy; AF=atrial fibrillation; QRSd=QRS duration; CKD=chronic kidney disease; LA=left atrial; LVEF=left ventricular ejection fraction BMI=body mass index; LVESV=left ventricular end systolic volume

Table 57. Definitions of response for CRT-P predictors

Author, year	All-cause mortality	Cardiovascular mortality	Combined endpoint	HF hospitalizations	LVEF	LVESV continuous	LVESV ≥10%	LVEDV continuous	LVEDV ≥10%	Quality of life score (MLHFQ)	6 Minute Hall Walk Distance	Clinical Composite Score
Stabile, 2009[100]	X											
Zhang, 2009[101]		X										

LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; LVESVi: left ventricular end-systolic volume index; LVEDV left ventricular end diastolic volume; HF: heart failure; NYHA: New York Heart Association; MLHFQ: Minnesota Living with Heart failure Questionnaire

Clinical Predictors

Table 58. Evidence addressing predictors of response to CRT-P

Predictor	Outcome (number of studies)	Author, year	Model	Key findings
Age	Mortality (2)	Stabile,2009[100] Zhang,2009[101]	Multivariate Cox regression	Age is not a predictor of mortality in patients receiving a CRT-P device although more data are needed
	Heart failure hospitalizations (0)	NA	NA	Unclear
	LVEF (0)			
	LVESV (0)			
	LVEDV (0)			
	MLHFQ (0)			
	Clinical Composite Score (0)			
	SF-36 (0)			
	6MHWD (0)			
Gender	Mortality (2)	Stabile,2009[100] Zhang,2009[101]	Multivariate Cox regression	Overall, the predictive nature of gender on mortality is conflicted amongst patients receiving a CRT-P device although the data are significantly limited
	Heart failure hospitalizations (0)	NA	NA	Unclear
	LVEF (0)			
	LVESV (0)			
	LVEDV (0)			
	MLHFQ (0)			
	Clinical Composite Score (0)			
	SF-36 (0)			
	6MHWD (0)			
Cardiomyopathy subtype	Mortality (2)	Stabile,2009[100] Zhang,2009[101]	Multivariate Cox regression	The predictive nature of cardiomyopathy subtype on mortality is conflicted amongst patients receiving a CRT-P device although the data are significantly limited
	Heart failure hospitalizations (0)	NA	NA	Unclear
	LVEF (0)			
	LVESV (0)			
	LVEDV (0)			
	MLHFQ (0)			
	Clinical Composite Score (0)			
	SF-36 (0)			
	6MHWD (0)			
Atrial fibrillation	Mortality (1)	Stabile,2009[100]	Multivariate Cox regression	Unclear

Predictor	Outcome (number of studies)	Author, year	Model	Key findings
	Heart failure hospitalizations (0)	NA	NA	
	LVEF (0)			
	LVESV (0)			
	LVEDV (0)			
	MLHFQ (0)			
	Clinical Composite Score (0)			
	SF-36 (0)			
	6MHWD (0)			
QRS duration	Mortality (2)	Stabile,2009[100] Zhang,2009[101]	Multivariate Cox regression	QRS duration is not a predictor of mortality in patients receiving a CRT-P device.
	Heart failure hospitalizations (0)	NA	NA	Unclear
	LVEF (0)			
	LVESV (0)			
	LVEDV (0)			
	MLHFQ (0)			
	Clinical Composite Score (0)			
	SF-36 (0)			
	6MHWD (0)			
QRS morphology	Mortality (0)	NA	NA	Unclear
	Heart failure hospitalizations (0)			
	LVEF (0)			
	LVESV (0)			
	LVEDV (0)			
	MLHFQ (0)			
	Clinical Composite Score (0)			
	SF-36 (0)			
	6MHWD (0)			
Chronic kidney disease	Mortality (0)	NA	NA	Unclear
	Heart failure hospitalizations (0)			
	LVEF (0)			
	LVESV (0)			
	LVEDV (0)			
	MLHFQ (0)			
	Clinical Composite Score (0)			
	SF-36 (0)			
	6MHWD (0)			
Left atrial volume	Mortality (0)	NA	NA	Unclear
	Heart failure hospitalizations (0)			
	LVEF (0)			
	LVESV (0)			
	LVEDV (0)			
	MLHFQ (0)			
	Clinical Composite Score (0)			
	SF-36 (0)			
	6MHWD (0)			

Predictor	Outcome (number of studies)	Author, year	Model	Key findings
Left ventricular ejection fraction	Mortality (2)	Stabile,2009[100] Zhang,2009[101]	Multivariate Cox regression	LVEF was not predictive of outcomes in patients receiving a CRT-P device although the data are substantially limited
	Heart failure hospitalizations (0)	NA	NA	Unclear
	LVEF (0)			
	LVESV (0)			
	LVEDV (0)			
	MLHFQ (0)			
	Clinical Composite Score (0)			
	SF-36 (0)			
	6MHWD (0)			
Body mass index	Mortality (0)	NA	NA	Unclear
	Heart failure hospitalizations (0)			
	LVEF (0)			
	LVESV (0)			
	LVEDV (0)			
	MLHFQ (0)			
	Clinical Composite Score (0)			
	SF-36 (0)			
	6MHWD (0)			
Left ventricular end-diastolic volume	Mortality (0)	NA	NA	Unclear
	Heart failure hospitalizations (0)			
	LVEF (0)			
	LVESV (0)			
	LVEDV (0)			
	MLHFQ (0)			
	Clinical Composite Score (0)			
	SF-36 (0)			
	6MHWD (0)			

LVESV-Left Ventricular End Systolic Volume, LVEDV- Left Ventricular End Diastolic Volume, LVEF-Left Ventricular Ejection Fraction, QOL-Quality of Life, 6MHWD-6 Minute Hall Walk Distance, MLHFQ - Minnesota Living with Heart Failure Questionnaire , NA-Not applicable

Age

In the study by Stabile et al. (2009), over a mean followup of 58 months, age was not predictive of all-cause mortality.[100] In the study by Zhang et al. (2009), over a mean followup of 37 months, age was not a predictor of cardiovascular mortality.[101] No studies examined age as a predictor of LVEF, CHF hospitalizations, 6MHWD, or QOL. Taken together age is not a predictor of mortality in patients receiving a CRT-P device although more data are needed (Table 56 and 57).

Gender

In the study by Stabile et al. (2009), over a mean followup of 58 months, male gender was predictive of worsened survival (HR: 3.62, 95% CI, 1.88 to 6.99, p=0.006).[100] In the study by Zhang et al. (2009), over a mean followup of 37 months, gender was not a predictor of cardiovascular mortality (HR: 0.679, 95% CI, 0.329 to 1.399, p=0.294).[101] No studies examined gender as a predictor of LVEF, CHF hospitalizations, 6MHWD, or QOL. Overall, the predictive nature of gender on mortality is conflicted amongst patients receiving a CRT-P device although the data are significantly limited (Table 56 and 57).

Cardiomyopathy Subtype

In the study by Stabile et al. (2009), over a mean followup of 58 months, cardiomyopathy subtype was not predictive of worsened survival (for ICM HR: 1.08, 95% CI, 0.63 to 1.85, p=0.405).[100] In the study by Zhang et al. (2009), over a mean followup of 37 months, ICM was a predictor of cardiovascular mortality (HR: 2.696, 95% CI, 1.487 to 4.889, p=0.001).[101] No studies examined cardiomyopathy subtype as a predictor of LVEF, CHF hospitalizations, 6MHWD, or QOL. Taken together, the predictive nature of cardiomyopathy subtype on mortality is conflicted amongst patients receiving a CRT-P device although the data are significantly limited (Table 56 and 57).

Atrial Fibrillation

One study reported history of AF as a predictor of survival in patients receiving a CRT-P device.[100] This study reported a mean followup of 58 months; a history of AF was predictive of worsened survival (HR: 1.96, 95% CI, 1.01 to 3.94, p=0.038). No studies examined AF as a predictor of LVEF, CHF hospitalizations, 6MHWD, or QOL. Therefore, there is insufficient evidence to determine the predictive nature of AF on outcomes following CRT-P (Table 56 and 57).

QRS Duration

Both studies assessed QRS duration as a predictor of survival in patients receiving a CRT-P device.[100,101] In the study by Stabile et al. (2009), over a mean followup of 58 months, QRS duration ≥160ms was not predictive of worsened survival.[100] In the study by Zhang et al. (2009), over a mean followup of 37 months, QRS duration was not a predictor of cardiovascular mortality.[101] No studies examined QRS duration as a predictor of LVEF, CHF hospitalizations, 6MHWD, or QOL. Taken together QRS was not predictive of outcomes in patients receiving a CRT-P device although the data are substantially limited (Table 56 and 57).

QRS Morphology

No studies included QRS morphology as a predictor of any outcome in patients receiving CRT-P (Table 56 and 57).

Chronic Kidney Disease

No studies included CKD as a predictor of any outcome in patients receiving CRT-P (Table 56 and 57).

Left Atrial Volume

No studies included LAV as a predictor of any outcome in patients receiving CRT-P (Table 56 and 57).

Left Ventricular Ejection Fraction

Two studies examined baseline LVEF as a predictor of survival in patients receiving a CRT-P device.[100,101] In the study by Stabile et al. (2009), over a mean followup of 58 months, baseline LVEF was not predictive of worsened survival.[100] In the study by Zhang et al. (2009), over a mean followup of 37 months, baseline LVEF was not a predictor of cardiovascular mortality.[101] No studies examined baseline as a predictor of LVEF response, CHF hospitalizations, 6MHWD, or QOL. Taken together LVEF was not predictive of outcomes in patients receiving a CRT-P device although the data are substantially limited (Table 56 and 57).

Body Mass Index

No studies of CRT-P included BMI as a potential predictor of response (Table 56 and 57).

Left Ventricular End-Diastolic Volume

No studies of CRT-P included LVEDV as a potential predictor of response (Table 56 and 57).

Table 59. Summary of findings of predictors of response to CRT-P, by outcomes

Outcome	Predictor (number of studies)	Key findings
Mortality	Age (2)	Age is not a predictor of mortality in patients receiving a CRT-P device although more data are needed
	Gender (2)	Overall, the predictive nature of gender on mortality is conflicted amongst patients receiving a CRT-P device although the data are significantly limited
	Cardiomyopathy subtype (2)	The predictive nature of cardiomyopathy subtype on mortality is conflicted amongst patients receiving a CRT-P device although the data are significantly limited
	Atrial fibrillation (1)	Unclear
	QRS duration (2)	QRS duration was not a significant predictor of mortality
	QRS morphology (0)	Analysis suggests that a native LBBB is predictive of improved survival early, one year, and three year followup after CRT-D, compared to an RBBB or NSIVCD pattern
	Chronic kidney disease (0)	Unclear
	Left atrial volume (0)	Unclear
	Left ventricular ejection fraction (2)	LVEF was not predictive of outcomes in patients receiving a CRT-P device although the data are substantially limited
	Body mass index (0)	Unclear
	Left ventricular end-diastolic volume (0)	Unclear
Heart failure hospitalizations, LVEF, LVESV, LVEDV, MLHFQ, Clinical composite score, SF-36, 6MHWD	Age (0)	Unclear
	Gender (0)	
	Cardiomyopathy subtype (0)	
	Atrial fibrillation (0)	
	QRS duration (0)	
	QRS morphology (0)	
	Chronic kidney disease (0)	
	Left atrial volume (0)	
	Left ventricular ejection fraction (0)	
	Body mass index (0)	
	Left ventricular end-diastolic volume (0)	
	Left atrial volume (0)	
	Left ventricular ejection fraction (0)	
	Body mass index (0)	
	Left ventricular end-diastolic volume (0)	

LVESV-Left Ventricular End Systolic Volume, LVEDV- Left Ventricular End Diastolic Volume, LVEF-Left Ventricular Ejection Fraction, MLHFQ-Minnesota Living with Heart Failure Questionnaire, 6MHWD-6 Minute Hall Walk Distance

Discussion

Key Findings and the Strength of Evidence

Efficacy and Safety of CRT-D (KQ1a, KQ2)

There is convincing evidence that CRT-D devices are effective in reducing heart failure symptoms, improving myocardial function, and reducing hospitalizations for heart failure in patients with an LVEF≤35% and a QRS duration ≥120 ms compared to therapy with an ICD alone. Specifically, we found moderate strength of evidence for benefit of CRT-D versus ICD alone for all-cause mortality in minimally symptomatic patients. This statement is derived from data looking primarily at NYHA class II patients. The applicability of this finding to NYHA class I patients, a population significantly under-represented in studies, is unclear. There is insufficient evidence to determine whether CRT-D devices are effective in improving survival compared to an ICD alone in an advanced heart failure population (NYHA III-IV).(Table 60)

In terms of pre-specified subgroups, there is compelling evidence that in CRT-D patients (compared to an ICD alone), female gender, a left bundle branch block, and non-ischemic cardiomyopathy are associated with superior outcomes. Sinus rhythm (as opposed to a history of atrial fibrillation) and a wider QRS complex and also associated with superior outcomes in patients undergoing CRT-D implant compared to an ICD alone although the data for this are less compelling.

Prevalence of harms associated with CRT-D devices were as follows: cardiac perforation/tamponade (0.1-1.4%), pocket hematoma (0.9-2.8%), pneumothorax (1.3-2.8%), device infection (0.9-2.8%), and lead dislodgement (2.4% to 9.8%). No conclusions could be drawn about the association between CRT-D implant and both ventricular arrhythmias and inappropriate shocks. Death within one week of implantation was 0 percent although only two studies reported this outcome.

Efficacy and Safety of CRT-P (KQ3a, KQ4)

There is moderate evidence that CRT-P, compared to optimal medical therapy, is effective in improving survival, reducing LESV, and reducing hospitalizations for heart failure in patients with an LVEF≤35% and a QRS duration ≥120 ms compared to optimal medical therapy alone**.** These data are largely derived from patients with NYHA class III-IV heart failure. The applicability of these findings to patient with NYHA class I-II heart failure is unclear. We found insufficient evidence about the effect of CRT-P on quality of life as measured with the MLHFQ.

Harms associated with CRT-P were as follows: cardiac perforation/tamponade (0-1.6%), pocket hematoma (0.2-9.5%), pneumothorax (0.5-1.5%), device infection (0.7-4.8%), and lead dislodgement (1.7-17%). Death within one week of implantation was reported in only very small studies making the true incidence unclear.

Efficacy and Safety of CRT-D versus CRT-P (KQ5, KQ6)

Only one included trial contained both CRT-D and CRT-P arms, and direct comparisons between those arms were lacking. Therefore there is insufficient evidence to determine the effectiveness of CRT-D compared to CRT-P. In comparing harms between CRT-D and CRT-P devices, there was also insufficient evidence to draw any conclusions except for device infections, which appear to be slightly more common for CRT-D devices.

Predictors of Response: CRT-D and CRT-P (KQ1b, KQ3b)

The evidence regarding predictors of a favorable response following CRT varied considerably based on outcome. In addition, the high likelihood of reporting bias qualifies these results. Age was not an important predictor of outcomes in patients receiving CRT-D devices. However, data for very elderly patients (> 75 years of age) was limited. Non-ischemic cardiomyopathy, female gender, and a left bundle branch block morphology were strongly associated with improved outcomes. A history of atrial fibrillation and a narrower QRS duration were associated with poorer outcomes although the evidence for this was less robust. There was insufficient data to determine the predictive nature of chronic kidney disease, left atrial volume, baseline LVEF, body mass index, and left ventricular end-diastolic volume on outcomes following CRT-D implant. There was also insufficient evidence to draw conclusions as to the predictive nature of baseline characteristics and outcomes in patients receiving a CRT-P device. However, of the outcomes that were assessed, the ICD function would impact only the mortality endpoint. Therefore similar conclusions as to those noted for CRT-D can likely be drawn for CRT-P devices for the other, non-mortality endpoints (Table 60).

Table 60. Summary of the strength of evidence for key effectiveness outcomes

Comparisons	All-cause mortality	Hospitalizations for heart failure	Left ventricular end systolic volume (or index)	Minnesota Living with Heart Failure Questionnaire
Cardiac resynchronization therapy with defibrillator (CRT-D) vs. ICD alone	Moderate In patients with minimally symptomatic CHF (primarily class NYHA class II), data from the RAFT trial (a larger, slightly more symptomatic population, with a longer followup) demonstrates a mortality benefit, The MADIT-CRT trial did not report a mortality benefit with CRT-D in primarily NYHA class II patients. Long-term followup of a subset of patients demonstrated a mortality benefit in patients with LBBB but not with a non-LBBB and did not report a mortality comparison for the group as a whole. The other trials assessing mortality in minimally symptomatic patients were either too small in size or followup to add significant additional evidence. The trials assessing mortality in patients with NYHA class III-IV symptoms were limited in terms of followup and size, therefore there is insufficient evidence to determine the effect of CRT-D on mortality compared to an ICD alone.	High The large RAFT and MADIT-CRT trials showed a reduction in CHF events for CRT-D compared to an ICD alone. Subgroup analyses from both trials demonstrate the effect to be primarily in patients with an LBBB morphology	High The trials were consistent in demonstrating a reduction in LVESV with CRT-D compared to an ICD alone. Meta-analysis of trials in patients with NYHA I-II (primarily NYHA class II patients), mean difference -22.55 (95% CI, -40.66 to -9.56).	High The current data suggest that CRT-D does not improve QOL in minimally symptomatic patients compared to an ICD alone. The data does suggest a significant improvement in QOL in patients with NYHA class III-IV CHF (mean difference -10.91 (95% CI -12.03 to 7.27).
Cardiac resynchronization therapy with pacemaker vs. optimal medical therapy	Moderate Studies showed statistically significant differences in mortality favoring CRT-P	Moderate Studies showed fewer hospitalizations in the CRT-P group	Low CRT-P significantly reduced LESV compared with optimal medical therapy.	Insufficient
cardiac resynchronization therapy with pacemaker or with defibrillator	Insufficient	Low Compared with optimal medical therapy, CRT-P and CRT-D were associated with 44% and 41% reduction in heart failure hospitalizations (not significantly different).	Insufficient	Insufficient

Relationship of Findings to Existing Literature

Several systematic reviews have focused on CRT but none has performed a comprehensive assessment of predictors of outcomes following CRT (see Table 61). Our current review also differs from prior reviews in that only studies with patients with an LVEF≤35% and a baseline QRS duration≥120 ms undergoing biventricular pacing were included. These criteria were developed in consultation with our key informants and largely mirror the current appropriate use criteria for CRT based on guidelines.[1] This eliminated the REVERSE, BLOCK-HF, and HOBIPACE trials which included patients with LVEFs >35%.[102-104] In addition, all trials looking at the effects of CRT in a narrow QRS population,[105-107] and studies of LV only pacing were excluded.[108,109] We considered the appropriate control for the CRT-D effectiveness question to be an ICD alone given the compelling data demonstrating improvements in mortality with an ICD that evolved concomitantly with studies of CRT effectiveness. We considered the appropriate control and for CRT-P to be optimal medical therapy alone to assess the impact of cardiac resynchronization. We did not assess the comparison of CRT-D to optimal medical therapy as we determined this to be an inappropriate comparison, given the known improvements in mortality by defibrillation. Also, in contrast to several previous reviews, we included only RCTs to assess the key questions regarding effectiveness.

In terms of minimally symptomatic patients, the results of our review largely agree with those of prior reviews, which focused on the same population. Similarly, the current review is in agreement with the systematic review performed in 2007 by Mcallister et al., which included studies primarily involving an advanced heart failure population.[110] Our review arrived at somewhat different conclusions in terms of the efficacy of CRT-D vs. CRT-P compared to that by Jiang et al.[111] Given that we considered only RCTs for determination of effectiveness, only the COMPANION trial was included in our review, which likely explains the discrepancy in conclusions.[4]

In our systematic analysis of predictors of outcomes following CRT, many studies assessing the capacity for baseline characteristics to predict responses (defined in many different ways) were identified. The large majority of studies were small (<100 patients) and not properly controlled. At a minimum, we pre-specified that a cohort study address our questions about predictors of response to CRT had to include at least gender and either QRS duration or morphology in a multivariate model to address confounding. Such criteria eliminated many studies. Despite this, the positive predictive effect noted with LBBB, female gender, non-ischemic cardiomyopathy, a wider QRS duration, and normal sinus rhythm on multiple outcomes was supportive of the similar findings noted from the pre-specified subgroup analyses of the RCTs. There are other potential predictors we did not consider (e.g. lead position). Given the large number of potential predictors in the literature, a review of all predictors was not practical. Our predictors were chosen based on prevailing knowledge of the most important predictors, identified in consultation with our key informants.

Finally, we did not conduct individual patient data meta-analysis to assess predictors meaning that our analyses may suggest that clinically relevant subgroup effects exist, but we are unable to quantify the effects reliably or precisely.

Table 61. Prior Systematic Reviews of Cardiac Resynchronization Therapy

Author, year	Review scope	Number of studies	Findings	Key differences compared to current systematic review
Adabag, 2011[112]	Effectiveness of CRT in patients with minimally symptomatic heart failure	5	Cardiac resynchronization therapy decreases all-cause mortality, reduces HF hospitalizations, and improves LVEF in NYHA functional class I/II HF patients.	Focused on minimally symptomatic patients (NYHA I-II). Included LVEF≤40%.
Bryant, 2013[113]	CRT and QRS duration	44	The benefit of CRT appears restricted to those with a baseline QRS duration > 150ms	Focused on the effect of QRS duration and response to CRT. Included studies with QRS duration <120ms. Included studies enrolling patients with LVEF>35%
Ganesan, 2012[114]	AV node ablation and CRT	6	AV nodal ablation was associated with a reduction in mortality and improvements in NYHA functional class compared with medical therapy.	Focused exclusively on patients with AF.
Garg, 2013[115]	CRT and chronic kidney disease	18	CRT improves left ventricular and renal function in patients with CKD heart failure	Restricted to assessing the effect of CRT on kidney function. Did not restrict studies to an LVEF≤35% and QRS duration ≥120ms.
Hess,2013[116]	CRT and AF	12	The combined rate of conversion from persistent or permanent AF to sinus rhythm was 0.107 amongst CRT patients.	Focused on studies reporting the effect of CRT on AF Note: Only 1 reviewer assessed studies
Jiang, 2012[111]	Comparison of CRT-D vs CRT-P	7	There is evidence of some superiority of CRT-D over CRT-P, combining randomized and non-randomized trials.	Included observational studies as well as RCTs in effectiveness analysis of CRT-D vs. CRT-P.
Lubitz,2010[117]	Effectiveness of CRT in patients with minimally symptomatic heart failure	2	CRT reduces heart failure events in patients with mild heart failure symptoms, left ventricular dysfunction, sinus rhythm, and a prolonged QRS duration.	Enrolled only NYHA Class I and II patients.
McAlister, 2004[118]	Effectiveness and harms of CRT in patients with NYHA class III and IV.	27	CRT improves functional and hemodynamic status, reduces heart failure hospitalizations, and reduces all-cause mortality.	Older systematic review which thus did not include several large RCTs published subsequently (contained only patients with NYHA class III-IV symptoms)

Author, year	Review scope	Number of studies	Findings	Key differences compared to current systematic review
				Included trials of LV only pacing. Did not examine remodeling outcomes (changes in LVEF, LVESV, or LVEDV)
McAlister,2007[110]	Effectiveness and harms of CRT	195	CRT reduces morbidity and mortality in patients with LV systolic dysfunction, prolonged QRS duration, and NYHA class III or IV when combined with optimal medical therapy.	Older systematic review which thus did not include several large RCTs published subsequently Included trials of LV only pacing. Did not look at changes in LVESV or LVEDV
Nery, 2011[119]	Effect of CRT in patients with RBBB	5	There is no benefit of patients with RBBB although more data are needed.	Looked at RBBB population specifically.
Proietti, 2014[120]	CRT and cognitive improvement	3	There were not enough data to assess CRT effect on cognitive function.	Focused on the effect of CRT on cognitive function. Did not restrict studies to an LVEF≤35% and QRS duration ≥120ms.
Santangeli, 2011[121]	Effectiveness of CRT in patients with minimally symptomatic heart failure	5	Among patients with mild (NYHA II) heart failure, CRT reduces mortality and the risk of heart failure events, induces LV reverse remodeling and slows the progression of heart failure symptoms.	Focused on minimally symptomatic patients (NYHA I-II). Included LVEF≤40%.
Tu R, 2011[122]	Effectiveness of CRT in patients with minimally symptomatic heart failure	8	CRT improves outcomes in patients with mild heart failure and ventricular dyssynchrony. The improvements are accompanied by more adverse events.	Focused on minimally symptomatic patients (NYHA I-II). Included LVEF≤40%.
Van Rees, 2011[123]	Complications of CRT-D vs. an ICD alone	18	Lead dislodgement was higher for CRT-D vs. an ICD alone. Incidence of pneumothorax were similar between ICD vs. CRT.	Included randomized controlled trials only. Excluded crossover trials. Included trials with QRS<120 ms Included non-CRT trials. Focused exclusively on complications.
Wilton, 2011[124]	Effect of CRT in patients with AF	23	The benefits of CRT appear to be attenuated in patients with AF.	Focused exclusively on atrial fibrillation population.

Applicability

The generalizability of these results is slightly limited. Race was reported very infrequently, prohibiting an assessment of applicability based on racial differences. The majority of patients included in the RCTs were male, although a large focus in sub-studies has been given to the role of CRT in women, given the heightened response to therapy seen in this population. The average age in the RCTs and cohort studies was in the mid 60s although many patients included were in the age range of the elderly Medicare population. There has not been an RCT that specifically enrolled Medicare eligible patients. Also, data for very elderly patients (> 75 years of age) are limited. In cohort studies and subgroup analyses from the RCTs, age was not found to be an important predictor of outcomes. Taken together, the results of our review are fairly generalizable to the Medicare population although given the absence of dedicated RCTs, a definitive statement of generalizability to this population is not possible.

Limitations of the Comparative Effectiveness Review Process

In addressing the questions of efficacy of CRT-D and CRT-P (KQs 1A, 3A, and 5), several studies potentially of interest were excluded since they were non-randomized. For the questions about the predictors of response to CRT (KQs 1b and 3b), many retrospective cohort studies were excluded because of a mixed population of patients who received CRT-D or CRT-P devices. We attempted to contact the authors of such studies to obtain the device-specific data. We contacted the authors of 24 studies, of which we received responses from 2 authors with sufficient information to include in our review. In addition, many cohorts, which contained outcomes of interest were excluded due to failure to control for gender and QRS duration and/or morphology, important baseline confounders. Finally, we did not include prior or conduct new individual patient data meta-analyses to assess predictors. Therefore, our analyses may suggest that clinically relevant subgroup effects exist, but we are unable to quantify the effects reliably or precisely.

Limitations of the Evidence Base

Multiple well-conducted RCTs were identified addressing the questions about the efficacy or CRT-D and CRT-P (KQs 1a and 3a). The majority of patients enrolled in the clinical trials had NYHA class II-IV heart failure symptoms. The applicability of the current findings to class I patients is less clear. In contrast, for the comparison of CRT-D with CRT-P (KQ 5), only the COMPANION trial was found to include both CRT-D and CRT-P arms.[4] However, a direct comparison of the CRT-D to CRT-P arms was not reported for several outcomes. For the questions examining predictors of response to CRT (KQs 1b and 3b), many of the included cohort studies were relatively small. While all studies controlled for gender and either QRS duration or morphology based on our pre-specified inclusion criteria, the remaining variables in the model varied widely between studies. Similarly, many studies used statistical criteria to create their multivariate adjustments, not including important *a priori* clinical factors.

Research Gaps

There is convincing evidence that CRT-D results in reverse ventricular remodeling and improvements in quality of life compared to an ICD alone. However, only two trials showed a mortality benefit of CRT-D over ICD alone. One trial primarily contained patients with minimally symptomatic heart failure. A second study found a mortality advantage in minimally symptomatic patients with LBBB but not non-LBBB morphologies. This study did not report the mortality data in the non-subdivided population and had an issue with significant patient loss to follow up. Whether CRT-D results in improved survival compared to an ICD alone in patients with advanced heart failure is unclear.

Several subgroup analyses from the RCTs as well as cohort studies demonstrate superior outcomes in patients with a native LBBB compared to a non-LBBB. Subgroup analysis from the MADIT-CRT trial suggested possible harm for CRT-D versus an ICD alone in non-LBBB patients.[6,41] Subgroup analyses from other RCTs suggested little benefit of CRT in non-LBBB patients (but no convincing trend towards harm).[7] One important issue with the assessment of CRT efficacy according to QRS morphology is the interaction between QRS duration, another variable with impact on outcome, and morphology. Patients with a LBBB tend to have wider QRS durations than patients with non-LBBBs. Several retrospective studies have attempted to determine the relative impact on outcomes of QRS duration within various QRS morphology groups in patients receiving a CRT device with mixed results.[125,126] There has not been an RCT which compares CRT to a control in patients with a non-LBBB morphology. Given the lack of such a trial, the ability to conclude definitively that CRT is ineffective or, in fact harmful, in patients with non-LBBB morphology is limited.

Similarly, subgroup analyses from RCTs suggest limited benefit of CRT in patients with atrial fibrillation. Outside the small MUSTIC-AF study, CRT trial data focused on the AF population are lacking.[45] Therefore, the ability to definitively conclude a lack of benefit in patients with AF receiving CRT is not possible.

The effectiveness of CRT-D versus CRT-P in patients with an LVEF≤35% has not been adequately addressed. The COMPANION trial which included both arms, did not directly compare the CRT types and is therefore inadequate to answer this question definitively.[4]

In Tables 62 to 64, we use the PICOS (Population, Intervention, Comparison, Outcomes, and Study design) framework to outline characteristics of an ideal study.

Table 62: Characteristics of an ideal study to compare the effectiveness of CRT-D vs. CRT-P

PICOS	Characteristics

Population	• Patients with an LVEF≤35% despite optimal medical therapy
	• Patients with a QRS duration ≥120%
	• NYHA class:
	  Subgroup 1: NYHA I-II heart failure
	  Subgroup 2: NYHA III-IV heart failure

Intervention	• Cardiac resynchronization therapy with defibrillator
Comparisons	• Cardiac resynchronization therapy without defibrillator
Outcomes and timing	• All-cause mortality with followup at least 3 years • Heart failure hospitalizations with followup at least 3 years • Quality of life score (Minnesota Living with Heart Failure Questionnaire) at 6 months • Harms: lead dislodgement, infection, cardiac perforation/tamponade with followup at least 3 years
Study design	• Randomized controlled trial

Table 63. Characteristics of an ideal study to compare the effectiveness of CRT-D in patients with a non-left bundle branch block morphology

PICOS	Characteristics

Population	• Patients with an LVEF≤35% despite optimal medical therapy
	• Patients with a QRS duration ≥120%
	• NYHA class:
	  Subgroup1: NYHA I-II heart failure
	  Subgroup 2: NYHA III-IV heart failure
	  Subgroup 3: QRs duration >150 ms
	  Subgroup 4: QRS duration 120-150 ms
	• Non-LBBB morphology on 12 lead ECG prior to CRT:
	  Right bundle branch block or non-specific intraventricular conduction delay

Intervention	• Cardiac resynchronization therapy with defibrillator
Comparisons	• ICD alone
Outcomes and timing	• All-cause mortality with followup at least 3 years • Heart failure hospitalizations with followup at least 3 years • Change in left ventricular ejection fraction at 6 months • Change in left ventricular end-systolic volume (ml) at 6 months • Change in 6 minute hall walk distance at 6 months • Quality of life score (Minnesota Living with Heart Failure Questionnaire) at 6 months • Harms: pneumothorax, inappropriate ICD shocks, lead dislodgement, infection, cardiac perforation/tamponade with followup at least 3 years
Study design	• Randomized controlled trial

Table 64. Characteristics of an ideal study to compare the effectiveness of CRT-D in patients with atrial fibrillation

PICOS	Characteristics
Population	• Patients with an LVEF≤35% despite optimal medical therapy • Patients with a QRS duration ≥120% • NYHA III-IV heart failure • Arm 1: Paroxysmal or persistent atrial fibrillation with controlled rates either medically or with concomitant AV node ablation • Arm 2 Permanent AF with controlled rates either medically or with concomitant AV node ablation
Intervention	• Cardiac resynchronization therapy with defibrillator
Comparisons	• ICD alone
Outcomes and timing	• All-cause survival with followup at least 3 years • Heart failure hospitalizations with followup at least 3 years • Change in LVEF at 6 months • Change in LVESV at 6 months • Change in 6 minute hall walk distance at 6 months • Quality of life score (Minnesota Living with Heart Failure Questionnaire) at 6 months • Harms: pneumothorax, inappropriate ICD shocks, lead dislodgement, infection, cardiac perforation/tamponade with followup at least 3 years
Study design	• Randomized controlled trial

Conclusion

We performed a systematic review to evaluate the efficacy and safety of CRT-D and CRT-P devices as well as predictors of outcomes following implant of such devices. There is convincing evidence that CRT-D is effective with regard to improvements in multiple outcomes compared to an ICD alone in patients with an LVEF≤35% and a QRS duration ≥120ms. These findings are

based on patients primarily with NYHA class II-IV heart failure. The applicability of these findings to patients with NYHA class I symptoms is unclear. Similarly, there is convincing evidence that CRT-P is effective in improving multiple endpoints compared to optimal medical therapy alone in the same population. These data are primarily derived from NYHA class III-IV and the applicability to patients with NYHA class I and II is less clear. Female gender, LBBB, a widened QRS duration, sinus rhythm, and non-ischemic cardiomyopathy are associated with improved outcomes following CRT.

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List of Abbreviations

Abbreviations	Definitions
6MHWD	6 Minute Hall Walk Distance
AF	Atrial fibrillation
AHRQ	Agency for Healthcare Research and Quality
CABG	Coronary Artery Bypass Grafting
CAG	Coverage and Analysis Group
CARE HF	Cardiac Resynchronization-Heart Failure
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMS	Centers for Medicare and Medicaid services
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure
CRT	Cardiac resynchronization
CRT-D	Cardiac resynchronization defibrillator
CRT-P	Cardiac resynchronization pacemaker
GFR	Glomerular Filtration Rate
HR	Hazard Ratio
ICD	Implantable Cardiac Defibrillator
ICM	Ischemic Cardiomyopathy
IHD	Ischemic Heart Disease
IS	Inappropriate shocks
IVCD	Intra Ventricular Conduction Delay
KQ	Key question
LAV	Left Atrial Volume
LBBB	Left Bundle Branch Block
LV	Left Ventricle
LVEDV	Left Ventricular End Systolic Volume Index
LVEDVi	Left Ventricular End Systolic Volume Index
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
LVESVi	Left Ventricular End Systolic Volume Index
MADIT	Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy
MASCOT	Management of Atrial fibrillation Suppression in AF-HF Comorbidity Therapy
MeSH	Medical subject headings
MLHFQ	Minnesota Living With Heart Failure Questionnaire
MUSTIC	Multisite Stimulation in Cardiomyopathy
NA	Not Applicable
NICM	Non Ischemic Cardiomyopathy
NR	Not reported
NSIVCD	Non-Specific Intra Ventricular conduction defect
NYHA	New York Heart Association
OMT	Optimal Medical Therapy
OPT	Optimal Pharmacological Therapy

OR	Odds Ratio
PBBBlock	Paced Bundle Branch Block
PICOTS	Population , intervention, comparison, outcome, timing, setting
QOL	Quality of life
QUIPS	Quality In Prognosis Studies
RAFT	Resynchronization–Defibrillation for Ambulatory Heart Failure Trial
RBBB	Right Bundle Branch Block
RCT	Randomized controlled trial
SIP	Scientific Information Packets
SD	Standard deviation
SMART AV	Smart Delay Determined AV Optimization
U.S.	United States
VA	Ventricular Arrhythmia