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Use of Cardiac Resynchronization Therapy

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Use of Cardiac Resynchronization Therapy

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Key Messages

Purpose of review

To reassess the effectiveness and harms of cardiac resynchronization therapy with (CRT-D) and without defibrillator (CRT-P) in patients with an left ventricle ejection fraction (LVEF) ≤35% and a QRS duration ≥120 ms, the effectiveness and harms of alternative cardiac resynchronization therapy techniques in the same patient population, and cardiac resynchronization therapy or His bundle pacing in patients with an left ventricle ejection fraction between 36% and 50% and atrioventricular block. A key question that drove the request for this report update was: Is there any new evidence since the 2015 report that the addition of a defibrillator to CRT improves health outcomes in heart failure patients with LVEF ≤35% and a QRS duration ≥120 ms, on optimal medical therapy?

Key messages

- There is insufficient evidence, including no new definitive evidence since the 2015 report, that CRT-D improves health outcomes compared to CRT-P in patients with heart failure, LVEF ≤35% and QRS duration ≥120 ms, on optimal medical therapy.
- CRT-D compared with an implantable cardioverter-defibrillator and CRT-P compared with optimal medical therapy continue to be effective in improving multiple clinical endpoints.
- As in our prior report, the evidence suggests that left bundle branch morphology, non-ischemic cardiomyopathy, and female sex are generally associated with improved outcomes following CRT-D.
- No significant and consistent differences were seen in pneumothorax, pocket hematomas, device infection, ventricular arrhythmias, inappropriate shocks, or cardiac perforation/tamponade when CRT-D and ICD devices were compared. Studies suggest a potential increase in the number of procedural complications and LV lead dislodgement within 24 hours of implantation for CRT-D compared with ICD devices. Procedure-related complications rates are generally higher for CRT-D versus CRT-P devices. Studies suggest that the risk of device infection and lead dislodgment is higher for CRT-D versus CRT-P devices, but additional studies are needed to confirm this finding.
- The evidence for effectiveness and harms of alternative cardiac resynchronization therapy techniques is limited. However, quadripolar leads compared with bipolar leads result in fewer lead dislodgments, likely owing to more stable positioning and greater sensing and pacing configurations.
- The evidence for effectiveness and harms of cardiac resynchronization therapy or His bundle pacing in patients with left ventricle ejection fraction between 36% and 50% and atrioventricular block is limited; the completion of several ongoing randomized controlled trials is expected in a few years.
- Overall, there remains a paucity of data in older patients, especially for those over 75 years of age, or with increased comorbidities, frailty, cognitive and/or functional impairment.

This report is based on research conducted by the Johns Hopkins University Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA-290-201-500006-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The Centers for Medicare and Medicaid Services (CMS) requested this report from the Evidence-based Practice Center (EPC) Program at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the following EPC: Johns Hopkins University (Contract Number: HHSA 290-2015-00006I).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

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

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

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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Structured Abstract

Objectives. To update a 2015 systematic review on the effectiveness and harms of cardiac resynchronization therapy with (CRT-D) and without (CRT-P) a defibrillator in patients with a left ventricular ejection fraction (LVEF) ≤35% and QRS duration ≥120 ms. We also assessed the effectiveness and harms of alternative cardiac resynchronization therapy techniques in the same patient population and CRT or His bundle pacing in patients with an LVEF between 36% and 50% and atrioventricular block (AVB).

Data sources. We searched PubMed, Embase™, and the Cochrane Central Register of Controlled Trials (CENTRAL) from 2013 to 2019. We updated an existing review addressing the use of CRT or His bundle pacing in patients with an LVEF between 36% to 50% and AVB.

Review methods. We synthesized the evidence from randomized controlled trials (RCTs) and nonrandomized studies published in English. Two reviewers independently screened search results for eligibility and sequentially abstracted data. They also independently assessed the risk of bias of the studies and graded the strength of evidence for pre-specified critical outcomes: QOL, hospitalizations for heart failure and all-cause mortality.

Results. We identified a total of 84 studies. The findings from the prior report for the effectiveness of CRT-D, CRT-P, and CRT-D versus CRT-P remain unchanged. CRT-D improved multiple endpoints compared with an ICD alone with a high strength of evidence. There was moderate strength of evidence that CRT-P increased all-cause survival and reduced heart failure hospitalizations compared with optimal medical therapy alone. There was insufficient evidence to determine a survival advantage of CRT-D over CRT-P. There were fewer heart failure hospitalizations with quadripolar leads compared with bipolar leads, but there was insufficient evidence to draw conclusions about other alternative CRT techniques and other outcomes. Studies suggested a potential increase in the number of procedural complications and LV lead dislodgement within 24 hours of implantation for CRT-D compared with ICD devices. Overall, rate of complications was low when CRT-D and ICD devices were compared. CRT-D devices may also confer protection against first ventricular arrhythmia. Procedure-related complication rates were generally higher for CRT-D versus CRT-P devices. Studies suggested that the risk of device infection and lead dislodgment was higher for CRT-D versus CRT-P devices, but additional studies are needed to confirm this finding. Quadripolar lead compared with bipolar leads resulted in fewer lead dislodgments. However, incidence of ventricular arrhythmia appeared to be similar with quadripolar and bipolar leads.

Conclusions. There is insufficient evidence, including no new definitive evidence since the 2015 report, that CRT-D improves health outcomes compared to CRT-P in patients with heart failure, LVEF ≤35% and QRS duration ≥120 ms, on optimal medical therapy. In patients with an LVEF ≤35% and QRS duration ≥120 ms, there is evidence that CRT-D compared with an ICD alone and CRT-P compared with optimal medical therapy alone are effective in improving multiple clinical endpoints. The strength of these findings varies based on New York Heart Association (NYHA) class. Procedure-related complication rates, infections, and lead dislodgement were higher for CRT-D versus CRT-P devices. The current evidence is very limited for effectiveness and harms of alternative CRT techniques in LVEF ≤35% and QRS duration ≥120 ms and for CRT or His bundle pacing in patients with LVEF between 36% and 50% and AVB.

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Evidence Summary

Introduction

This is an update of an earlier technology assessment (TA) report published in 2015 that evaluated questions related to Use of Cardiac Resynchronization Therapy in the Medicare Population.[1]

Given the increased incidence of frailty, co-morbid illness, and cognitive impairment in the elderly population, reassessing the general appropriateness of cardiac resynchronization therapy **(**CRT) with or without a defibrillator in this population via a systematic review update provides additional guidance to physicians and the Medicare population.

Changes from the 2015 review include the following:

a. Removed the clinical predictors of response questions and added sub-questions to the CRT-P, CRT-D, and alternative CRT techniques (adaptive CRT, multipoint pacing, His bundle pacing, quadripolar) questions to examine subgroup differences.
b. Added new key questions to assess the effectiveness and harms of alternative cardiac resynchronization therapy techniques (adaptive CRT, multipoint pacing, His bundle pacing, quadripolar)
c. Added a new quality of life instrument - Kansas City Cardiomyopathy Questionnaire (KCCQ)
d. Added a new key question to assess the effectiveness of CRT or HBP versus RV pacing for LVEF 36% - 50% and AV block. For this key question we used the 2018 systematic review on CRT or HBP versus that informed the new ACC/AHA/HRS bradycardia guidelines.
e. For the critical outcomes, removed left ventricular end systolic volume (LESV) and broadening quality of life to include KCCQ and SF-36 as well as MLHF.

Potential Audiences

Cardiac electrophysiologists, heart failure specialists, general cardiologists, general internists, patients interested in heart failure, patients with heart failure, allied professionals who care for heart failure patients, and cardiac implantable electronic device manufacturers.

Key Questions

KQ1a: Is cardiac resynchronization therapy with defibrillator effective in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with a left ventricular ejection fraction ≤35% and a QRS duration ≥120 ms?

KQ1b: Does the effectiveness of cardiac resynchronization therapy with defibrillator vary by the following subgroups: age, gender, cardiomyopathy subtype, QRS morphology, left ventricular ejection fraction, New York Heart Association class, atrial fibrillation?

KQ2: What are the adverse effects or complications associated with cardiac resynchronization therapy with defibrillator implantation?

KQ3a: Is cardiac resynchronization therapy in the absence of defibrillator capacity effective in

reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with a left ventricular ejection fraction ≤35% and a QRS duration ≥120 ms?

KQ3b: Does the effectiveness of cardiac resynchronization therapy in the absence of defibrillator capacity vary by the following subgroups: age, gender, cardiomyopathy subtype; QRS morphology, left ventricular ejection fraction, New York Heart Association class, atrial fibrillation?

KQ4: What are the adverse effects or complications associated with cardiac resynchronization therapy in the absence of defibrillator implantation?

KQ5: What is the effectiveness of cardiac resynchronization therapy with defibrillator versus cardiac resynchronization therapy in the absence of defibrillator in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with a left ventricular ejection fraction ≤35% and a QRS duration ≥120 ms?

KQ6: What are the adverse effects or complications associated with cardiac resynchronization therapy with defibrillator versus cardiac resynchronization therapy in the absence of defibrillator implantation?

KQ7a: What is the effectiveness of alternative cardiac resynchronization therapy techniques (adaptive cardiac resynchronization therapy, multipoint pacing, His bundle pacing, quadripolar lead pacing) versus conventional cardiac resynchronization therapy techniques in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with a left ventricular ejection fraction ≤35% and a QRS duration ≥120 ms?

KQ7b: Does the effectiveness of alternative cardiac resynchronization therapy techniques (adaptive cardiac resynchronization therapy, multipoint pacing, His bundle pacing, quadripolar lead pacing) vary by the following subgroups: age, gender, cardiomyopathy subtype, QRS morphology, left ventricular ejection fraction, New York Heart Association class, atrial fibrillation?

KQ8: What are the adverse effects or complications associated with alternative cardiac resynchronization therapy techniques (adaptive cardiac resynchronization therapy, multipoint pacing, His bundle pacing, quadripolar lead pacing)?

KQ9: What is the effectiveness of His bundle pacing or cardiac resynchronization therapy versus right ventricle pacing in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with a left ventricular ejection fraction between 36% and 50% and atrioventricular block?

KQ10: What are the adverse effects or complications associated with His bundle pacing or cardiac resynchronization therapy versus right ventricle pacing in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with a left ventricular ejection fraction between 36% and 50% and atrioventricular block?

Methods

We followed the Agency for Healthcare Research and Quality's (AHRQ's) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[2] Our protocol for this update is posted on the AHRQ TA Program Website (https://www.ahrq.gov/research/findings/ta/index.html). The PROSPERO registration is CRD42014009981. We updated our prior report for Key Questions 1 through 8 and updated an existing review to address Key Questions 9 and 10.[3] Details of our methodology can be found in the full report.

Results

We identified 74 studies addressing the use of CRT in patients with LVEF ≤35% and a QRS duration ≥120 ms (Key Questions 1 through 8), and 10 studies that addressed use of CRT in patients with an LVEF between 36% and 50% and atrioventricular block (AVB) (Key Questions 9 and 10). The two new studies we identified did not change the findings of the existing review on the use of CRT in patients with a left ventricle ejection fraction (LVEF) between 36% and 50% and AVB. Results for use of CRT in patients with an LVEF ≤35% and QRS duration ≥120 ms (Key Questions 1 through 8) are summarized in Table A (effectiveness) and Table B (harms) with shading indicated changes in question, comparison or findings compared with the prior report. Cardiac resynchronization therapy with defibrillator (CRT-D) compared with an implantable cardioverter defibrillator (ICD) alone and cardiac resynchronization therapy in the absence of defibrillator (CRT-P) compared with optimal medical therapy (OMT) alone continues to be effective in improving multiple clinical endpoints. Patients who are female, have left bundle branch block (LBBB) morphology, or have non-ischemic cardiomyopathy generally have better outcomes with CRT-D compared with ICD alone.

Table A. Summary of the findings for effectiveness outcomes by comparator in participants with LVEF ≤35% and a QRS duration ≥120 ms

Outcomes	CRT-D vs. ICD Number of studies (participants)	CRT-P vs. Optimal medical therapy Number of studies (participants)	CRT-P vs. CRT-D Number of studies (participants)	Alternative CRT technique vs. Conventional CRT techniques Number of studies (participants)
Heart failure hospitalizations	6 (reported in 11 articles) .[4-14] (4736) CRT-D results in fewer hospitalizations for CHF compared with an ICD alone especially in patients with LBBB (high strength).	5 (reported in 6 articles) [15-20] (1666) CRT-P resulted in fewer hospitalizations for CHF compared with optimal medical therapy (moderate strength).	1[18] (1520) There was no difference between CRT-P versus CRT-D in hospitalizations (low strength).	2[21, 22] (662) Fewer HF hospitalizations with quadripolar LV leads compared with bipolar LV leads and no difference with addition of MPP (low strength).

Outcomes	CRT-D vs. ICD Number of studies (participants)	CRT-P vs. Optimal medical therapy Number of studies (participants)	CRT-P vs. CRT-D Number of studies (participants)	Alternative CRT technique vs. Conventional CRT techniques Number of studies (participants)
All-cause mortality	7 (reported in 14 articles) [4-14, 23-25] (5812) CRT-D improves mortality in patients with minimally symptomatic CHF especially in patients with LBBB (moderate strength).	5 (reported in 8 articles) [15, 16, 20, 26-30] (2635) CRT-P improves mortality versus optimal medical therapy (moderate strength).	1(reported in 3 articles)[26, 31, 32] (1520) The study made no direct comparison between the CRT-P versus CRT-D arms, but the results appear similar (insufficient evidence).	2[21, 22] (662) No difference in mortality in those with quadripolar LV leads versus bipolar LV leads and MPP vs. conventional CRT (insufficient evidence).
Left ventricular end-systolic volume/volume index†	5 (reported in 8 articles)[4, 6, 8-10, 13, 14, 23] (2539) CRT-D is better than ICD alone in terms of LVESV reduction.	3[29, 33, 34] (1871) CRT-P significantly improves LVESV versus optimal medical therapy.	NR	1[22] (467) No difference
Left ventricular end-diastolic volume/volume index	4 (reported in 7 articles)[4, 6, 8-10, 23, 35] (2447) CRT-D demonstrated a reduction in LVEDV compared with an ICD alone.	2[33, 34] (1058) CRT-P likely reduces LVEDV compared with optimal medical therapy.	1[32] (1520) No difference	NR
Left ventricular ejection fraction	6 (reported in 9 articles) [4, 6-10, 13, 14, 35] (2980) CRT-D demonstrated an improvement in LVEF compared with ICD alone.	4[15, 20, 29, 34] (1322) CRT-P improved LVEF compared with optimal medical therapy.	NR	1.[36] (43) The study identified significantly greater improvement in LVEF in those with quadripolar LV leads versus those with bipolar LV leads after 3 months followup.
6-Minute Hall Walk Distance	4(reported in 5 articles) .[9, 10, 12, 14, 35] (1346) CRT-D is effective in improving 6MHWD in patients with minimally symptomatic CHF compared with those receiving an ICD alone.	4(reported in 5 articles) [15, 17, 19, 20, 26] (2096) CRT-P improved 6MHWD as compared with optimal medical therapy.	1[26] (1520) The study made no direct comparison between the CRT-P versus CRT-D arms, but the results appear similar.	NR

Outcomes	CRT-D vs. ICD Number of studies (participants)	CRT-P vs. Optimal medical therapy Number of studies (participants)	CRT-P vs. CRT-D Number of studies (participants)	Alternative CRT technique vs. Conventional CRT techniques Number of studies (participants)
Packer score	2[9, 10] (555) CRT-D likely results in greater improvement in clinical composite score compared with an ICD alone.	NR	NR	NR
Quality of life[†§]	5 (reported in 6 articles) .[9, 10, 12-14, 35] (2895) CRT-D does not improve QOL in patients with NYHA class I-II CHF compared with an ICD alone (high strength). CRT-D does result in significant improvement in QOL in patients with NYHA class III-IV CHF compared with an ICD alone (high strength).	4(reported in 7 articles) [15-17, 19, 26, 29, 37] (2267) Outcome assessed at different endpoints and with different comparisons (insufficient strength).	1[26] (1520) The study made no direct comparison between the CRT-P versus CRT-D arms, but the results appear similar (insufficient evidence).	NR

Shaded column/cells represent: new question/comparison/changes in the findings in this update compared with prior report

[†]In defining critical outcomes, this update removed left ventricular end systolic volume (LESV) and broadened the outcome of quality of life to include KCCQ and SF-36 as well as MLHF.

§ In this update, we added a new quality of life instrument - Kansas City Cardiomyopathy Questionnaire (KCCQ)

6MHWD=6-minute hall walk distance; CHF=chronic heart failure; CRT=cardiac resynchronization therapy; CRT-D=cardiac resynchronization therapy with defibrillator; CRT-P=cardiac resynchronization therapy in the absence of defibrillator capacity; ICD=implantable cardioverter defibrillator; LV=left ventricular; LVEDV=left ventricular end-diastolic volume; LVEF=left ventricular ejection fraction; LVESV=left ventricular end-systolic volume; NR=not reported; NYHA=New York Heart Association; QOL=quality of life

Table B. Summary of findings for harms by comparator in participants with LVEF ≤35% and a QRS duration ≥120 ms

Harms	CRT-D vs. ICD Number of studies (participants)	CRT-P vs. Optimal medical therapy Number of studies (participants)	CRT-P vs. CRT-D Number of studies (participants)	Alternative CRT technique vs. Conventional CRT techniques Number of studies (participants)
Procedure-related complications	9[38-46] [7 new]* (44,990) Complications are slightly more common with a CRT-D device compared with an ICD alone, especially within the first 24 hours.	2[47, 48] (66) The small sample sizes and the small number of studies mean we are unable to draw a conclusion.	6[26, 49-53] [4 new] (31,970) Procedure-related complication rates are generally higher for CRT-D versus CRT-P devices	NR
Length of hospital stay	1.[38] (60) The average length of hospital stay (per stay) was significantly less in the CRT-D group vs. the ICD-only group.	2[28, 47] (430) Length of hospital stay might not be significantly different in those receiving CRT-P.	3[49, 53, 54] [1 new] (27,307) No studies provided direct comparison of CRT-P and CRT-D for length of hospital stay for the initial device implantation.	NR
Pneumothorax	10 studies[4, 9, 42, 44, 46, 55-59] (4 new) (15,987) The incidence of pneumothorax appears to be similar in patients receiving a CRT-D device compared with an ICD alone.	1(reported in 2 articles)[16, 60] (409) Unable to draw any conclusions.	7[51, 52, 54, 61-64] [3 new] (5,798) No study directly compared pneumothorax by CRT type.	NR
Pocket hematoma	11 studies[4, 38, 40, 42, 44, 46, 55-59] [5 new] (17,741) Compared to patients receiving an ICD alone, pocket hematoma appears to be similar in patients receiving a CRT-D device.	3[47, 60, 65] (619) The heterogeneity of these studies means unable to draw definitive conclusions.	6,[50-53, 62, 63] [4 new] (4,595) Larger pockets from the larger leads, connectors, and size of the CRT-D devices may predispose for hematoma but the newer studies suggest only a slight increased risk for CRT-D.	1[66] (418) Study did not distinguish between the bipolar or quadripolar lead study arms.

Harms	CRT-D vs. ICD Number of studies (participants)	CRT-P vs. Optimal medical therapy Number of studies (participants)	CRT-P vs. CRT-D Number of studies (participants)	Alternative CRT technique vs. Conventional CRT techniques Number of studies (participants)
Device infection	15[4, 38-40, 42, 44, 46, 55-59, 67-69] [6 new] (25,272) The incidence of device infection is similar in patients receiving a CRT-D device compared with an ICD alone.	3(reported in 4 articles)[16, 47, 60, 70] (533) The heterogeneity of these studies mean we cannot draw definitive conclusions.	10[53, 54, 61-63, 71, 50-52, 64] [5 new] (6,577) CRT-D tended to be associated with higher risk of device infections, but additional studies are needed to confirm this finding.	1[66] (418) Unable to draw conclusions.
Cardiac perforation/tamponade	12[9, 10, 38, 40, 42, 44, 55, 57-59, 72, 73] [5 new] (17,829) 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 with an ICD alone.	3[26, 70, 74] (1,630) These studies seem to indicate that the risk of this outcome is not prevalent.	6[26, 51, 53, 54, 61, 62] (5,921) A definitive conclusion regarding the comparative risk for CRT-P vs. CRT-D for cardiac perforation/tamponade cannot be made.	NR
Lead dislodgement	13[10, 40, 44, 46, 55, 56, 58, 59, 69, 72, 75-77] [6 new] (6,726) The data are insufficient to determine whether there is a difference in lead dislodgement rates between patients receiving a CRT-D device vs. an ICD alone, but there may be an increased risk of dislodgement for CRT-D devices within 24 hours post-implantation.	7[16, 48, 60, 65, 70, 78, 79] (903) Unable to draw conclusions as the studies did not report the recorded time point of the dislodgement, and the studies followed their populations for different lengths of time.	7,[50, 51, 53, 54, 61-63] [3 new] (4,881) CRT-D devices had more dislodgement, but further studies are needed.	3[21, 66, 80] (843) Quadripolar leads compared with bipolar leads appear to have less lead dislodgment owing to more stable positioning and greater sensing and pacing configurations, which decreases the need for intervention.

Harms	CRT-D vs. ICD Number of studies (participants)	CRT-P vs. Optimal medical therapy Number of studies (participants)	CRT-P vs. CRT-D Number of studies (participants)	Alternative CRT technique vs. Conventional CRT techniques Number of studies (participants)
Ventricular arrhythmias	23.[9, 10, 14, 35, 40, 55, 75, 81-96] [8 new] (9,569) There is conflicting evidence as to whether CRT-D is protective from VAs compared with an ICD alone. The data, however, are consistent that CRT-D does not appear to increase the rate of VAs compared with an ICD alone.	NR	2[61, 64] [1 new] (1,360) No direct comparison of ventricular arrhythmia was made for CRT-P vs, CRT-D.	2[21, 97]. (200) No definitive conclusion can be made, although incidence of ventricular arrhythmia appears similar by lead type.
Inappropriate implantable cardioverter defibrillator shocks	12[9, 10, 38, 59, 72, 82, 86, 89, 90, 96, 98, 99] [4 new] (9115) There is no apparent difference in the incidence of inappropriate ICD shocks in patients receiving a CRT-D device compared with an ICD alone.	NA	5[53, 62, 64, 100, 101] [3 new] (2,460) Unable to draw conclusions due to the variation in followup and reporting of number of inappropriate shocks vs. number of participants with inappropriate shocks.	1[21] (195) The study did not distinguish between appropriate and inappropriate shocks, and no definitive conclusion can be made.
Death within one week	4[42, 57, 59, 72] [2 new] (12,425) Three of these studies reported zero deaths. One study reported 0.1% participants with ICD compared with 0.2% of participants with CRT-D who experienced in-hospital death at time of implant.	2[17, 48] (157) The risk of death within one week with CRT-P is present, though exact estimations remain unclear.	2[61, 102] (284) The studies rarely specified the exact timing of death and are not comparable in their followup and definition of mortality.	1[97] (5) A single patient died post-implantation from a large LV thrombus, likely unrelated to the procedure.

Shaded column/cells represent: new question/comparison/changes in the findings in this update compared with prior report
*Number of "new" studies in brackets denotes studies that were not included in 2015 AHRQ report
CRT=cardiac resynchronization therapy; CRT-D=cardiac resynchronization therapy with defibrillator; CRT-P=cardiac resynchronization therapy in the absence of defibrillator capacity; ICD=implantable cardioverter defibrillator; NR=not reported; VA=ventricular arrythmia

Limitations

In addressing the questions of efficacy, several studies potentially of interest (e.g., REVERSE, HOBI-PACE, BLOCK-HF) were excluded because outcomes were reported for mixed populations or for different types of CRT without device-specific results. We attempted to obtain population or device-specific data from the authors of such studies but response was limited.

We did not consider non-randomized studies for the questions addressing efficacy due to concerns of potential residual confounding. A prior systematic review assessing the effectiveness of CRT-D versus CRT-P included both RCTs and non-randomized studies and purported superiority of the CRT-D.[103] However, the authors noted moderate selection bias of included studies, and that findings were driven by the observational studies due to their combined large size and longer followup compared to the sole RCT (COMPANION). They cautioned that the results should be considered preliminary, with a need for further RCTs, which our report also concludes.

Implications and conclusions

For the questions of effectiveness included in the prior report we found no new studies. There is insufficient evidence that CRT-D improves health outcomes compared to CRT-P in patients with heart failure, LVEF ≤35% and QRS duration ≥120 ms, on optimal medical therapy.CRT-D compared to an ICD alone and CRT-P compared to optimal medical therapy alone in patients with LVEF ≤35% and a QRS duration ≥120 ms are effective in improving multiple clinical endpoints with the strength of these findings varying based on severity of illness. Evidence for harms is limited by study-defined outcomes and different followup times, but procedure-related complication rates, infections, and lead dislodgement were higher for CRT-D versus CRT-P devices.

The evidence is limited on effectiveness and harms of CRT alternative techniques and CRT or His bundle pacing in eligible patients. However, owing to the advantage of quadripolar leads in left ventricle (LV) pacing programming for both CRT-D and CRT-P recipients, we anticipate that quadripolar lead technology will rapidly supplant bipolar lead technology in clinical practice.

The existing review[3] we updated led to the 2018 ACC/AHA/HRS[104] recommendation to pursue cardiac resynchronization therapy or His bundle pacing in patients with an LVEF between 36% and 50% and AVB who have an indication for permanent pacing and are expected to require ventricular pacing >40% of the time. There have been no studies in the interim that changed the findings from this review. Since AVB constitutes the second most common indication for conventional pacing therapy, this new recommendation will likely lead to a rapid expansion of CRT-pacemaker implantation which has hitherto been an uncommon option in the U.S.

Important clinical questions remain regarding the long-term efficacy of quadripolar LV leads versus bipolar LV leads for CRT as well as the long-term efficacy and harms of CRT versus His bundle pacing in eligible patients. Standardizing both harms definitions and timing of assessment would allow for direct comparisons between studies to be made. One could also consider including these standardized definitions in the registries that are available to track medical devices.

References

1. Rickard J, Michtalik H, Sharma R, et al. 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) Agency for Healthcare Research and Quality. Rockville, MD: 2015. www.effectivehealthcare.ahrq.gov.

2. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF Agency for Healthcare Research and Quality. Rockville, MD: 2014. www.effectivehealthcare.ahrq.gov

3. Slotwiner DJ, Raitt MH, Del-Carpio Munoz F, et al. Impact of Physiologic Pacing Versus Right Ventricular Pacing Among Patients With Left Ventricular Ejection Fraction Greater Than 35% A Systematic Review for the 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2018 Oct 31doi: 10.1016/j.hrthm.2018.10.035. PMID: 30412776.

4. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009 2009 Oct 1;361(14):1329-38.

5. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med. 2010 2010 Dec 16;363(25):2385-95.

6. Zareba W, Klein H, Cygankiewicz I, et al. Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation. 2011 2011 Mar 15;123(10):1061-72.

7. Arshad A, Moss AJ, Foster E, et al. Cardiac resynchronization therapy is more effective in women than in men: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. J Am Coll Cardiol. 2011 2011 Feb 15;57(7):813-20.

8. Barsheshet A, Goldenberg I, Moss AJ, et al. Response to preventive cardiac resynchronization therapy in patients with ischaemic and nonischaemic cardiomyopathy in MADIT-CRT. Eur Heart J. 2011 2011 Jul;32(13):1622-30.

9. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA. 2003 2003 May 28;289(20):2685-94.

10. Abraham WT, Young JB, Leon AR, et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. Circulation. 2004 2004 Nov 2;110(18):2864-8.

11. Birnie DH, Ha A, Higginson L, et al. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: Results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). Circ Heart Fail. 2013 2013 Nov;6(6):1190-8.

12. Healey JS, Hohnloser SH, Exner DV, et al. Cardiac resynchronization therapy in

patients with permanent atrial fibrillation: results from the Resynchronization for Ambulatory Heart Failure Trial (RAFT). Circ Heart Fail. 2012 2012 Sep 1;5(5):566-70.

13. Diab IG, Hunter RJ, Kamdar R, et al. Does ventricular dyssynchrony on echocardiography predict response to cardiac resynchronisation therapy? A randomised controlled study. Heart. 2011 2011 Sep;97(17):1410-6.

14. Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol. 2003 2003 Oct 15;42(8):1454-9.

15. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002 2002 Jun 13;346(24):1845-53.

16. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005 2005 Apr 14;352(15):1539-49.

17. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med. 2001 2001 Mar 22;344(12):873-80.

18. Anand IS, Carson P, Galle E, et al. Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure: results from the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial. Circulation. 2009 2009 Feb 24;119(7):969-77.

19. Leclercq C, Walker S, Linde C, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J. 2002 2002 Nov;23(22):1780-7.

20. Leclercq C, Cazeau S, Lellouche D, et al. Upgrading from single chamber right ventricular to biventricular pacing in permanently paced patients with worsening heart failure: The RD-CHF Study. Pacing Clin Electrophysiol. 2007 2007 Jan;30 Suppl 1:S23-30.

21. Sardu C, Barbieri M, Santamaria M, et al. Multipolar pacing by cardiac resynchronization therapy with a defibrillators treatment in type 2 diabetes mellitus failing heart patients: impact on responders rate, and clinical outcomes. Cardiovasc Diabetol. 2017 Jun 9;16(1):75. doi: 10.1186/s12933-017-0554-2. PMID: 28599667.

22. Leclercq C, Burri H, Curnis A, et al. Cardiac resynchronization therapy non-responder to responder conversion rate in the more response to cardiac resynchronization therapy with MultiPoint Pacing (MORE-CRT MPP) study: results from Phase I. Eur Heart J. 2019 Mar 11doi: 10.1093/eurheartj/ehz109. PMID: 30859220.

23. Tompkins C, Kutyifa V, McNitt S, et al. Effect on cardiac function of cardiac resynchronization therapy in patients with right bundle branch block (from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy. Am J Cardiol. 2013 2013 Aug 15;112(4):525-9.

24. Goldenberg I, Kutyifa V, Klein HU, et al. Survival with cardiac-resynchronization therapy in mild heart failure. New England Journal of Medicine. 2014;370(18):1694-701. doi: 10.1056/NEJMoa1401426.

25. Lozano I, Bocchiardo M, Achtelik M, et al. Impact of biventricular pacing on mortality

in a randomized crossover study of patients with heart failure and ventricular arrhythmias. Pacing Clin Electrophysiol. 2000 2000 Nov;23(11 Pt 2):1711-2.

26. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004 2004 May 20;350(21):2140-50.

27. Cleland JGF, Daubert J-C, Erdmann E, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. Eur. Heart J. 2006 2006;27(16):1928-32.

28. Cleland JG, Calvert MJ, Verboven Y, et al. Effects of cardiac resynchronization therapy on long-term quality of life: an analysis from the CArdiac Resynchronisation-Heart Failure (CARE-HF) study. Am Heart J. 2009 2009 Mar;157(3):457-66.

29. Wikstrom G, Blomstrom-Lundqvist C, Andren B, et al. The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE-HF trial. Eur Heart J. 2009 2009 Apr;30(7):782-8.

30. Cleland JG, Freemantle N, Erdmann E, et al. Long-term mortality with cardiac resynchronization therapy in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial. Eur J Heart Fail. 2012 2012 Jun;14(6):628-34.

31. Carson P, Anand I, O'Connor C, et al. Mode of death in advanced heart failure: the Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial. J Am Coll Cardiol. 2005 2005 Dec 20;46(12):2329-34.

32. Shamoun F, De Marco T, DeMets D, et al. Impact of Degree of Left Ventricular Remodeling on Clinical Outcomes From Cardiac Resynchronization Therapy. JACC: Heart Failure. 2019;7(4):281-90. doi: 10.1016/j.jchf.2018.11.004.

33. Ghio S, Freemantle N, Scelsi L, et al. Long-term left ventricular reverse remodelling with cardiac resynchronization therapy: results from the CARE-HF trial. Eur J Heart Fail. 2009 2009 May;11(5):480-8.

34. St John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation. 2003 2003 Apr 22;107(15):1985-90.

35. Pinter A, Mangat I, Korley V, et al. Assessment of resynchronization therapy on functional status and quality of life in patients requiring an implantable defibrillator. Pacing Clin Electrophysiol. 2009 2009 Dec;32(12):1509-19.

36. Bencardino G, Di Monaco A, Russo E, et al. Outcome of Patients Treated by Cardiac Resynchronization Therapy Using a Quadripolar Left Ventricular Lead. Circ J. 2016;80(3):613-8. doi: 10.1253/circj.CJ-15-0932. PMID: 26821688.

37. Cleland JG, Freemantle N, Daubert JC, et al. Long-term effect of cardiac resynchronisation in patients reporting mild symptoms of heart failure: a report from the CARE-HF study. Heart. 2008 2008 Mar;94(3):278-83.

38. Gillis AM, Kerr CR, Philippon F, et al. Impact of Cardiac Resynchronization Therapy on Hospitalizations in the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial. Circulation. 2014 2014 Mar 7.

39. Masoudi FA, Mi X, Curtis LH, et al. Comparative effectiveness of cardiac resynchronization therapy with an

implantable cardioverter-defibrillator versus defibrillator therapy alone: a cohort study. Ann Intern Med. 2014 2014 May 6;160(9):603-11.

40. Looi KL, Sidhu K, Cooper L, et al. Long-term outcomes of heart failure patients who received primary prevention implantable cardioverter-defibrillator: An observational study. J Arrhythm. 2018 Feb;34(1):46-54. doi: 10.1002/joa3.12027. PMID: 29721113.

41. Echouffo-Tcheugui JB, Masoudi FA, Bao H, et al. Diabetes Mellitus and Outcomes of Cardiac Resynchronization With Implantable Cardioverter-Defibrillator Therapy in Older Patients With Heart Failure. Circ Arrhythm Electrophysiol. 2016 Aug;9(8)doi: 10.1161/circep.116.004132. PMID: 27489243.

42. Friedman DJ, Singh JP, Curtis JP, et al. Comparative Effectiveness of CRT-D Versus Defibrillator Alone in HF Patients With Moderate-to-Severe Chronic Kidney Disease. J Am Coll Cardiol. 2015 Dec 15;66(23):2618-29. doi: 10.1016/j.jacc.2015.09.097. PMID: 26670062.

43. Steffel J, Robertson M, Singh JP, et al. The effect of QRS duration on cardiac resynchronization therapy in patients with a narrow QRS complex: a subgroup analysis of the EchoCRT trial. Eur Heart J. 2015 Aug 7;36(30):1983-9. doi: 10.1093/eurheartj/ehv242. PMID: 26009595.

44. Hoke U, Putter H, Van Der Velde ET, et al. Left ventricular reverse remodeling, device-related adverse events, and long-term outcome after cardiac resynchronization therapy in the elderly. Circ Cardiovasc Qual Outcomes. 2014 May;7(3):437-44. doi: 10.1161/circoutcomes.113.000821. PMID: 24823954.

45. Khazanie P, Greiner MA, Al-Khatib SM, et al. Comparative Effectiveness of Cardiac Resynchronization Therapy Among Patients With Heart Failure and Atrial Fibrillation: Findings From the National Cardiovascular Data Registry's Implantable Cardioverter-Defibrillator Registry. Circ Heart Fail. 2016 Jun;9(6)doi: 10.1161/circheartfailure.115.002324. PMID: 27296396.

46. Essebag V, Joza J, Birnie DH, et al. Incidence, predictors, and procedural results of upgrade to resynchronization therapy: the RAFT upgrade substudy. Circ Arrhythm Electrophysiol. 2015 Feb;8(1):152-8. doi: 10.1161/circep.114.001997. PMID: 25417892.

47. Garikipati NV, Mittal S, Chaudhry F, et al. Comparison of endovascular versus epicardial lead placement for resynchronization therapy. Am J Cardiol. 2014 2014 Mar 1;113(5):840-4.

48. Krahn AD, Snell L, Yee R, et al. Biventricular pacing improves quality of life and exercise tolerance in patients with heart failure and intraventricular conduction delay. Can J Cardiol. 2002 2002 Apr;18(4):380-7.

49. Swindle JP, Rich MW, McCann P, et al. Implantable cardiac device procedures in older patients: use and in-hospital outcomes. Arch Intern Med. 2010 2010 Apr 12;170(7):631-7.

50. Doring M, Ebert M, Dagres N, et al. Cardiac resynchronization therapy in the ageing population - With or without an implantable defibrillator? Int J Cardiol. 2018 Jul 15;263:48-53. doi: 10.1016/j.ijcard.2018.03.087. PMID: 29754922.

51. Barra S, Providencia R, Boveda S, et al. Device complications with addition of defibrillation to cardiac resynchronisation therapy for primary prevention. Heart. 2018 Sep;104(18):1529-35. doi: 10.1136/heartjnl-2017-312546. PMID: 29540431.

52. Nevzorov R, Porter A, Mostov S, et al. Gender-Related Differences in Outcomes of Patients with Cardiac Resynchronization Therapy. Isr Med Assoc J. 2018 May;5(20):311-5. PMID: 29761679.

53. Looi KL, Gavin A, Sidhu K, et al. Utilization of cardiac resynchronization therapy in patients with heart failure in the Northern Region of New Zealand. J Arrhythm. 2018((Looi K.-L., khanglil@adhb.govt.nz; Sidhu K.; Cooper L.; Lever N.) Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand)doi: 10.1002/joa3.12134.

54. Verbrugge FH, Dupont M, De Vusser P, et al. Response to cardiac resynchronization therapy in elderly patients ((greater-than or equal to)70 years) and octogenarians. Eur. J. Heart Fail. 2013 2013;15(2):203-10.

55. Jamerson D, McNitt S, Polonsky S, et al. Early Procedure-Related Adverse Events by Gender in MADIT-CRT. J Cardiovasc Electrophysiol. 2014 2014 Sep;25(9):985-9.

56. Auricchio A, Gold MR, Brugada J, et al. Long-term effectiveness of the combined minute ventilation and patient activity sensors as predictor of heart failure events in patients treated with cardiac resynchronization therapy: Results of the Clinical Evaluation of the Physiological Diagnosis Function in the PARADYM CRT device Trial (CLEPSYDRA) study. Eur J Heart Fail. 2014;16(6):663-70. doi: 10.1002/ejhf.79.

57. Duray GZ, Israel CW, Pajitnev D, et al. Upgrading to biventricular pacing/defibrillation systems in right ventricular paced congestive heart failure patients: prospective assessment of procedural parameters and response rate. Europace. 2008 2008 Jan;10(1):48-52.

58. Kuhlkamp V. Initial experience with an implantable cardioverter-defibrillator incorporating cardiac resynchronization therapy. J Am Coll Cardiol. 2002 2002 Mar 6;39(5):790-7.

59. Adelstein EC, Liu J, Jain S, et al. Clinical outcomes in cardiac resynchronization therapy-defibrillator recipients 80 years of age and older. Europace. 2016 Mar;18(3):420-7. doi: 10.1093/europace/euv222. PMID: 26487669.

60. Gras D, Bocker D, Lunati M, et al. Implantation of cardiac resynchronization therapy systems in the CARE-HF trial: procedural success rate and safety. Europace. 2007 2007 Jul;9(7):516-22.

61. Azizi M, Castel MA, Behrens S, et al. Experience with coronary sinus lead implantations for cardiac resynchronization therapy in 244 patients. Herzschrittmacherther Elektrophysiol. 2006 2006 Mar;17(1):13-8.

62. Killu AM, Wu JH, Friedman PA, et al. Outcomes of cardiac resynchronization therapy in the elderly. Pacing Clin Electrophysiol. 2013 2013 Jun;36(6):664-72.

63. Romeyer-Bouchard C, Da Costa A, Dauphinot V, et al. Prevalence and risk factors related to infections of cardiac resynchronization therapy devices. Eur Heart J. 2010 2010 Jan;31(2):203-10.

64. Kober L, Thune JJ, Nielsen JC, et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med. 2016 Sep 29;375(13):1221-30. doi: 10.1056/NEJMoa1608029. PMID: 27571011.

65. Mortensen PT, Sogaard P, Mansour H, et al. Sequential biventricular pacing: evaluation of safety and efficacy. Pacing Clin

Electrophysiol. 2004 2004 Mar;27(3):339-45.

66. Forleo GB, Di Biase L, Panattoni G, et al. Improved implant and postoperative lead performance in CRT-D patients implanted with a quadripolar left ventricular lead. A 6-month follow-up analysis from a multicenter prospective comparative study. J Interv Card Electrophysiol. 2015 Jan;42(1):59-66. doi: 10.1007/s10840-014-9956-1. PMID: 25504267.

67. Knight BP, Desai A, Coman J, et al. Long-term retention of cardiac resynchronization therapy. J Am Coll Cardiol. 2004 2004 Jul 7;44(1):72-7.

68. Landolina M, Gasparini M, Lunati M, et al. Long-term complications related to biventricular defibrillator implantation: rate of surgical revisions and impact on survival: insights from the Italian Clinical Service Database. Circulation. 2011 2011 Jun 7;123(22):2526-35.

69. Ziacchi M, Diemberger I, Corzani A, et al. Cardiac resynchronization therapy: a comparison among left ventricular bipolar, quadripolar and active fixation leads. Sci Rep. 2018 Sep 5;8(1):13262. doi: 10.1038/s41598-018-31692-z. PMID: 30185834.

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

71. Schuchert A, Muto C, Maounis T, et al. Lead complications, device infections, and clinical outcomes in the first year after implantation of cardiac resynchronization therapy-defibrillator and cardiac resynchronization therapy-pacemaker. Europace. 2013 2013 Jan;15(1):71-6.

72. Strimel W, Koplik S, Chen HR, et al. Safety and effectiveness of primary prevention cardioverter defibrillators in octogenarians. Pacing Clin Electrophysiol. 2011 2011 Jul;34(7):900-6.

73. Maron BJ, Weiner HL, Maron MS, et al. Surviving malignant hypertrophic cardiomyopathy with all major complications in a single patient. Am J Cardiol. 2015 Feb 1;115(3):402-4. doi: 10.1016/j.amjcard.2014.11.004. PMID: 25499402.

74. de Cock CC, van Campen CM, Visser CA. Major dissection of the coronary sinus and its tributaries during lead implantation for biventricular stimulation: angiographic follow-up. Europace. 2004 2004 Jan;6(1):43-7.

75. Bossard M, Sticherling C, Kuhne M, et al. Outcome of patients with cardiac resynchronisation defibrillator therapy and a follow-up of at least five years after implant. Swiss Med Wkly. 2014 2014;144:w13938.

76. Vado A, Menardi E, Rossetti G, et al. Single-center experience of a quadripolar pacing lead for cardiac resynchronization therapy. J Interv Card Electrophysiol. 2014 2014 Mar;39(2):161-5.

77. Crossley GH, Biffi M, Johnson B, et al. Performance of a novel left ventricular lead with short bipolar spacing for cardiac resynchronization therapy: primary results of the Attain Performa quadripolar left ventricular lead study. Heart Rhythm. 2015 Apr;12(4):751-8. doi: 10.1016/j.hrthm.2014.12.019. PMID: 25533587.

78. Stahlberg M, Braunschweig F, Gadler F, et al. Three year outcome of cardiac resynchronization therapy: a single center evaluation. Pacing Clin Electrophysiol. 2005 2005 Oct;28(10):1013-7.

79. Niu HX, Hua W, Wang FZ, et al. Complications of cardiac resynchronization therapy in patients with congestive heart failure. Chin Med J (Engl). 2006 2006 Mar 20;119(6):449-53.

80. Ziacchi M, Zucchelli G, Ricciardi D, et al. Performance and clinical comparison between left ventricular quadripolar and bipolar leads in CRT: Observational research. Indian Heart J. 2018((Ziacchi M., matteo.ziacchi@gmail.com; Boriani G.; Biffi M.) Istituto di Cardiologia, Policlinico S. Orsola-Malpighi, Università di Bologna, Bologna, Italy)doi: 10.1016/j.ihj.2018.05.007.

81. Ouellet G, Huang DT, Moss AJ, et al. Effect of cardiac resynchronization therapy on the risk of first and recurrent ventricular tachyarrhythmic events in MADIT-CRT. J Am Coll Cardiol. 2012 2012 Oct 30;60(18):1809-16.

82. Ruwald MH, Solomon SD, Foster E, et al. Left ventricular ejection fraction normalization in cardiac resynchronization therapy and risk of ventricular arrhythmias and clinical outcomes: results from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) trial. Circulation. 2014 Dec 23;130(25):2278-86. doi: 10.1161/circulationaha.114.011283. PMID: 25301831.

83. Luo NS, Yuan WL, Lin YQ, et al. Potential proarrhythmic effect of cardiac resynchronization therapy during perioperative period: data from a single cardiac center. Chin Med J (Engl). 2010 2010 Sep;123(17):2295-8.

84. Theuns DA, Thornton AS, Klootwijk AP, et al. Outcome in patients with an ICD incorporating cardiac resynchronisation therapy: differences between primary and secondary prophylaxis. Eur J Heart Fail. 2005 2005 Oct;7(6):1027-32.

85. Gasparini M, Menozzi C, Proclemer A, et al. A simplified biventricular defibrillator with fixed long detection intervals reduces implantable cardioverter defibrillator (ICD) interventions and heart failure hospitalizations in patients with non-ischaemic cardiomyopathy implanted for primary prevention: the RELEVANT. Eur Heart J. 2009 2009 Nov;30(22):2758-67.

86. Van Boven N, Bogaard K, Ruiter J, et al. Functional response to cardiac resynchronization therapy is associated with improved clinical outcome and absence of appropriate shocks. J Cardiovasc Electrophysiol. 2013 2013 Mar;24(3):316-22.

87. Haugaa KH, Marek JJ, Ahmed M, et al. Mechanical dyssynchrony after cardiac resynchronization therapy for severely symptomatic heart failure is associated with risk for ventricular arrhythmias. J Am Soc Echocardiogr. 2014 2014 Aug;27(8):872-9.

88. Gopalamurugan AB, Ganesha Babu G, Rogers DP, et al. Is CRT pro-arrhythmic? A comparative analysis of the occurrence of ventricular arrhythmias between patients implanted with CRTs and ICDs. Front Physiol. 2014 2014;5:334.

89. Ricci RP, Pignalberi C, Landolina M, et al. Ventricular rate monitoring as a tool to predict and prevent atrial fibrillation-related inappropriate shocks in heart failure patients treated with cardiac resynchronisation therapy defibrillators. Heart. 2014 2014 Jun;100(11):848-54.

90. Kronborg MB, Johansen JB, Haarbo J, et al. Association between implantable cardioverter-defibrillator therapy and different lead positions in patients with cardiac resynchronization therapy. Europace. 2018 Sep 1;20(9):e133-e9. doi: 10.1093/europace/eux296. PMID: 29036292.

91. Sapp JL, Parkash R, Wells GA, et al. Cardiac Resynchronization Therapy Reduces Ventricular Arrhythmias in Primary but Not Secondary Prophylactic Implantable Cardioverter Defibrillator Patients: Insight From the Resynchronization in Ambulatory Heart Failure Trial. Circ Arrhythm Electrophysiol. 2017 Mar;10(3)doi: 10.1161/circep.116.004875. PMID: 28292754.

92. Xue C, Hua W, Cai C, et al. Acute and Chronic Changes and Predictive Value of Tpeak-Tend for Ventricular Arrhythmia Risk in Cardiac Resynchronization Therapy Patients. Chin Med J (Engl). 2016 Sep 20;129(18):2204-11. doi: 10.4103/0366-6999.189916. PMID: 27625093.

93. Biton Y, Ng CY, Xia X, et al. Baseline adverse electrical remodeling and the risk for ventricular arrhythmia in Cardiac Resynchronization Therapy Recipients (MADIT CRT). J Cardiovasc Electrophysiol. 2018 Jul;29(7):1017-23. doi: 10.1111/jce.13640. PMID: 29846992.

94. Sardu C, Santamaria M, Funaro S, et al. Cardiac electrophysiological alterations and clinical response in cardiac resynchronization therapy with a defibrillator treated patients affected by metabolic syndrome. Medicine (Baltimore). 2017 Apr;96(14):e6558. doi: 10.1097/md.0000000000006558. PMID: 28383431.

95. Sabbag A, Goldenberg I, Moss AJ, et al. Predictors and Risk of Ventricular Tachyarrhythmias or Death in Black and White Cardiac Patients: A MADIT-CRT Trial Substudy. JACC Clin Electrophysiol. 2016 Aug;2(4):448-55. doi: 10.1016/j.jacep.2016.03.003. PMID: 29759864.

96. Su H, Bao P, Chen KY, et al. Influence of the Right Ventricular Lead Location on Ventricular Arrhythmias in Cardiac Resynchronization Therapy. Chin Med J (Engl). 2018;131(20):2402-9. doi: 10.4103/0366-6999.243560.

97. Laish-Farkash A, Bruoha S, Khalameizer V, et al. Multisite cardiac resynchronization therapy for traditional and non-traditional indications. J Interv Card Electrophysiol. 2018 Mar;51(2):143-52. doi: 10.1007/s10840-018-0316-4. PMID: 29442199.

98. Boven NV, Theuns D, Bogaard K, et al. Atrial Fibrillation in Cardiac Resynchronization Therapy with a Defibrillator: A Risk Factor for Mortality, Appropriate and Inappropriate Shocks. J Cardiovasc Electrophysiol. 2013 2013 Jun 17.

99. Killu AM, Mazo A, Grupper A, et al. Super-response to cardiac resynchronization therapy reduces appropriate implantable cardioverter defibrillator therapy. Europace. 2017 Aug 4doi: 10.1093/europace/eux235. PMID: 29016821.

100. Verbrugge FH, De Vusser P, Rivero-Ayerza M, et al. Cardiac resynchronization therapy with or without defibrillator: experience from a high-volume Belgian implantation centre. Acta Cardiol. 2013 2013 Feb;68(1):37-45.

101. Nakajima I, Noda T, Kanzaski H, et al. Development of Heart Failure From Transient Atrial Fibrillation Attacks in Responders to Cardiac Resynchronization Therapy. JACC Clin Electrophysiol. 2018 Sep;4(9):1227-34. doi: 10.1016/j.jacep.2018.06.010. PMID: 30236398.

102. Takaya Y, Noda T, Nakajima I, et al. Electrocardiographic predictors of response to cardiac resynchronization therapy in patients with intraventricular conduction delay. Circ. J. 2014 2014;78(1):71-7.

103. Jiang M, He B, Zhang Q. Comparison of CRT and CRT-D in heart failure: systematic review of controlled trials. Int J Cardiol. 2012 Jun 28;158(1):39-45. doi: 10.1016/j.ijcard.2010.12.091. PMID: 21262545.

104. Kusumoto FM, Bailey KR, Chaouki AS, et al. Systematic review for the 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2018 Oct;15(10):e253-e74. doi: 10.1016/j.hrthm.2017.10.037. PMID: 29097318.

Introduction

Background

Cardiac resynchronization therapy (CRT) is a pacing modality using a left ventricular (LV) pacing lead with the goal of resynchronizing left ventricular myocardial contraction in participants with heart failure, depressed LV systolic function, and significant LV activation delay. CRT was originally indicated in participants with significant LV dysfunction, defined as a left ventricular ejection fraction (LVEF) ≤35%, with New York Heart Association (NYHA) class III-IV heart failure symptoms, and with a QRS duration ≥120 ms on optimal medical therapy (OMT), which varies in definition.[1-4] The focus of CRT has expanded to include not only the treatment of advanced heart failure but also the prevention of clinical deterioration in participants with mild heart failure and atrioventricular block (AVB).

CRT has been shown to improve exercise capacity and quality of life (QOL), induce favorable structural changes in the heart, reduce heart failure hospitalizations, and improve all-cause mortality.[1, 2, 5-8] While these outcomes have been demonstrated repeatedly in large scale clinical trials, roughly one-third of participants currently meeting guideline criteria fail to respond adequately.[9]

Appropriate patient selection for CRT has been a topic of much research but determining the utility of these devices in the elderly may be an even more important goal as device-related complications are known to rise sharply in this population. In a national registry of implantable cardioverter defibrillator (ICD) recipients, 40 percent of whom received CRT, the combined rate of procedural complications or death during the index admission was 3.9 percent in participants 75-79 years of age and 4.5 percent in those 80 years of age and older compared with 2.8 percent in those younger than 65 years of age.[10] CRT devices are currently available with and without defibrillator capability. While the vast majority of CRT devices in the United States are defibrillation-capable, the mortality advantage of CRT with and without a defibrillator has not been definitively determined. In an elderly population, the question of whether to implant a CRT device with or without defibrillation capability is important from the standpoints of a patient's life goals and utility.

Given the increased incidence of frailty, co-morbid illness, and cognitive impairment in the elderly population, reassessing the general appropriateness of CRT with or without a defibrillator in this population via a systematic review update would provide additional guidance to clinicians and the Medicare population. Similarly, new techniques such as adaptive CRT, multipoint LV pacing, His bundle pacing, and quadripolar LV lead pacing may be of additional benefit to the CRT population, and contemporary guidance is necessary.

Clinical Guidelines

The most comprehensive American guidelines for CRT-defibrillator therapy are the ACCF/HRS/AHA/ASE/HFSA/SCAI/ SCCT/SCMR Appropriate Use Criteria for Implantable Cardioverter-Defibrillators and Cardiac Resynchronization Therapy, issued in January 2013.[11] For the CRT section, nine references were cited, including two meta-analyses and a systematic review. However, there was insufficient high-level evidence for definitive evidence-based rules; therefore, the final recommendations were derived by expert opinion consensus.

Separate tables of CRT criteria were provided for people with ischemic cardiomyopathy (ICM), non-ischemic cardiomyopathy (NICM), LVEF >35%, LVEF ≤35%, pre-existing or

anticipated right ventricle pacing with a clinical indication for ICD or pacemaker implantation, refractory class III/IV heart failure (HF), <3 months post-revascularization and/or ≤40 days post-myocardial infarction (MI). Within each of these tables, separate recommendations for NYHA Classes I, II, and III–IV were based on four criteria:

- LVEF ≤30%
- LVEF 31% to 35%
- QRS duration categories of <120 ms, 120 ms to 149 ms, and ≥150 ms
- Left bundle branch block (LBBB) or non-LBBB morphology
- Sinus rhythm

A Canadian guideline update was published soon after the U.S. guideline update with similar evidence and recommendations.[12] In contrast, the more recently issued 2016 European Society of Cardiology Guidelines significantly differed in the minimum requirement for QRS duration, specifically stating that "CRT is contraindicated in participants with a QRS duration <130 ms" as a Class III recommendation (Level of evidence "A" based upon the two meta-analyses and two trials cited).[13] The significant effect of this difference from the prior guidelines is that it would further restrict those participants who are eligible for CRT.

Of major relevance for CRT therapy, the recently issued 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: Executive Summary recommended that "in patients with a left ventricular ejection fraction between 36% and 50% and AVB, who have an indication for permanent pacing and are expected to require ventricular pacing >40% of the time, techniques that provide more physiologic ventricular activation (e.g., cardiac resynchronization therapy, His bundle pacing) are preferred to right ventricular pacing to prevent heart failure."[14] This recommendation was based on a systematic review commissioned by the ACC/AHA/HRS.[15]

Scope and Key Questions

Scope of the Review

Our 2015 systematic review concluded that CRT-D improved multiple clinical outcomes when compared to an ICD alone in participants with an LVEF) ≤35% and a QRS duration ≥120 ms. There was also convincing evidence that CRT-P improves multiple clinical endpoints compared to OMT alone in the same population.

There have been new studies published since our 2015 review that may impact these findings. There is also an increased focus on identifying the subgroup for whom CRT works best, using simple electrocardiographic parameters.

In the 2015 review, we sought to address the following questions for participants with an LVEF ≤35% and a QRS duration ≥120 ms:

- What is the effectiveness and safety of CRT-D compared with an ICD alone?
- What is the effectiveness and safety of CRT-P compared with OMT alone?
- What is the comparative effectiveness and safety of CRT-D versus CRT-P?
- What are the clinical predictors of response in participants deemed appropriate candidates for CRT-D devices?
- What are the clinical predictors of response in participants deemed appropriate candidates for CRT-P devices?

Key Questions

In consultation with the topic nominator [Centers for Medicare and Medicaid Services (CMS)] and a variety of stakeholders, we refined the key questions from the prior review to address the following questions in this review:

KQ1a: Is cardiac resynchronization therapy with defibrillator effective in reducing heart failure symptoms, improving myocardial function, reducing hospitalization, and/or improving survival in patients with a left ventricular ejection fraction ≤35% and a QRS duration ≥120 ms?

KQ1b: Does the effectiveness of cardiac resynchronization therapy with defibrillator vary by the following subgroups: age, gender, cardiomyopathy subtype, QRS morphology, left ventricular ejection fraction, New York Heart Association class, atrial fibrillation?

KQ2: What are the adverse effects or complications associated with cardiac resynchronization therapy with defibrillator implantation?

KQ3a: Is cardiac resynchronization therapy in the absence of defibrillator effective in reducing heart failure symptoms, improving myocardial function, reducing hospitalization, and/or improving survival in patients with left ventricular ejection fraction ≤35% and a QRS duration ≥120 ms?

KQ3b: Does the effectiveness of cardiac resynchronization therapy in the absence of defibrillator vary by the following subgroups: age, gender, cardiomyopathy subtype, QRS morphology, left ventricular ejection fraction, New York Heart Association class, atrial fibrillation?

KQ4: What are the adverse effects or complications associated with cardiac resynchronization therapy in the absence of defibrillator implantation?

KQ5: What is the effectiveness of cardiac resynchronization therapy with defibrillator versus cardiac resynchronization therapy in the absence of defibrillator in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with left ventricular ejection fraction ≤35% and a QRS duration ≥120 ms?

KQ6: What are the adverse effects or complications associated with cardiac resynchronization therapy with defibrillator versus cardiac resynchronization therapy in the absence of defibrillator implantation?

KQ7a: What is the effectiveness of alternative cardiac resynchronization therapy techniques (adaptive cardiac resynchronization therapy, multipoint pacing, His bundle pacing, quadripolar lead pacing) versus conventional cardiac resynchronization therapy techniques in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with an left ventricular ejection fraction ≤35% and a QRS duration ≥120 ms?

KQ7b: Does the effectiveness of alternative cardiac resynchronization therapy techniques (adaptive cardiac resynchronization therapy, multipoint pacing, His bundle pacing, quadripolar lead pacing) vary by the following subgroups: age, gender, cardiomyopathy subtype, QRS

morphology, left ventricular ejection fraction, New York Heart Association class, atrial fibrillation?

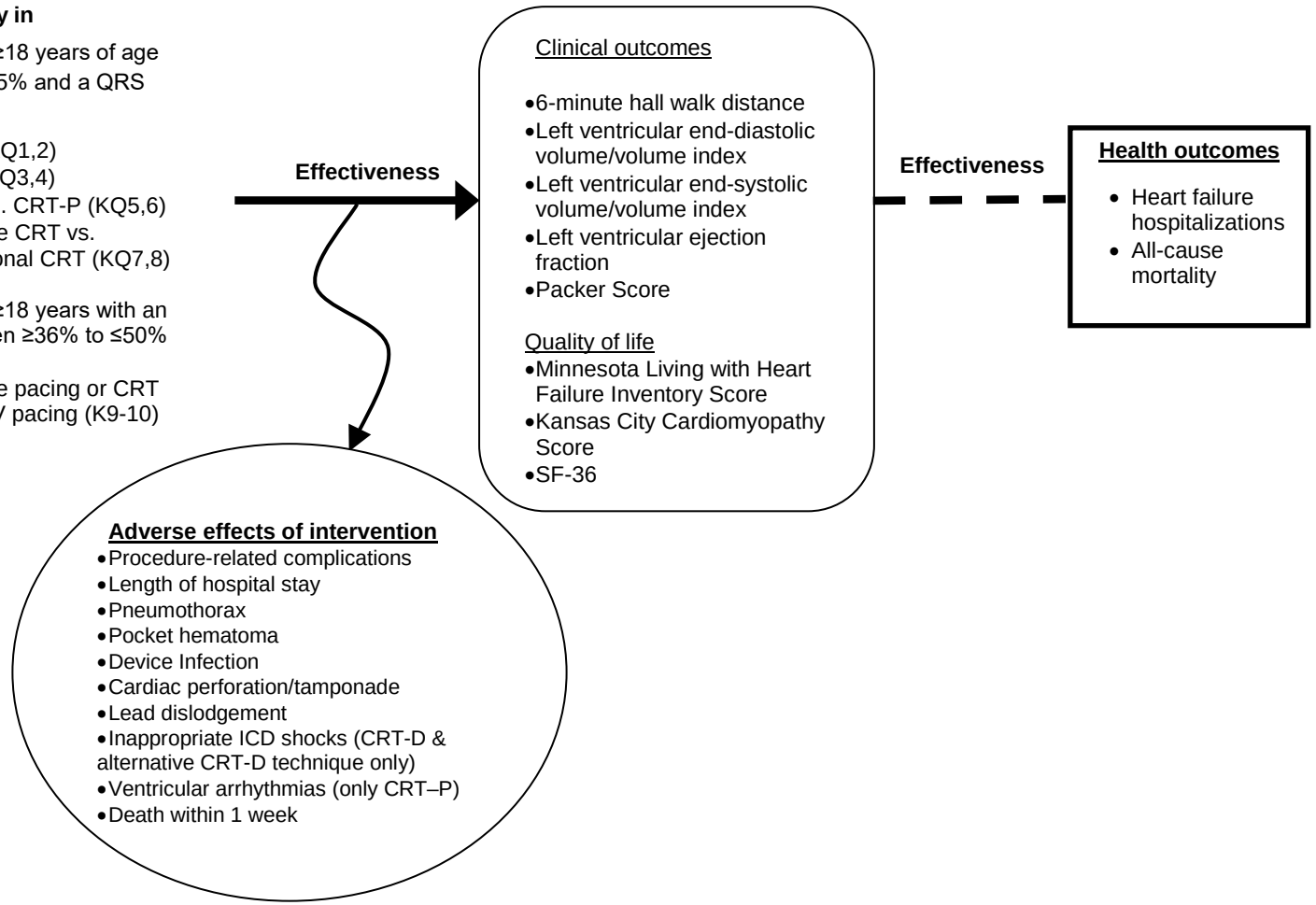
KQ8: What are the adverse effects or complications associated with alternative cardiac resynchronization therapy techniques (adaptive cardiac resynchronization therapy, multipoint pacing, His bundle pacing, quadripolar lead pacing)?

KQ9: What is the effectiveness of His bundle pacing or cardiac resynchronization therapy versus right ventricular pacing in reducing heart failure symptoms, improving myocardial function, reducing hospitalization and/or improving survival in patients with a left ventricular ejection fraction between 36% and 50% and atrioventricular block?

KQ10: What are the adverse effects or complications associated with His bundle pacing or cardiac resynchronization therapy versus right ventricular pacing in patients with a left ventricular ejection fraction between 36% and 50% and atrioventricular block?

Analytic Framework

Figure 1. Analytic Framework for Use of Cardiac Resynchronization Therapy with Different Techniques



AVB=atrioventricular block; CRT-D=cardiac resynchronization therapy with defibrillator; CRT-P=cardiac resynchronization therapy with pacemaker; ICD=implantable cardioverter defibrillator; KQ=Key Question; LVEF=left ventricular ejection fraction; RV=right ventricular; SF-36=short form survey-36

Methods

We followed the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[16]

Review Protocol

This systematic review is an update of an earlier report published in 2015[17].

We gathered input from a variety of stakeholders, including clinical and methodological experts, participants and caregivers, and AHRQ and CMS representatives. We used this input to revise the questions from the prior report as follows:

- Replaced the clinical predictors of response questions to instead assess pre-specified subgroup differences by question.
- Added a new key question to assess the effectiveness and harms of alternative cardiac resynchronization therapy techniques (adaptive CRT, multipoint LV lead pacing, His bundle pacing, quadripolar LV lead pacing).
- Added a new key question to assess the effectiveness of CRT or His bundle pacing versus RV pacing for participants with an LVEF of 36% to 50% and AVB.

Based on the discussions with stakeholders we also modified our methods to include the following changes:

- Add the Kansas City Cardiomyopathy Questionnaire (KCCQ) to the QOL outcome.
- For the critical outcomes or those graded, we removed the outcome of left ventricular end-systolic volume (LVESV) and broadened QOL to include KCCQ and the 36-Item Short Form Survey (SF-36) as well as the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

We posted the protocol to the AHRQ Technology Assessment Program Website (https://www.ahrq.gov/research/findings/ta/index.html) and registered the protocol on PROSPERO (CRD42014009981).

Literature Search Strategy

Search Strategy

For the 2015 review, we searched PubMed, Embase®, and the Cochrane Central Register of Controlled Trials from January 1, 1995 through 2014. We ran the same search strategy (see Appendix A) limited to publication dates 2013 to June 2019.

We identified an existing review that addressed the key question assessing CRT or His bundle pacing versus RV pacing for patients with an LVEF of 36% to 50% and AVB.[15] This is the recent aforementioned systematic review that informed the newly updated 2018 ACC/AHA/HRS bradycardia guidelines.[14] We then conducted an updated search using the same search strategy. We searched PubMed, Embase®, and the Cochrane Central Register of Controlled Trials from May 2016 to June 2019.

Inclusion and Exclusion Criteria

The eligibility criteria for the update are the same as those for the 2015 review, except as noted for changes in the questions [i.e., alternative CRT techniques (KQ7-8), KCCQ assessment of QOL (KQ1a, 3a, 5, and 7a-effectiveness)]. Table 1 lists our inclusion and exclusion criteria using the PICOTS (Population, Intervention, Comparison, Outcomes, Timing, Setting and Study) design framework.

Table 1. Inclusion and exclusion criteria for KQ1-8*

	Inclusion	Exclusion
Population	• Age ≥18 • KQ1 – KQ8: Subjects of age ≥18 years of age, with a left ventricular ejection fraction ≤35% and a QRS duration ≥120 ms	• Animal studies • Age <18 years of age • Baseline mean LVEF plus SD >35.5%** • QRS mean minus SD <115 ms**
Interventions	• CRT-D • CRT-P • Alternative CRT techniques (adaptive CRT, multipoint pacing, His bundle pacing, quadripolar LV lead pacing)	No intervention of interest
Comparisons	• CRT-D vs. ICD • CRT-P vs.OMT • CRT-D vs. CRT-P • Alternative CRT techniques vs. Conventional CRT techniques	
Outcomes	**KQ1a, 3a, 5, and 7a (effectiveness)** **Clinical outcomes** • 6-minute hall walk distance • Left ventricular end-diastolic volume/volume index • Left ventricular end-systolic volume/volume index • Left ventricular ejection fraction • Packer Score **QOL** • Minnesota Living with Heart Failure Inventory Score • Kansas City Cardiomyopathy Score • SF-36 **Health outcomes** • Hospitalizations for heart failure • All-cause mortality **KQ2, KQ4, KQ6, and KQ8 (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 1 week	No outcomes of interest

	Inclusion	Exclusion
Type of Study	• Studies published after 2013[a] • For effectiveness questions we included only RCTs • For all other questions we included any study design except case reports	• Publications with no original data (e.g., editorials, letters, comments, reviews) • Case reports • Non-English publications • Full text not presented or unavailable, abstracts only
Timing and Setting	KQ1a, KQ3a, KQ5, and KQ7a effectiveness outcomes (above) at 3-6 months, 1 year, and ≥2 year endpoints KQ2, KQ4, KQ6, and KQ8 harms outcomes (above) at any time point	

CRT=cardiac resynchronization therapy; CRT-D=cardiac resynchronization therapy with defibrillator; CRT-P=cardiac resynchronization therapy with pacemaker; ICD=implantable cardioverter defibrillator; KQ=Key Question; LV=left ventricular; LVEF=left ventricular ejection fraction; QRS=QRS complex; SD=standard deviation; SF-36=36-Item Short Form Survey

[a] The update searched for studies published since the end search date from the prior report (i.e., 2013).

* We identified an existing systematic review to address KQ9-10[15]

** We reviewed the included studies in the previous systematic review to determine which, if any, studies should be included or excluded as part of the update based on this revised criteria.

Process for Study Selection

We completed screening at the abstract and full-text level using two independent reviewers. Differences between reviewers regarding eligibility were resolved through consensus. We used DistillerSR (Evidence Partners, 2010) to manage the screening process.

Data Extraction and Data Management

We used the standardized forms from our prior report as templates for data extraction (Appendix B). 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. We also abstracted data, when available, by subgroups, such as female, QRS duration (≥120 ms, ≥130 ms, and ≥150 ms), LBBB, atrial fibrillation (AF) and non-ischemic cardiac conditions. For studies reporting undifferentiated CRT-D or CRT-P patient data, including outcomes, we contacted the authors for clarification and device-type specific data (see Data Synthesis).

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

Risk of Bias Assessment

We used the process and tools used in our prior report. The assessment of risk of bias was conducted independently and in duplicate using the Cochrane Risk of Bias Tool for randomized trials[18] and the Newcastle Ottawa Scale for nonrandomized studies.[19] Differences between reviewers were adjudicated 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 that 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 was not specified, we contacted the study authors to request information about type of device.
2. If the number of participants receiving each device was not specified, we contacted the study authors to request information about the number of participants receiving each device.
3. If the number of participants receiving each device was not specified and the outcomes not presented separately, we contacted the study author to request device-specific outcome data.
4. If the number of participants receiving each device was specified, but the outcomes were not presented separately, we attributed the reported outcomes to the device received by ≥90 percent of the participants.
5. If the number of participants receiving each device was specified and the outcomes were not presented separately and no more than 90 percent of the participants received any one type of device or all devices were received by an equal number of participants, 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 a 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 assessed publication bias using Beggs and Eggers tests (with alpha of 0.10), including assessing the asymmetry of funnel plots for each comparison of interest for the outcomes where meta-analyses were conducted. The criterion for testing for funnel plot asymmetry was at least 10 studies of unequal sizes contributing quantitative data for which there was 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).

Grading the Body of Evidence for Each Key Question

We graded the strength of evidence on the pre-specified critical outcomes of QOL (as assessed by MLWHF, SF-36 or KCCQ), hospitalizations for heart failure, and all-cause mortality by using the grading scheme recommended by the Methods Guide for Conducting Comparative Effectiveness Reviews.[16]

Following this standard EPC approach, for each critical outcome, we assessed the number of studies, study designs, study limitations (i.e., risk of bias and overall methodological quality),

directness of the evidence to the key questions, consistency of study results, precision of any estimates of effect, likelihood of reporting bias, and overall findings across studies. Based on these assessments, we assigned a strength of evidence rating as high, moderate, or low, or insufficient evidence to estimate an effect. Investigators writing each section completed the strength of evidence grading. The team members reviewed the assigned grade for each critical outcome and conflicts were resolved through consensus.

Results

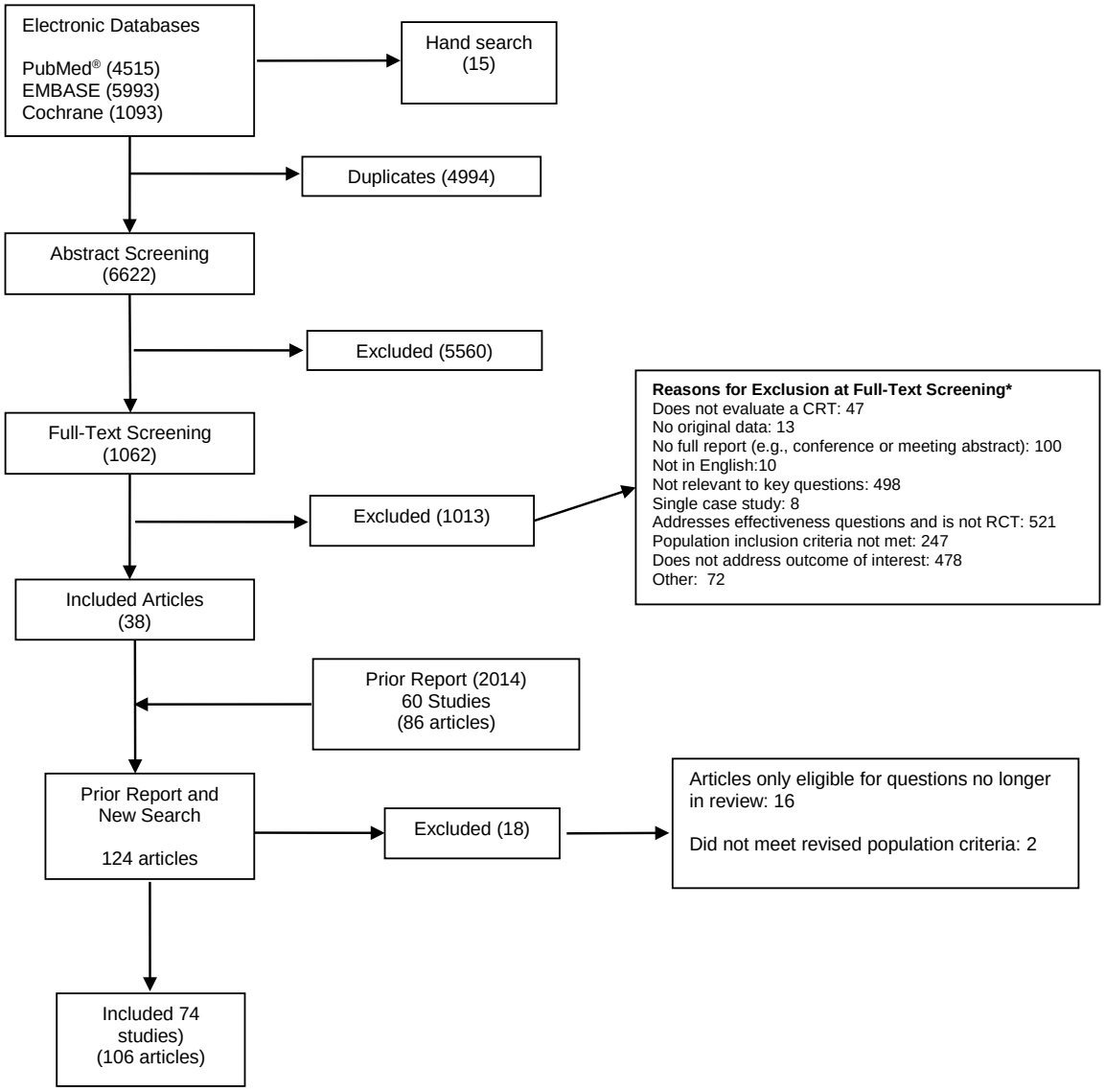
Results of the Search

For KQ1-8, we reconsidered the 60 studies from the prior report and screened 6,622 new citations. A total of 74 studies reported in 104 articles were eligible for KQ1-8. (Figure 2)

For KQ9-10, our search to update the existing review identified 708 unique citations. Two new studies were eligible for KQ9-10. (Figure 3)

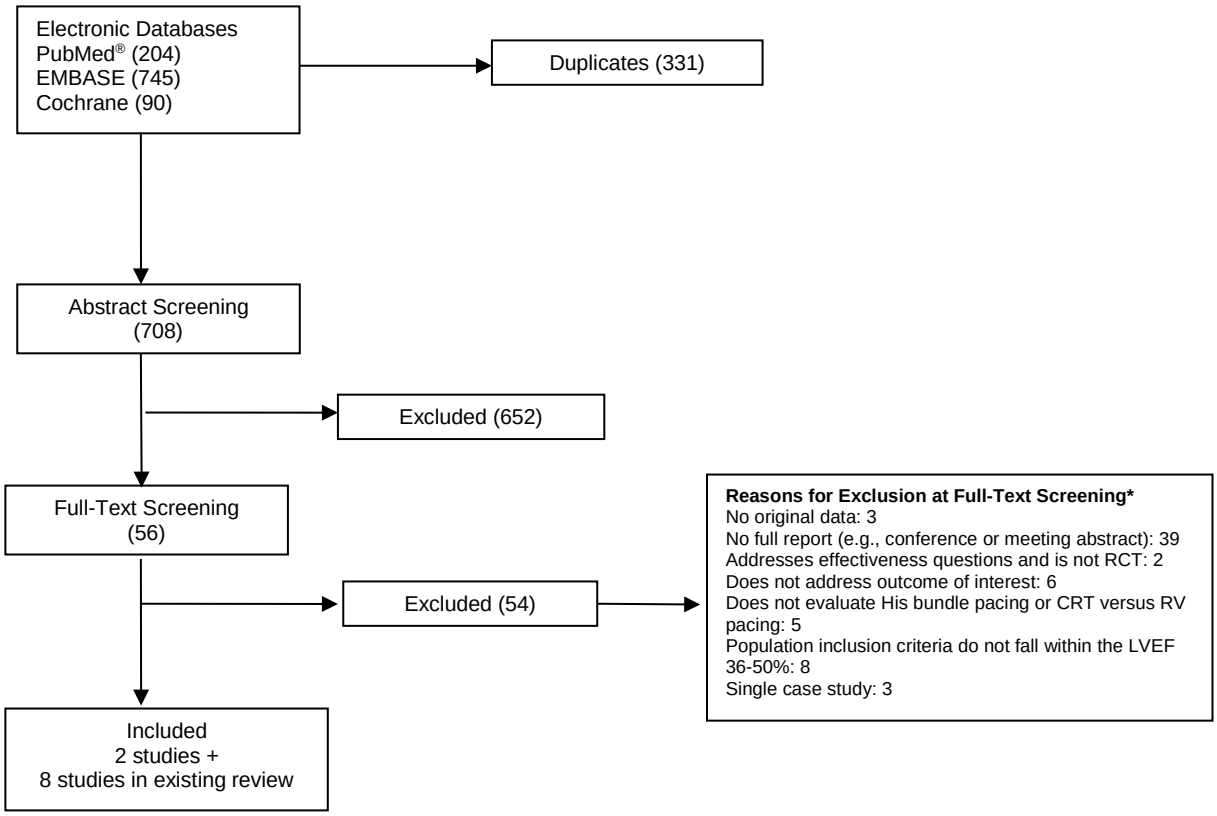
A listing of excluded studies is included in Appendix C.

Figure 2. Summary of search for Key Questions 1-8



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

Figure 3. Summary of search for Key Questions 9 and 10



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

Overview of Included Studies by Outcomes

We list the number of studies by device type or alternative CRT technique, and by type of outcome assessed in Table 2. A listing of RCTs, with eligible reports of additional analyses, is shown in Table 3.

Table 2. List of included studies by outcomes

Intervention	Effectiveness (Prior report)	Effectiveness (Updated search)	Effectiveness (Total)	Harms (Prior report)	Harms (Updated search)	Harms (Total)
CRT–D	8 trials (16 articles)	0 (3 new reports of additional analyses)	**8 trials (19 articles)**	23 studies (26 articles)	18 studies	**41 studies (44 articles)**
CRT–P	5 trials (15 articles)	0 (1 new report of additional analyses)	**5 trials (16 articles)**	10 studies (12 articles)	0	**10 studies (12 articles)**
CRT-P vs CRT-D	1 trial (reported in 3 articles)	0 (1 new report of additional analyses)	**1 trial (4 articles)**	9 studies	6 studies	**15 studies (17 articles)**
Adaptive CRT	NA	0		NA	0	**0**
Quadripolar lead pacing	NA	2 trials	**2 trials**	NA	3 studies	**3 studies**
Multipoint pacing	NA	1	**0**	NA	1 study	**1 study**
His bundle pacing or CRT versus RV pacing	8 studies*	0	**8 studies**	8 studies*	2 studies	**10 studies**

CRT-D=cardiac resynchronization therapy with defibrillator; CRT-P=cardiac resynchronization therapy with pacemaker; NA=not applicable * from Slotwiner, 2018 review

Table 3. List of included trials

Trial with Primary Publication	Secondary Analyses
CARE HF (Cardiac Resynchronization-Heart Failure), Cleland, 2004[1]	Cleland, 2006[20] Cleland, 2007[21] Cleland, 2009[22] Ghio, 2009[23] Gras, 2007[24] Wikstrom, 2009[25] Cleland, 2012[26]
COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure), Bristow, 2004[2]	Anand, 2009[27] Carson, 2005[28] Kalscheur, 2017[29]
MADIT CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) trial, Moss, 2009[6]	Arshad, 2011[30] Barsheshet, 2011[31] Biton, 2015[32] BIton, 2016[33] Ouellet, 2012[34] Solomon, 2010[35] Stockburger, 2016[32] Tompkins, 2013[36] Zareba, 2011[37] Jamerson, 2014[38] Ruwald, 2014[39] Goldenberg, 2014[40]
MIRACLE (Multicenter InSync Randomized Clinical Evaluation)	Sutton, 2003[41] Abraham, 2002[3]
MIRACLE-ICD (Multicenter InSync ICD Randomized Clinical Evaluation), Young, 2003[7]	-
MIRACLE-ICD II (Multicenter InSync ICD Randomized Clinical Evaluation II), Abraham, 2004[42]	-
MUSTIC (Multisite Stimulation in Cardiomyopathy), Cazeau, 2001[4]	Leclercq, 2002[8]
MASCOT (Management of Atrial fibrillation Suppression in AF-HF Comorbidity Therapy)	Schuchert, 2013[43]
RAFT (Resynchronization–Defibrillation for Ambulatory Heart Failure Trial), Tang, 2010[5]	Birnie, 2013[44] Gilis, 2014[45] Healey, 2012[46]
DANISH(The Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality), Kober, 2016[47]	-
Other trials	
Diab, 2011[48]	-
Garikipati, 2014[49]	-
Higgins, 2003[50]	-
Leclercq, 2007[51]	-
Lozanzo, 2000[52]	-
Pinter, 2009[53]	-
Bencardino, 2016 [54]	-
Sardu, 2017[55]	-

Organization of Results Chapter

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

Study Characteristics
Population Characteristics
Outcomes
A. Effectiveness

Health outcomes

- Hospitalizations for heart failure
- All-cause mortality

Clinical outcomes

- Left ventricular end-systolic volume/volume index
- Left ventricular end-diastolic volume/volume index
- Left ventricular ejection fraction
- 6-minute hall walk distance
- Packer Score

Quality of life

- Minnesota Living with Heart Failure Inventory Score
- Kansas City Cardiomyopathy Score
- SF-36

B. Harms

- Procedure-related complications
- Length of hospital stay
- Pneumothorax
- Pocket hematoma
- Device Infection
- Cardiac perforation/tamponade
- Lead dislodgement
- Ventricular arrhythmias
- Death within 1 week
- Inappropriate ICD shocks (CRT-D and alternative CRT-D techniques only)

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

Key Points

- CRT-D devices remain effective in reducing heart failure symptoms, improving myocardial function, and reducing hospitalizations for heart failure.
- We found moderate strength of evidence for the benefit of CRT-D versus ICD alone for all-cause mortality in participants with NYHA class II symptoms.
- 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).
- As in our prior report, recent evidence from three additional sub-studies suggests that left bundle branch (LBBB) morphology, NICM, and female gender are generally associated with improved outcomes following CRT-D.

Study Characteristics

Eight trials (reported in 19 articles) addressed the effectiveness of CRT-D.[5-7, 30-33, 35-37, 40, 42, 44, 46, 48, 50, 52, 53, 56]

We did not identify any new trials comparing CRT-D and ICD therapy, but our update did identify three additional analyses of the MADIT trial relevant to some of the pre-specified subgroups of interest.[32, 33, 56]

Overall, the trials used largely consistent comparators when assessing participants with an ICD and biventricular pacing versus an ICD and no biventricular pacing (Evidence Table 1).

One trial separated participants into two groups based on the presence or absence of baseline ventricular dyssynchrony.[48] Participants with dyssynchrony all received a CRT-D device. This trial randomized participants without dyssynchrony to a CRT-D device or an ICD alone. Another trial started as a crossover design with participants crossing over between active CRT-on versus CRT-off.[50] This trial changed to a parallel arm design after initiation. Two trials did not report funding status (Table 4).[48, 52]

Table 4. Study characteristics of trials assessing effectiveness of CRT-D

Author, year	Number of participants	Length of followup	Device manufacturer name/device model	Comparison	NYHA class	Funding source
MADIT-CRT						
Arshad, 2011[30]	Women: 453 Men: 1,367	12 months remodeling ; 2.4 years mortality and CHF	Boston Scientific devices		I: 14.8% II: 85.2%	Industry
Barsheshet, 2011[31]	Ischemic: 1,046 Non-ischemic: 774	12 months remodeling ; 2.4 years mortality and CHF	Boston Scientific devices	CRT-D vs. ICD alone	CRT-D vs. ICD alone	Industry
Biton, 2015[56]	Women: 394 Men: 887	84 months	Boston Scientific devices	CRT-D vs. ICD alone	Not reported	Industry
Biton, 2016[33]	ICD (QRS <150 msec): 139 CRT-D (QRS <150 msec): 204 ICD (QRS ≥150 msec): 70 CRT-D (QRS ≥150 msec): 124	84 months	Boston Scientific devices	CRT-D vs. ICD alone	Not reported	Industry
Goldenberg, 2014[40]	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[35]	CRT-D: 749 ICD: 623	12 months	Boston Scientific devices	CRT-D vs. ICD alone	I: 84.7% II: 15.3%	Industry
Stockburger, 2016[32]	ICD, long PR (≥230 ms): 36 ICD, normal PR (<230 ms): 171 CRT-D, long PR (≥230 ms): 60 CRT-D, normal PR (<230 ms): 267	median: 5.8 years	Boston Scientific devices	CRT-D vs. ICD alone	I: 22.7% II: Not reported	Industry

Author, year	Number of participants	Length of followup	Device manufacturer name/device model	Comparison	NYHA class	Funding source
Tompkins, 2013[36]	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[37]	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[7]	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[42]	CRT: 85 Control: 101	6 months	Model Insync 7272	CRT-on vs. CRT-off	Class II	Industry
Birnie, 2013[44]	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[46]	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
Tang, 2010[5]	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[48]	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 [50]	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[52]	CRT: 109 Control: 113	3 months	Not reported	CRT-D on vs. off	II: 35% III: 57% IV: 8%	Not reported
Pinter, 2009[53]	CRT: 36 Control: 36	6 months	Model1823 CONTAK CD CHF or the H135 CONTAK RENEWAL HF	CRT-on vs. CRT-off	Class II	Industry

CHF=chronic heart failure; CONTAK CD=Boston Scientific CONTAK CD device; CONTAK RENEW HF=Boston Scientific CONTAK RENEW HF device; CRT-D=cardiac resynchronization with defibrillator; ICD=implantable cardioverter defibrillator; LBBB=left bundle branch block; MADIT-CRT=Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy; MIRACLE-ICD=Multicenter InSync ICD Randomized Clinical Evaluation; NSIVCD=Non-Specific

Intra Ventricular conduction defect; NYHA= New York Heart Association; PR=PR-interval; QRS=QRS complex; RAFT=Resynchronization–Defibrillation for Ambulatory Heart Failure Trial

Participant Characteristics

The number of participants enrolled in the eight trials addressing effectiveness of CRT-D (reported in 19 articles) ranged from 73 to 1,820. The percentage of women was between 9.1 percent and 25.3 percent. [5-7, 30-33, 35-37, 40, 42, 44, 46, 48, 50, 52, 53, 56] The mean age ranged from 63.0 years of age to 67.6 years of age. Only one trial (MADIT-CRT) reported the racial distribution of subjects.[6] Approximately 90 percent of this trials participants was Caucasian. In terms of cardiomyopathy subtype, the proportion of participants 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.[7] In the MADIT CRT-Trial,[6] 28 percent of women had ICM compared to 64 percent of men.[30]

Three trials reported on history of AF in study participants.[6, 42, 53] 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.[53] The MADIT-CRT[6], MIRACLE-ICD[7], and MIRACLE-ICD II[42] trials excluded participants with atrial arrhythmias <1 month prior to implant, and the trial by Higgins et al. (2003) excluded participants with any history of AF.[50] Six of the eight trials reported mean QRS duration.[5, 7, 42, 48, 50, 53]

The MADIT-CRT trial dichotomized QRS duration into ≥150 ms or <150 ms categories.[6] In subgroup analyses from MADIT-CRT, women and men had a similar QRS duration (158±17 ms vs. 158±20 ms, respectively).[30] Participants with an LBBB had a mean QRS duration of 163±19 ms, right bundle branch block (RBBB) 153±15 ms, and non-specific intraventricular conduction delay (NSIVCD) 142±14 ms.[37] In the RAFT trial, participants with LBBB had a mean QRS duration of 161.0±23.5 ms, RBBB 159.9±19.3 ms, and NSIVCD 138.6±18.4 ms.[44] The mean QRS duration was generally similar amongst the trials with only the much smaller trial by Diab et al. (2011) with 43 participants as an outlier.[48]

Four trials reported the incidence of LBBB ranging from 54 percent to 72.9 percent.[5, 6, 50, 53] One study reported no QRS morphology data.[48] Two trials[7, 42] reported on the incidence of RBBB. While these two studies excluded paced participants, given a lack of data on the number of NSIVCD participants, we could not determine the number of LBBB participants from these two studies. Six trials reported the number of RBBB participants, ranging from 7.6 percent in the CRT arm of the RAFT trial[5] to 20.8 percent in the CRT-off arm from the MIRACLE-ICD II trial.[42] Three trials reported participants with NSIVCD ranging from roughly 11 percent to 32 percent.[5, 37, 50]

Only the RAFT trial included participants with a paced ventricular rhythm prior to CRT.[5] These participants represented 7.4 percent to 7.6 percent of the participants in this trial. All paced participants in the RAFT trial had a QRS duration >200 ms.[5]

The NYHA class was a key inclusion criterion in all trials. Three trials included only participants with NYHA class III–IV symptoms.[7, 48, 53] One trial included primarily class III participants, however roughly one-third of the participants in this trial were NYHA class II.[50] The trial by Lozano et al. (2000) included participants with class II, III, and IV symptoms.[52] The RAFT trial included primarily NYHA class II participants, although roughly 20 percent were NYHA class III.[5] The MIRACLE-ICD trial included only NYHA class II participants.[7] The

MADIT-CRT trial enrolled only participants with NYHA class I or II symptoms, of which NYHA class II represented roughly 85 percent.[6]

All trials reported the mean LVEF and it was similar across studies ranging from 21 percent to 26 percent. Only two trials reported serum creatinine.[6, 53] Mean serum creatinine ranged from 1.1-1.2 mg/dL. These trials were homogeneous in patient population with the exception of NYHA class.

Risk of Bias

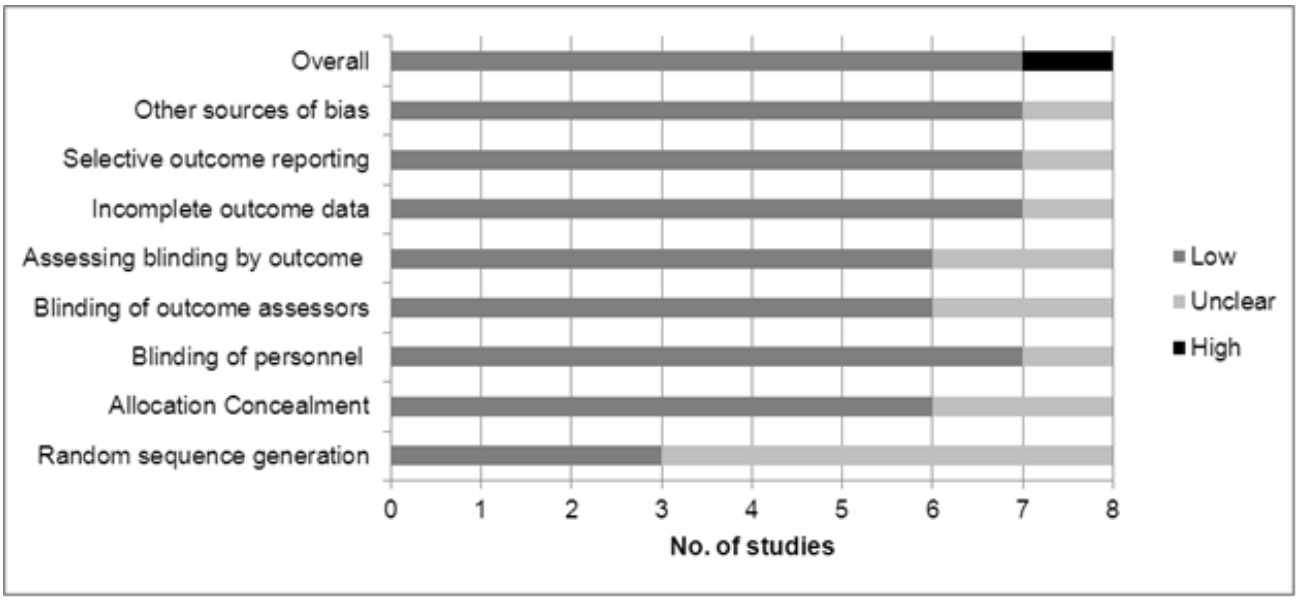
The majority of the eight trials did not report whether they performed random sequence generation; therefore, we cannot rule out selection bias. In the MADIT-CRT trial, the treating physicians were aware of study-group assignments introducing possible performance bias.[6, 30-33, 35-37, 56] The RAFT trial conducted 6-minute hall walk tests and administered quality-of-life questionnaires.[5] However, this outcome was only reported as a secondary analysis limited to participants with permanent AF.[46] Despite these limitations, overall, the included RCTs have a low risk of bias (Table 5 and Figure 4).

Table 5. 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[30] Barsheshet, 2011[31] Biton, 2015[56] Biton, 2016[33] Goldenberg, 2014[40] Moss, 2009[6] Solomon,2010[35] Stockburger, 2016[32] Tompkins, 2013[36] Zareba, 2011[37]	?	-	-	-	-	-	-	-	-
MIRACLE-ICD									
Young, 2003[7]	-	-	-	-	-	-	-	-	-
MIRACLE-ICD II									
Abraham, 2004[42]	-	-	-	-	-	-	-	-	-
RAFT									
Tang, 2010[5] Birnie, 2013[44] Healey, 2012[46]	?	-	-	-	-	-	-	-	-
Other trials									
Diab, 2011[48]	-	-	-	-	-	-	-	-	-
Higgins, 2003[50]	?	?	-	?	?	-	-	-	-
Lozanzo, 2000[52]	?	?	?	?	?	?	?	?	+
Pinter, 2009[53]	?	-	-	-	-	-	-	-	-

+=high; - =low; ?=unclear; MADIT CRT Trial= Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy; MIRACLE=Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD II=Multicenter InSync ICD Randomized Clinical Evaluation II; RAFT= Resynchronization–Defibrillation for Ambulatory Heart Failure Trial

Figure 4. 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 6). Multiple trials also measured indices of reverse ventricular remodeling changes including left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (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 trials assessed QOL as measured by the MLHFQ. Five trials reported functional capacity changes by noting variations in 6-minute hall walk distance (6MHWD), and two trials measured symptomatic improvement via the same Packer score (clinical composite) which assigned participants to one of three groups (worsened, improved, or unchanged).

Table 6. Outcomes reported in the trials assessing effectiveness of CRT-D

Author, year	All-cause mortality	HF hospitalization	LVESV	LVESVi	QOL (MLHFQ)	LVEF	LVEDV	LVEDVi	Packer score	6MHWD
MADIT-CRT										
Arshad, 2011[30]	X	X		X		X		X		
Barsheshet, 2011[31]	X	X	X			X	X			
Biton, 2015[56]	X	X								
Biton, 2016[33]	X	X								
Goldenberg, 2014[40]	X									
Moss, 2009[6]	X	X	X			X	X			
Solomon, 2010[35] (other endpoints are redundant from MADIT-CRT[6]				X				X		
Stockburger, 2016[32]	X									
Tompkins, 2013[36]	X		X				X			
Zareba, 2011[37]	X	X	X			X	X			
MIRACLE-ICD										
Young, 2003[7]	X	X (part of combined endpoint)	X		X	X	X		X	X
MIRACLE-ICD II										
Abraham, 2004[42]	X	X	X		X	X	X		X	X
RAFT										
Birnie, 2013[44]	X	X								
Healey, 2012[46]	X	X			X					X

Author, year	All-cause mortality	HF hospitalization	LVESV	LVESVi	QOL (MLHFQ)	LVEF	LVEDV	LVEDVi	Packer score	6MHWD
Tang, 2010[5]	X	X								
Other trials										
Diab, 2011[48]	X	X	X		X	X				
Higgins, 2003[50]	X	X			X	X				X
Lozano, 2000[52]	X									
Pinter, 2009[53]			X		X	X	X			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; QOL=quality of life

All-cause Mortality

Seven trials (reported in 14 articles) assessed the all-cause mortality outcome and findings were not impacted by recent reports of subanalyses.[5-7, 30, 31, 36, 37, 40, 42, 44, 46, 48, 50, 52] Three trials included participants with primarily minimally symptomatic (NYHA class I–II) CHF[5, 6, 42], two included participants with primarily advanced (NYHA class III–IV) CHF[7, 48] and two included both populations.[50, 52] 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 followup of 854 participants from MADIT-CRT (1,818 were originally followed), participants with a LBBB undergoing CRT derived a significant improvement in mortality compared with an ICD alone (log rank p=0.002) but those with a non-LBBB did not (log rank p=0.2).[40] Long-term mortality data comparing CRT-D with an ICD alone in were not reported. In another analysis from MADIT-CRT, women derived a significant benefit in survival from CRT-D compared with an ICD alone (log rank p=0.02), whereas men did not (log rank p=0.83).[30]

In a separate analysis from MADIT-CRT, in participants with RBBB with or without a left anterior fascicular block (LAFB), there was no difference in survival in participants receiving CRT-D compared with an ICD alone (log rank p=0.374).[36]

In another analysis from MADIT-CRT (stratified by cardiomyopathy subtype), participants 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).[31] Participants with 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).[31] In the RAFT trial (primarily NYHA class II participants), the 5-year actuarial rate of death in the CRT-D arm was 28.6 percent versus 34.6 percent in the ICD-alone arm (HR: 0.75, 95% CI, 0.562 to 0.91, p=0.0003).[5]

In participants with permanent AF, there was no difference in survival between participants in the CRT-D arm and the ICD-alone arm (HR: 1.04, 95% CI, 0.66 to 1.62, p=0.88).[46] 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, participants with an LBBB had improved survival with CRT-D compared with an ICD alone (HR: 0.664, 95% CI, 0.516 to 0.853, p=0.0013).[44] There was no statistically significant difference between the CRT-D and ICD arms for participants 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).[44] In MIRACLE-ICD II (enrolling participants with NYHA class II), there was no difference in mortality between the study arms at 6-month followup.[42]

In terms of the trials of participants with more advanced (NYHA class III–IV) CHF symptoms, in the MIRACLE-ICD trial the cumulative survival rate 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).[7] In the very small trial (n=43) 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 6-month followup.[48] 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-month followup.[50] 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).[52]

In summary, in participants with less symptomatic (NYHA class I–II) CHF, data from the RAFT trial demonstrated a mortality benefit, which conflicts with the originally reported median

2.4 year followup of the MADIT-CRT trial, which did not show a mortality benefit. However, long-term followup of the MADIT-CRT demonstrated a mortality benefit in LBBB but not in non-LBBB morphology. Whether CRT-D produced a mortality improvement in the cohort as a whole was not reported and many participants in the original trial were lost to followup. The other trials assessing mortality in minimally symptomatic participants were either too small in size or too short in followup to add significant additional evidence. Given this, the strength of evidence that CRT-D improves mortality in participants with minimally symptomatic CHF is moderate. The trials assessing mortality in participants 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 with an ICD alone, although we needed more data to confirm this finding.

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

Heart Failure (HF) Hospitalizations

Six trials (reported in 11 articles) assessed HF hospitalization outcomes and were not impacted by recent sub-study reports.[5-7, 30, 31, 37, 42, 44, 46, 48, 50] 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).[5] In participants with permanent AF from this trial, 19.3 percent of participants 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).[46] 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, participants with an LBBB had fewer HF hospitalizations with CRT-D compared with an ICD alone (HR: 0.603, 95% CI, 0.469 to 0.774, p<0.001).[44] There was no statistically significant difference in HF hospitalizations between the CRT-D and ICD arm for participants 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).[44]

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 the MADIT-CRT trial, both women and men required fewer heart failure hospitalizations with CRT-D compared with 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, p=0.001, respectively).[30] In another analysis from the MADIT-CRT trial, stratified by QRS morphology, participants with a LBBB morphology had fewer HF events with CRT-D compared with an ICD alone (HR: 0.41, 95% CI, 0.31to 0.54, p<0.001).[37] Participants with an RBBB had no statistically significant difference in CHF events with CRT-D versus an ICD alone (HR: 0.88, 95% CI, 0.46 to 1.67, p=0.690).[37] Participants with a NSIVCD morphology had no statistically significant difference in HF events with CRT-D versus an ICD alone (HR: 1.31, 95% CI, 0.78 to 2.16, p<0.306).[37] In another analysis from the MADIT-CRT trial (stratified by cardiomyopathy subtype), participants with both ICM and NICM had fewer HF events with CRT-D compared with 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).[31]

The MIRACLE-ICD trial did not report HF hospitalizations alone (without combination with all-cause survival).[7] The very small study by Diab et al. (2011) with 43 participants hospitalized two participants in the CRT arm (both in the dyssynchrony-present arm) and two in the ICD arm for HF over 6-month followup.[48] 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.[53] In the study by Higgins et al. (2003) there was a non-statistically significant 15 percent reduction in HF progression in participants receiving CRT-D (CRT-on) compared with ICD (CRT-off) (p=0.35).[50]

Both the large RAFT and MADIT-CRT trials showed a reduction in HF events for CRT-D compared with an ICD alone. Subgroup analyses from both trials demonstrate the effect to occur primarily in participants 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.

We found high strength of evidence that CRT-D results in fewer hospitalizations for CHF compared with an ICD alone.

Left Ventricular End-systolic Volume/Volume Index

Five trials (reported in 8 articles) reported change in LVESV.[6, 7, 31, 36, 37, 42, 48, 50] In MADIT-CRT there was a significant decrease in LVESV in the CRT-D arm compared with the ICD arm alone (reduction of 57 ml vs. 18 ml, p<0.001, respectively).[6]

In an analysis from the RAFT trial (grouped by bundle branch block morphology), participants with an LBBB had a significant reduction in LVESV compared with those receiving an ICD alone (62.1±31.5ml vs. 18.3±16.5ml, p<0.01).[44] Participants with a non-LBBB morphology (RBBB and NSIVCD grouped together), derived a significant reduction in LVESV with CRT-D compared with ICD alone (45.7±27.3 ml vs. 17.5±16.1 ml, p<0.01).[44]

In an analysis from MADIT-CRT (stratified by cardiomyopathy subtype), participants with both ICM and NICM demonstrated reduction in LVESV with CRT-D versus an ICD alone compared with baseline (-29% vs. -10% and -37% vs. -11%, respectively).[31]

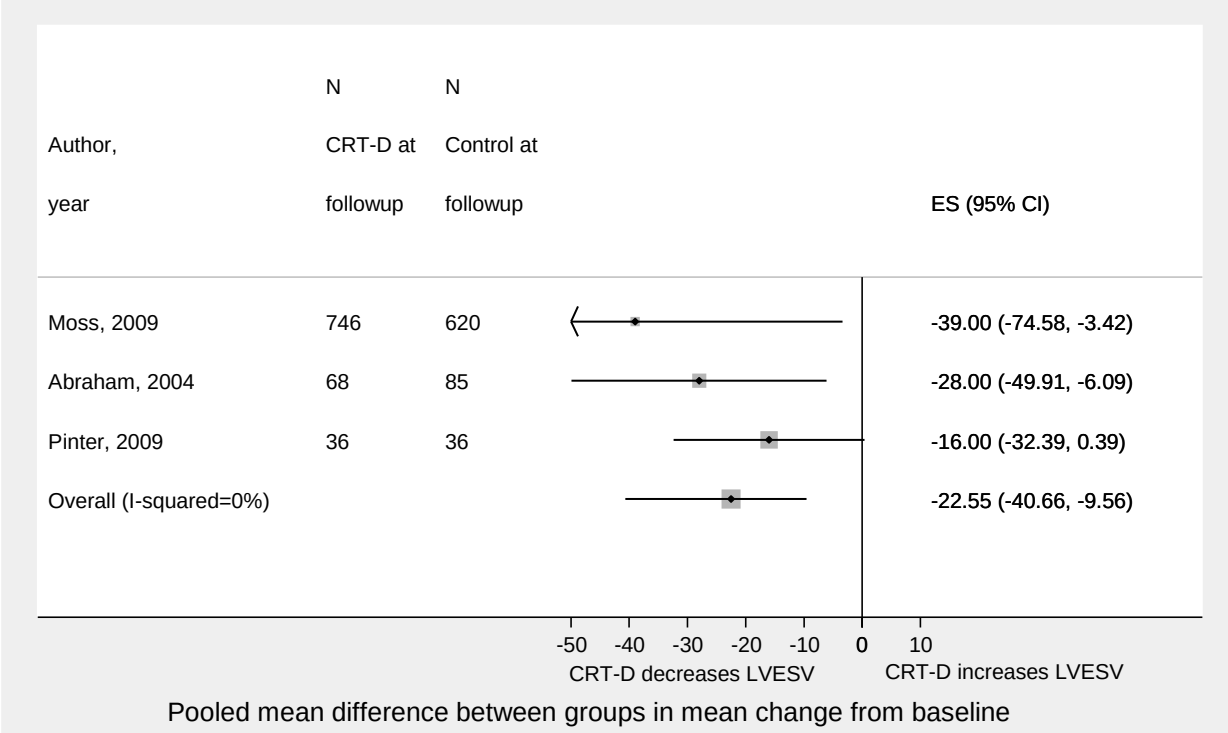
In the MIRACLE-ICD trial, the median change in LVESV in the control group was -8.2 ml (with a range from -19.1 to 0.6) compared with -22.2 ml (with a range from -32.8 to -10.7) in the CRT-D arm (p=0.06).[7] In the MIRACLE-ICD II trial, the mean change in LVESV in the CRT-D (CRT-on) arm compared with ICD (CRT-off) arm was -42 ml versus -14 ml, p=0.01, respectively.[42]

In the trial by Pinter et al. (2009), the mean change in the CRT-D (CRT-on) arm was -21±45 ml versus -5+22 ml in the ICD (CRT-off) arm—a change which was not statistically significant.[53] In the very small study by Diab et al. (2011) with 43 participants, the change in LVESV was dichotomized into reduction ≥15 percent from baseline.[48] Amongst participants with no dyssynchrony at baseline, participants with CRT-D were more likely to have a reduction in LVESV from baseline of at least 15 percent compared with participants receiving an ICD alone (57% vs. 11%, p=0.002).

The MADIT-CRT also reported changes in LVESVi.[6, 35] At 12-month followup, participants receiving CRT-D derived a greater improvement in LVESVi compared with participants receiving an ICD alone (-28.7±15.5 vs. -9.1±8.2, p=0.0001).[35] In an analysis from MADIT-CRT, both women and men derived improvements in LVESVi compared with an ICD alone (ml/body surface area, -31 vs. -10 and -27 vs. -8, respectively, p<0.001). [30]

The trials were generally consistent in demonstrating a reduction in LVESV with CRT-D compared with an ICD alone. This effect was noted across multiple subgroups, including participants with non-LBBB block morphologies. We performed a meta-analysis incorporating the three trials, which enrolled minimally symptomatic (NYHA class I–II) CHF. This meta-analysis demonstrated a clear benefit in terms of LVESV reduction favoring CRT-D compared with an ICD alone (mean difference: -22.55 ml, 95% CI, -40.66 to -9.56) (Figure 5).
There were not enough trials enrolling participants with 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 in this population.

Figure 5. Meta-analysis of left ventricular end-systolic volume comparing CRT-D with ICD alone in minimally symptomatic participants (NYHA class I–II)



Left Ventricular End-diastolic Volume/Volume Index

Four trials (reported in 7 articles) reported change in LVEDV.[6, 7, 31, 36, 37, 42, 53] In the MADIT-CRT trial, there was a significant decrease in LVEDV in the CRT-D arm compared with the ICD arm alone (52 ml vs. 15 ml, p<0.001).[6]

In an analysis from the RAFT trial, grouped by bundle branch block morphology,[44] participants with an LBBB had a significant reduction in LVEDV compared with an ICD alone (56.7±34.1 ml vs. 14.8±14.5 ml, p<0.01). Participants with a non-LBBB morphology (RBBB and NSIVCD grouped together), derived a significant reduction in LVEDV with CRT-D compared with ICD alone (41.0±28.13 ml vs. 14.4±14.2 ml, p<0.01).

In an analysis from MADIT-CRT, stratified by cardiomyopathy subtype, participants with both ICM and NICM demonstrated reductions in LVEDV with CRT-D versus an ICD alone compared with baseline (-18% vs. -5% and -24% vs. -7%, respectively).[31]

In the MIRACLE-ICD trial, the median change in LVEDV in the ICD (CRT-off) arm was -5.7 ml (with a range from -16.2 to 1.8) compared with -19.9 ml (with a range from -39.7 to -6.3) in the CRT-D arm (p=0.06).[7] In the MIRACLE-ICD II trial, the mean change in LVEDV in the CRT-D arm compared with ICD (CRT-off) arm was -42ml vs. -16ml, respectively, p=0.04.[42]

In the study by Pinter et al. (2009), the mean change in the CRT-D arm was -16±44 ml vs. -13±47 ml in the ICD (CRT-off) arm, a change which was not statistically significant.[53]

The MADIT-CRT trial also reported changes in LVEDV indexed to body surface area (LVESDi).[6, 35] At 12-month followup, participants receiving CRT-D derived a greater reduction in LVEDVi compared with participants receiving an ICD alone (-26.2±16.5 vs. -7.4±7.2, p=0.0001).[35] In an analysis from MADIT-CRT, both women and men derived reductions in LVEDVi compared with an ICD alone (ml/body surface area) (-29 vs. -9 and -22 vs. -7, respectively, p<0.001).[30]

The trials were consistent in demonstrating a reduction in LVEDV with CRT-D compared with an ICD alone. This effect existed across multiple subgroups regardless of QRS morphologies, cardiomyopathy subtype, and sex. However, given differences in NYHA class in participants included in these trials, there were not enough trials enrolling participants of similar NYHA class to perform a meta-analysis.

Left Ventricular Ejection Fraction

Six trials (reported in 9 articles) reported change in LVEF.[6, 7, 30, 31, 37, 42, 48, 50, 53] In the MADIT-CRT trial, there was a significant improvement in LVEF in the CRT-D arm compared with 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 with an ICD alone, although the magnitude was significantly greater in women.[30]

In another analysis from MADIT-CRT (stratified by QRS morphology), participants with an LBBB morphology had significant improvement in LVEF (3.4% in the ICD arm compared with 11.9% in the CRT-D arm, p<0.01).[37] The analysis grouped RBBB and NSIVCD participants as "non-LBBB." This cohort similarly showed an improvement in LVEF with CRT-D compared with ICD alone (8.8% vs. 3.4%, p<0.01).[37] The improvement in LVEF was larger in participants with LBBB compared with non-LBBB. In subgroup analyses (stratified by cardiomyopathy subtype), participants with both ICM and NICM showed improvement in LVEF with CRT-D compared with an ICD alone (10.5% vs. 3% and 12% vs. 3%, respectively).[31]

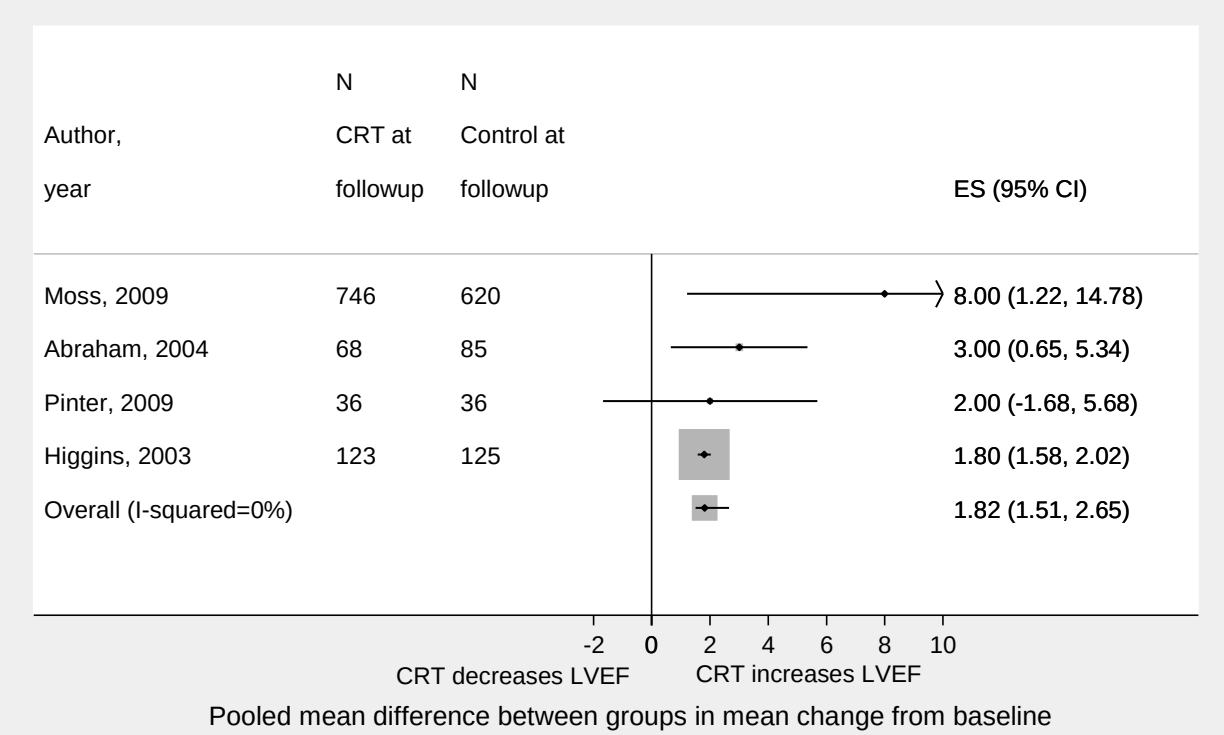
In the MIRACLE-ICD trial, the median change in LVEF was 2.1 percent in the CRT-D arm (95% CI, 0.12 to 4.1) compared with 1.7 percent in the ICD (CRT-off) arm (95% CI, 0.7 to 2.4, p=0.12).[7] In the MIRACLE-ICD II trial, the mean change in LVEF was 3.8 percent in the CRT-D arm compared with 0.8 percent in the ICD (CRT-off) arm (p=0.02).[42]

In the trial by Higgins et al. (2003), the mean change in LVEF was 5.1 percent ±0.7 in CRT-D participants compared with 2.8 percent ±0.7 in the ICD (CRT-off) arm (p=0.02).[50] In the trial by Pinter et al. (2009), the change in LVEF was 3.9 percent ±8.9 in the CRT-D arm versus 1.9 percent ±6.8 in the ICD (CRT-off) arm, which was not statistically different.[53]

In the very small study by Diab et al. (2011) with 43 participants, the change in LVEF was dichotomized into improvement ≥15 percent from baseline.[48] The study made a comparison between CRT-D and ICD alone in participants who lacked baseline dyssynchrony. The proportion of participants demonstrating >15 percent improvement in LVEF was greater in the CRT-D arm than in the ICD-alone arm (p=0.007).

The majority of studies, including the very large MADIT-CRT trial (n=1,820), consistent in demonstrating an improvement in LVEF with CRT compared with ICD alone.[6] This effect existed across multiple subgroups regardless of QRS morphologies, cardiomyopathy subtype, and sex. The study by Higgins et al. (2003) reported the changes in LVEF in the NYHA class I–II and NYHA class III–IV cohorts separately.[50] We performed a meta-analysis incorporating the four trials enrolling participants with minimally symptomatic (NYHA class I–II) 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 6). There were not enough trials enrolling participants with NYHA class III–IV status to perform meta-analysis.

Figure 6. Meta-analysis of LVEF comparing CRT-D with ICD alone in minimally symptomatic (NYHA class I–II) participants



Packer Score

Two trials reported a Packer score.[7, 42] In each trial, the score categorized participants as improved, worsened, or unchanged following CRT. In the MIRACLE-ICD trial, 42.9 percent, 23.6 percent, and 33.5 percent of participants in the ICD (CRT-off) arm were improved, unchanged, or worsened, respectively, compared with 52.4 percent, 15.0 percent, and 32.6 percent in the CRT-D arm (p=0.06).[7] In the MIRACLE-ICD II trial, 36 percent, 34 percent, and 31 percent of participants in the control arm were improved, unchanged, or worsened, respectively, compared with 58 percent, 22 percent, and 17 percent in the CRT-D arm (p=0.06).[42]

The current data suggest that CRT-D likely results in greater improvement in clinical composite score (Packer score) compared with an ICD alone. More data are needed to confirm this trend towards statistical significance.

6-Minute Hall Walk Distance

Four trials (reported in 5 articles) reported changes in 6MHWD.[7, 42, 46, 50, 53]

In the MIRACLE-ICD trial, there was no statistically significant change in median 6MHWD in the CRT-D arm compared with the ICD (CRT-off) arm (55m vs. 53m, p=0.36).[7]

In the trial by Pinter et al. (2009), there was no statistically change in 6MHWD between the CRT-D and ICD (CRT-off) arms (53.3±113.3m vs. 27.3±71.1m, p=NS).[53] 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).[50] This effect was limited to the participants with advanced CHF symptoms (NYHA class III–IV).

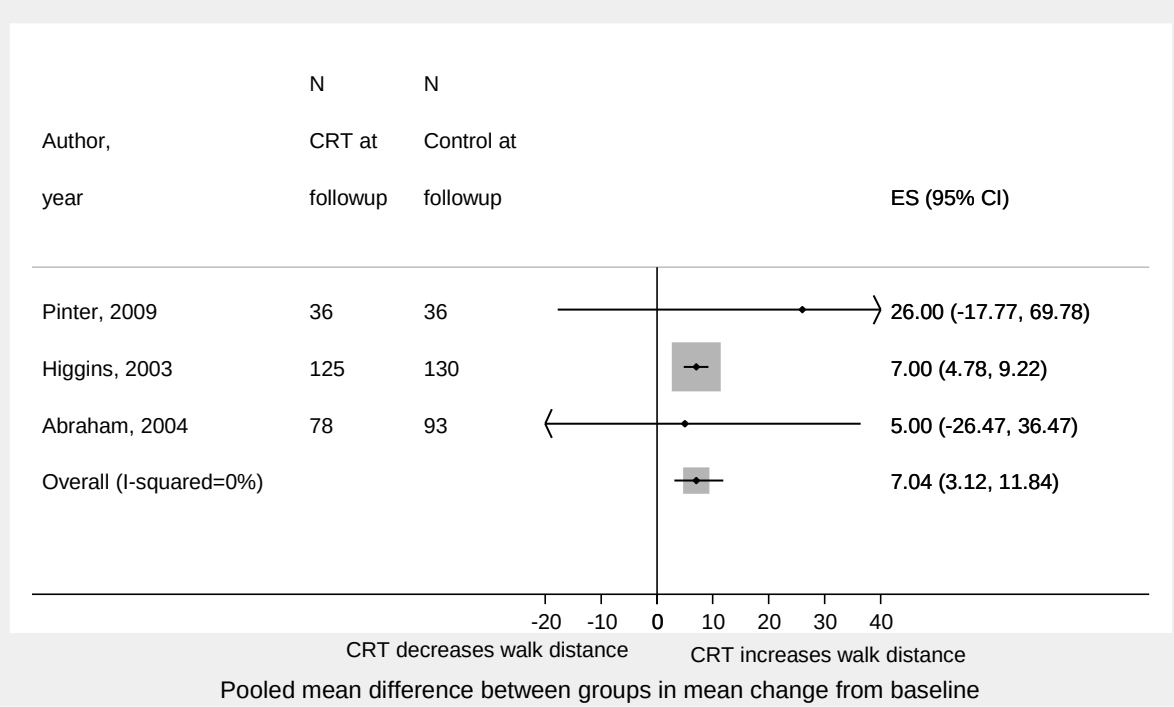
In the MIRACLE-ICD II trial, there was no difference in change in 6MHWD in the CRT-D arm compared to the ICD (CRT-off) arm (38±109m vs. 33m±98m, p=0.59).[42]

In the permanent AF cohort from the RAFT trial, there was no difference in change in 6MHWD in participants receiving CRT-D versus an ICD alone (19±84m vs. 16±76m, p=0.88).[46]

We performed a meta-analysis incorporating the three trials, which included minimally symptomatic (NYHA class I–II) participants and reported changes in 6MHWD.[42, 50, 53] In this analysis, CRT-D resulted in a significant improvement in 6MHWD compared with an ICD alone (7.04, 95% CI, 3.12 to 11.84) (Figure 7). Not enough studies of participants 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 participants 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 participants with advanced CHF.

Figure 7. Meta-analysis of 6MHWD comparing CRT- D with ICD alone in minimally symptomatic participants (NYHA I-II)



Quality of Life

Five trials (reported in 6 articles) reported QOL assessed with the MLHFQ and were not impacted by recent sub-study reports.[7, 42, 46, 48, 50, 53] We identified no studies that assessed QOL using the KCCQ. 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).[50] When divided by NYHA class I–II versus NYHA class III–IV subgroups, participants 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 participants with less symptomatic CHF (NYHA class I–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 with the ICD (CRT-off) arm [-17.5 (with a range from -21 to -14) vs. -11 (with a range from -16 to -7), p=0.02].[7]

In the very small trial by Diab et al. (2011), there was an improvement in MLHFQ score in participants receiving CRT-D with dyssynchrony present at baseline (-29), without dyssynchrony at baseline (-16), and in participants without dyssynchrony receiving an ICD alone (-8).[48] While a global p-value was presented comparing all three arms, the impact of baseline dyssynchrony makes this difficult to interpret, especially because even the ICD alone (control) arm showed improvement.

In the trial by Pinter et al. (2009), there was no statistically significant change in MLHFQ scores between participants with CRT-D compared with ICD (CRT-off) (-7.8±20.1 vs. -0.2±13.5, p=NS).[53]

In the MIRACLE-ICD II trial, there was no significant change in MLHFQ scores between those receiving CRT-D and participants in the ICD (CRT-off) arm (-13.3±25.1 vs. -10.7±21.7, p=0.49).[42]

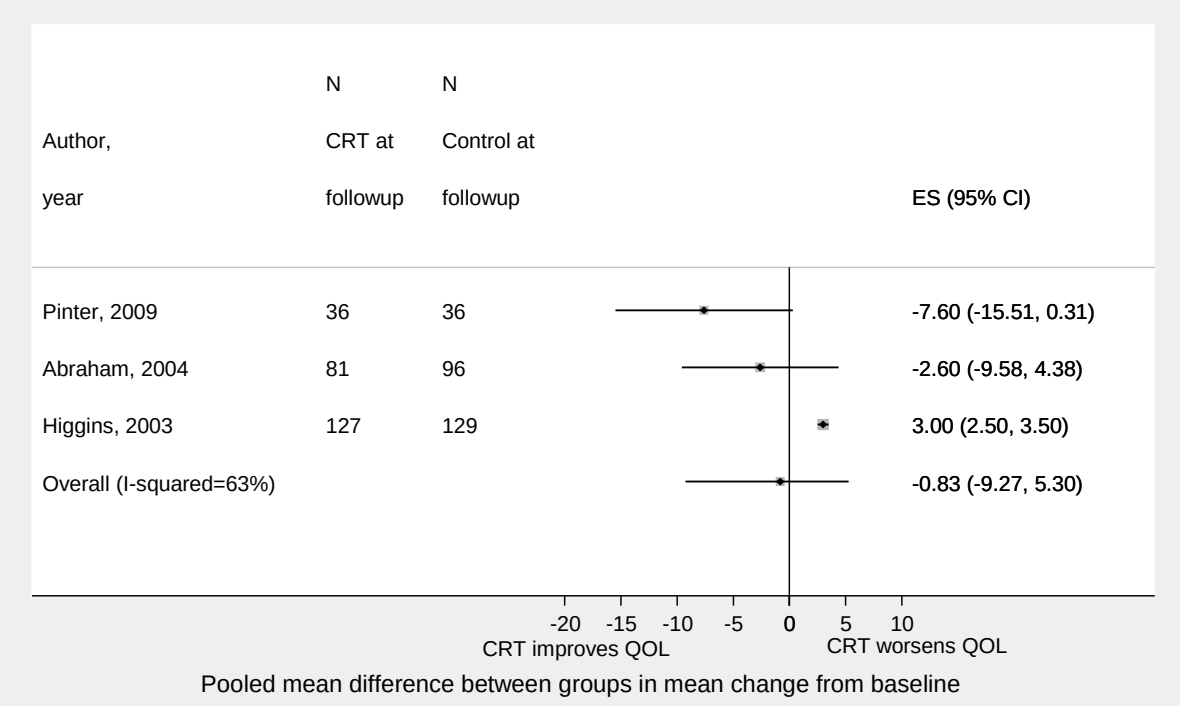
In the permanent AF subgroup from the RAFT trial, there was a non-significant improvement in MLHFQ scores with CRT-D compared with an ICD alone (-11±18 vs. -5±21, p=0.057).[46]

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 participants with CRT-D and ICD alone (CRT-off) (-5.8±14.9 vs. -5.8±13.9, p=0.02).[53]

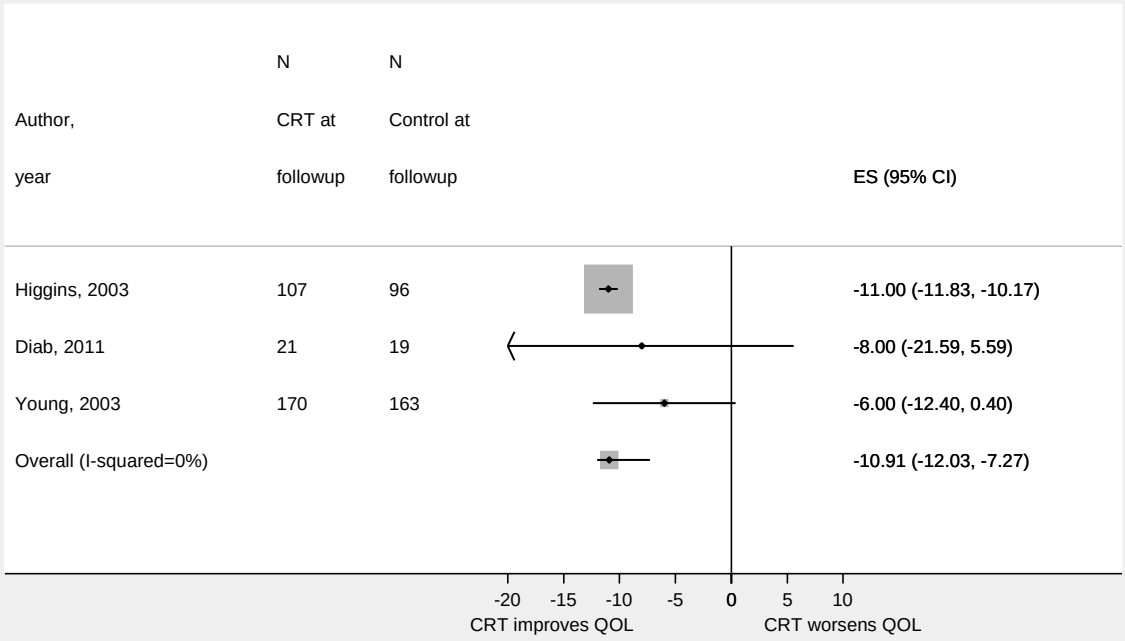
The current data suggest that CRT-D does not improve QOL in minimally symptomatic (NYHA class I–II) participants compared to an ICD alone, though the meta-analysis below should be interpreted with caution given the substantial heterogeneity as reflected in the wide confidence intervals (0.83, 95% CI, -9.27 to 5.30) (Figure 8a). The data suggest a significant improvement in QOL in participants 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 8b and Table 8).

Figures 8a and b. Meta-analysis of QOL, as measured with the MLHFQ, comparing CRT-D with ICD alone in (a) minimally symptomatic participants (NYHA class I–II) and (b) participants with advanced heart failure (NYHA class III–IV)

8a. Meta-analysis NYHA class I–II



8b. Meta-analysis NYHA class III–IV



Pooled mean difference between groups in mean change from baseline

Summary of Findings for Specific Subgroups of Interest

In this update, we identified three additional analyses of MADIT-CRT providing information on the pre-specified subgroups of interest.[32, 33, 56] To avoid "double counting" patient populations in regards to the same endpoints we focused on the largest analyses or subgroup studies identified in the prior report or in our update (Table 7).

Two trials[5, 6] demonstrated benefit for participants with LBBB morphology with CRT-D compared with ICD alone in the outcomes of heart failure hospitalization and total mortality. These same studies demonstrated no benefit, and potential harm, from CRT-D compared with ICD alone in participants with non-LBBB morphology in the outcomes of heart failure hospitalization and total mortality.

Two sub-studies of MADIT-CRT from this update[32, 33] confirmed no benefit from CRT-D compared with ICD alone in participants with non-LBBB morphology, regardless of QRS duration. One of these studies did demonstrate benefit for those participants with a non-LBBB morphology *and* first-degree AV block (electrocardiographic PR interval ≥230 ms) owing to significant reductions in heart failure hospitalization and total mortality. However, the validity of this observation is limited by the small size of the subgroup with first-degree AV block examined (< 100 participants).

Two large trials[5, 6] demonstrated benefit from CRT-D compared with ICD alone in women for the outcomes of heart failure hospitalization and total mortality. Furthermore, one sub-study in this update of MADIT-CRT[56] confirmed benefit from CRT-D compared with ICD alone in women with LBBB morphology, regardless of QRS duration.

Moss et al.[6] and Tang et al.[5] demonstrated benefit from CRT-D compared with ICD alone in both participants with ICM and NICM for the combined outcome of heart failure hospitalization and total mortality.

The same two trials demonstrated benefit from CRT-D compared with ICD alone in participants both <65 years of age and ≥65 years of age for the combined outcome of heart failure hospitalization or total mortality.[5, 6] Post-hoc sub-group analysis from one trial further stratified age comparisons in participants <60 years of age, 60 to 74 years of age, and ≥75 years of age, with significant reduction in heart failure hospitalizations in all age categories but a mortality benefit only in the 60 to 74 years of age category. However, the validity of this observation is limited by the substantial size differences in the groups (i.e., the majority of participants were 60 to 74 years of age) and the unexplained rationale for the age categories used.

As in our prior report, the evidence suggests that LBBB morphology (vs. non-LBBB morphology), NICM (vs. ICM), and female sex (vs. male sex) are generally associated with improved outcomes following CRT-D.

Table 7. Summary of CRT-D effectiveness outcomes reported by subgroup

Gender (no. of trial)	Age (no. of trial)	LVEF (no. of trial)	NYHA class (no. of trial)	LBBB (no. of trial)	QRS duration >150 ms (no. of trial)	Non-ischemic cardiac conditions /Cardiomyopathy subtype (no. of trial)	AF (no. of trial)
All-cause mortality							
2 trials Beneficial in women	2 trials	NR	NR	2 trials Beneficial in LBBB	NR	1 trial No difference in survival	1 trial No difference in survival
Hospitalizations for heart failure							
2 trials Beneficial in women	2 trials	NR	NR	2 trials Beneficial in LBBB participants	NR	1 trial Beneficial in NICM participants	1 trial Beneficial in participants with AF
Quality of Life							
NR	NR	NR	NR	NR	NR	NR	1 trial No difference in outcome
6-minute hall walk distance							
NR	NR	NR	NR	NR	NR	NR	1 trial No difference in outcome
Left ventricular ejection fraction							
1 trial Beneficial in women	NR	NR	NR	1 trial Beneficial in LBBB participants	NR	1 trial Beneficial in NICM participants	NR
Left ventricular end-diastolic volume/volume index							
1 trial Beneficial in women	NR	NR	NR	1 trial Beneficial in LBBB participants	NR	1 trial Beneficial in NICM participants	NR
Packer score							
NR	NR	NR	NR	NR	NR	NR	NR

CRT-D=cardiac resynchronization therapy with defibrillator; LBBB=left bundle branch block; NR=not reported; NICM=non-ischemic cardiomyopathy

Table 8. Strength of evidence for key effectiveness outcomes of CRT-D

Key outcomes	No. Studies (number of participants)	Study limitations	Directness	Consistency	Precision	Reporting bias	Strength of evidence Finding
All-cause mortality	7 (5812)	Low	Direct	Inconsistent	Precise	Undetected	Moderate CRT-D improves mortality in participants with minimally symptomatic CHF (primarily class NYHA class II) compared with ICD alone. There is insufficient evidence to determine the effect on mortality of CRT-D compared with an ICD alone in patients with NYHA class III-IV symptoms.
Heart failure hospitalizations	6 (4736)	Low	Direct	Consistent	Precise	Undetected	High Reduction in HF events for CRT-D compared with an ICD alone, primarily in participants with an LBBB morphology.
MLHFQ	5 (2895)	Low	Direct	Inconsistent	Precise	Selective outcome reporting (not reported in main RAFT cohort)	High CRT-D compared with ICD alone improves QOL in participants with NYHA class III-IV CHF [mean difference -10.91 (95% CI, -12.03 to 7.27)]. However, CRT-D does not improve QOL in minimally symptomatic participants compared with an ICD alone [mean difference -0.83 (95% CI, -9.27 to 5.30)].

CHF=chronic heart failure; CRT-D=cardiac resynchronization therapy with defibrillator; ICD=implantable cardioverter defibrillator; LBBB=left bundle brunch block; NYHA=New York Heart Association; QOL=quality of life

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

Key Points

- In this update, no significant and consistent differences were seen in pneumothorax, pocket hematomas, device infection, ventricular arrhythmias, inappropriate shocks, or cardiac perforation/tamponade when CRT-D and ICD devices were compared. Additional study is needed for length of hospitalization and death within 7 days of device implantation.
- Studies suggest a potential increase in the number of procedural complications and LV lead dislodgement within 24 hours of implantation for CRT-D compared with ICD devices.
- CRT-D devices may confer protection against first VA. However, given the limited number of studies, heterogeneous study design, variable definitions of the harms, and overall low rate of complications, we could not made a definitive conclusion.

Study Characteristics

Forty-one studies, 23 from the prior review and 18 from the update (presented in 44 articles) reported on the harms of CRT-D[6, 7, 34, 38, 39, 42, 45, 50, 53, 57-91] There were 11 RCTs, three identified in the update (reported in eleven articles)[6, 7, 34, 38, 39, 42, 45, 50, 53, 80, 92] and the rest were prospective or retrospective cohorts along with subset analyses of the RCTs. The largest study enrolled 11,345[87] participants per study arm and the smallest enrolled 34,[74] both of which were cohort studies. Planned followup ranged from 30 days[6, 38] to 9 years.[76] Sixteen studies were industry-supported.[6, 7, 34, 42, 45, 53, 57, 60, 64, 75, 82, 85, 86, 88, 90] Two studies were supported by grants from AHRQ.[70, 89] In the update, three studies were supported by non-profit organizations: one by the American College of Cardiology,[83, 87] one by the Heart and Stroke Foundation of Canada,[80], and one by the Canadian Institutes of Health Research.[90]. An additional study was supported by a grant from the Chinese Central Guidance for Local Science and Technology Development.[91] The remaining studies did not report their funding source or reported that they received no external funding.

Population Characteristics

The percentage of women in the studies ranged from eight percent [90] (overall) to 49 percent[78] per study arm. The mean age ranged from 58 years of age in the primary ICD arm of the study by Looi et al.[76] to 83 years of age in the study by Adelstein et al. (2016)[88] (a study comparing participants above and below 80 years old). Three studies did not report the mean age.[61, 79, 82] Eight studies reported racial distribution of participants, ranging from 54.7 percent[76] to 100 percent[82] white (separated by race) per study arm.[6, 34, 76,13563, 82, 83, 85, 89]

Thirty-four studies reported the proportion of patients with ICM, ranging from 22 percent to 79 percent per study arm.[6, 7, 38, 39, 42, 45, 50, 53, 58, 60-62, 65-67, 69-73, 75-77, 79-81, 83, 84, 86-91] Nine studies did not report on the proportion with ICM.[34, 57, 59, 63, 64, 74, 78, 82, 85] The proportion of patients with AF ranged from 5 percent[82] to 100 percent[89] (a study of AF and heart failure) per study arm. Eighteen studies did not report the proportion of patients with AF.[7, 34, 42, 50, 58, 61, 62, 65, 69, 71, 72, 76-79, 84, 85 , 91]

The proportion of patients in NYHA class IV per study arm ranged from 1.6 percent[66] to 30.5 percent[91]. The proportion of patients in NYHA class III ranged from 11.9 percent[76] to 95

percent[83]. The proportion of patients in NYHA class II ranged from 2.9 percent[84] (overall) to 100 percent.[42] The proportion of patients in NYHA class I ranged from 0 percent[88, 91] to 34.2 percent.[76] Eleven studies did not report the breakdown of NYHA class of participants. [6, 34, 60, 61, 69, 71, 74, 75, 77, 78,13491] Three studies had participants of all NYHA classifications represented.[84, 87, 89]

The mean LVEF per study arm ranged from 20 percent[68] to 32.1 percent[61]. Four studies did not report the mean LVEF.[45, 50, 58, 65] The proportion of participants with LBBB per study arm ranged from 10.8 percent[76] to 94 percent[58]. Sixteen studies did not report on the proportion of participants with LBBB.[7, 42, 53, 60-65, 69, 71, 73, 77, 79, 84, 86]

The mean QRS interval ranged from 125.2 ms[61] to 175.1 ms.[76] Fourteen studies did not report the mean QRS interval.[6, 34, 53, 62, 63, 65, 66, 68, 71, 82-84, 87, 88]. In the update, some studies reported a median QRS duration,[88] or QRS duration as a categorical variable with various cut points such as 120-129 ms, 130-149 ms, or 150 ms or greater[87], or intervals of 10 ms from 120 ms to 170 ms.[83]

The mean creatinine ranged from 1.05mg/dL to 1.4mg/dL.[78, 89] Thirty-two studies did not report mean creatinine.[7, 42, 45, 50, 58-65, 67, 69, 71, 72, 74, 76, 77, 79-88, 90, 91, 93] Renal function was also reported as glomerular filtration rate (GFR),[75, 76, 82, 86, 88] chronic kidney disease (CKD) stages,[83] categorical ranges of creatinine such as <1.5mg/dL, 1.5-2mg/dL, and >2mg/dL,[89] "renal dysfunction,"[79], "renal failure,"[91] or dialysis.[83, 87, 89]

Overall, the patient populations were generally homogenous, with the major exception being NYHA class which varied considerably across studies. In the update, race and measures of renal function were more likely to be reported. A wide range of interventricular delay was reported in participants, and QRS duration and renal function were sometimes included as categorical variables.

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 secondary analyses[6, 38, 39] 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 9 and Table 9).

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.[62] In the study by Nian-sang et al. (2010), the average age was 57 years, the mean LVEF was 32.1 percent, and the mean QRS duration was 125.2 ms.[61] In the study by Bossard et al. (2014), NICM represented 73 percent of the cohort.[58] Almost all studies ascertained exposure via medical record review. Significant differences in the comparability of the cohorts made the overall risk of bias high for several studies.[79, 86] Overall, the risk of bias in the included cohort studies is moderate (Figure 10 and Table 10).

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

Table 9. 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[34] Moss, 2009[6] Jamerson, 2014[38] Ruwald, 2014[39] Sabbag, 2016[82]	?	?	+	+	-	-	-	-	-
MIRACLE-ICD									
Young, 2003[7]	-	-	-	-	-	-	-	-	-
MIRACLE-ICD II									
Abraham, 2004[42]	?	-	-	-	-	-	-	-	-
RAFT									
Gilis, 2014[45] Sapp, 2017[80] Essebag, 2015[90]	?	-	-	-	-	-	-	-	-
Other trials									
Higgins, 2003[50]	?	-	-	-	-	-	-	-	-
Pinter, 2009[53]	?	-	-	-	-	-	-	-	-

+=high; -=low; ?=unclear; MADIT CRT Trial= Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy; MIRACLE=Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD II=Multicenter InSync ICD Randomized Clinical Evaluation II; RAFT= Resynchronization–Defibrillation for Ambulatory Heart Failure Trial

Figure 9. Summary of risk of bias for trials assessing harms of CRT-D

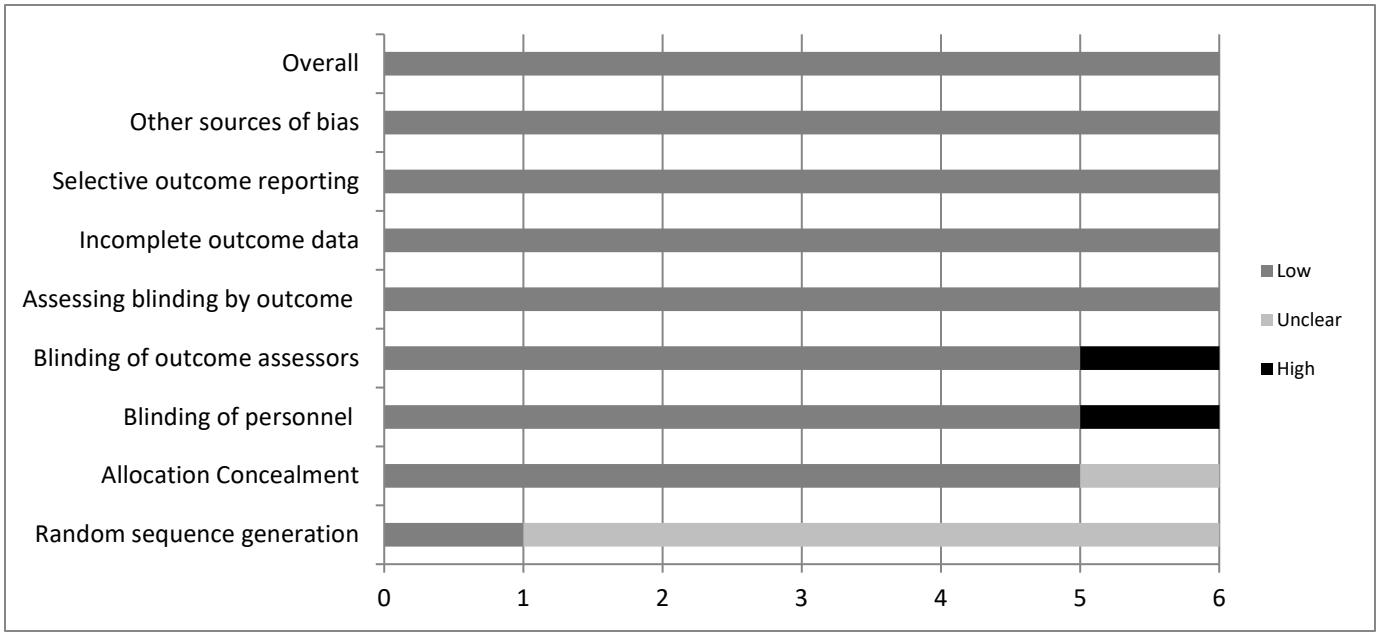


Table 10. Summary of risk of bias for cohort studies assessing harms of CRT-D

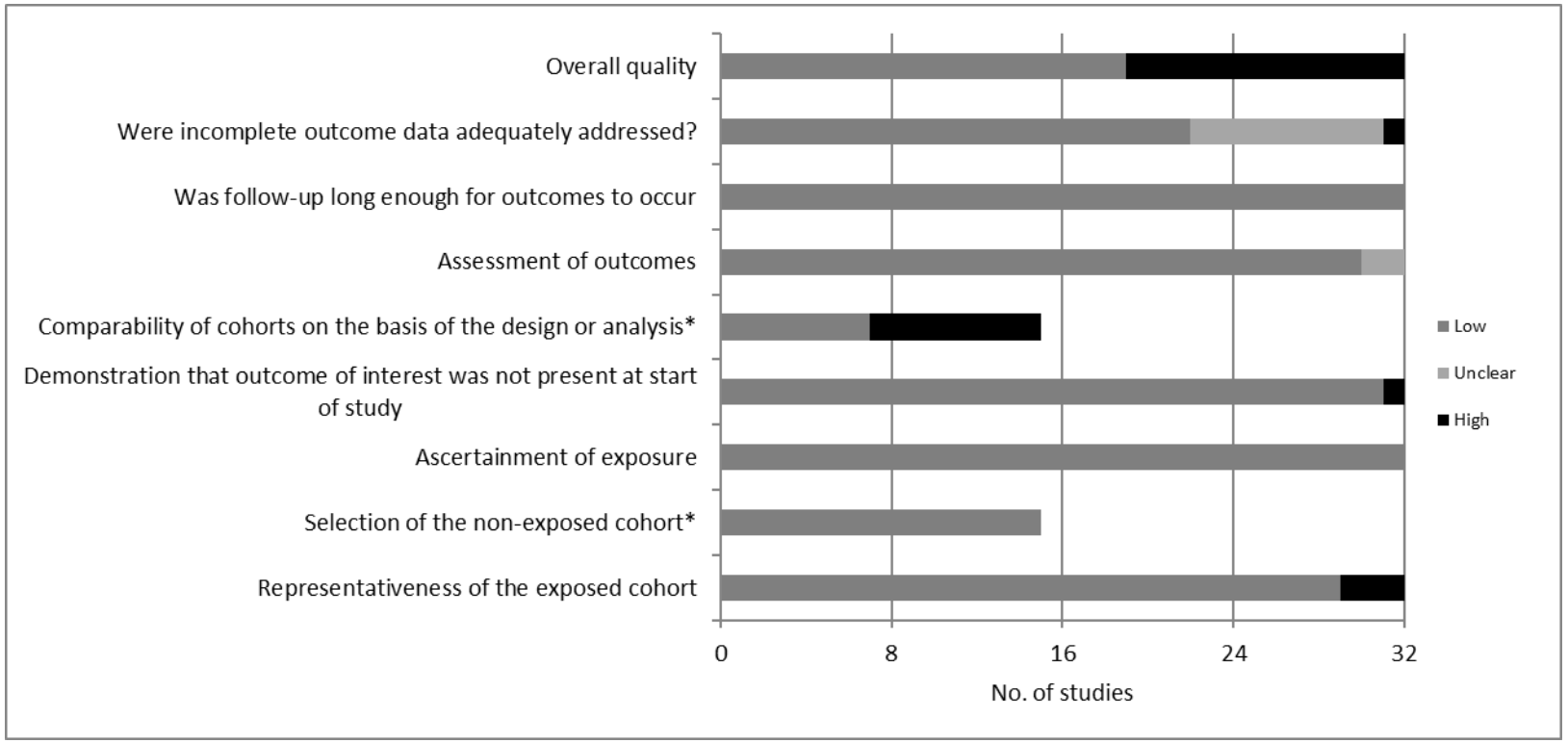
Author, year	Representativeness of the exposed cohort	Selection of the non-exposed cohort*	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis*	Assessment of outcomes	Was followup long enough for outcomes to occur	Were incomplete outcome data adequately addressed?	Overall quality
Adelstein, 2016[88]	-		-	-		-	-	?	+
Auricchio, 2014[57]	-		-	-		-	-	-	-
Biton, 2018[75]	-	-	-	-	+	-	-	?	+
Bossard, 2014[58]	+		-	-		-	-	-	+
Boven, 2013[66]	-		-	-		-	-	-	-
Boven, 2013[68]	-		-	-		-	-	-	-
Crossley, 2015[85]	-		-	-		-	-	?	-
Duray, 2008[65]	-		-	-		-	-	-	-
Echouffo-Tcheugui, 2016[87]	-	-	-	-	-	-	-	-	-
Friedman, 2015[83]	-	-	-	-	+	-	-	?	+
Gasparini, 2009[64]	-	-	-	-	-	?	-	-	-
Gopalamurugan, 2014[71]	-	-	-	-	-	-	-	-	-
Haugaa, 2014[69]	-		-	-		?	-	-	-
Hoke, 2014[86]	-	-	-	-	+	-	-	?	+
Khazanie, 2016[89]	-	-	-	-	+	-	-	?	+
Killu, 2017[78]	-	-	-	-	+	-	-	-	+

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
Knight, 2004[59]	-		-	-		-	-	-	-
Kronborg, 2018[77]	-	-	-	-	+	-	-	-	+
Kuhlkamp, 2002[67]	-		-	+		-	-	+	-
Landolina, 2011[60]	-		-	-		-	-	-	-
Looi, 2017[76]	-	-	-	-	+	-	-	-	+
Masoudi, 2014[70]	-	-	-	-	-	-	-	-	-
Nian-Sang, 2010[61]	+		-	-		-	-	-	+
Ricci, 2014[73]	-		-	-		-	-	-	-
Sardu, 2017[79]	-	-	-	-	+	-	-	?	+
Steffel, 2015, [84]	-		-	-		-	-	-	-
Strimel, 2011[62]	+		-	-		-	-	-	+
Su, 2018 [91]	-	-	-	-		-	-	-	-
Theuns, 2005[63]	-		-	-		-	-	?	-
Vado, 2013[72]	-		-	-		-	-	-	-
Ziacchi, 2018[74]	-	-	-	-	-	-	-	?	+
Zue, 2016[81]	-	-	-	-	-	-	-	-	-

+=high; -=low; ?=unclear

*Only applicable to studies with control groups

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



* Only applicable to studies with control groups.

Table 11. 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 1 week
RCTs										
MADIT-CRT										
Moss, 2009[6]			X	X	X					
Ouellet, 2012[34]								X		
Jamerson, 2014[38]			X	X	X	X	X	X		
Ruwald, 2014[39]								X	X	
Biton, 2018[75]								X		
Sabbag, 2016[82]								X		
MIRACLE-ICD										
Young, 2003[7]			X			X		X	X	
MIRACLE-ICD II										
Abraham, 2004[42]						X	X	X	X	
RAFT										
Gilis, 2014[45]	X	X		X	X	X			X	
Essebag, 2015, 14782	X		X	X	X	X	X			
Sapp, 2017[80]								X		
OTHER TRIALS										
Pinter,2009[53]								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 1 week
Higgins,2003[50]								X		
Kronborg, 2018[77]								X	X	
Steffel, 2015[84]	X									
Crossley, 2015[85]							X			
COHORT STUDIES										
Auricchio, 2014[57]			X	X	X		X			
Duray,2008[65]			X	X	X	X				X
Gasparini, 2009[64]								X		
Knight,2004[59]					X					
Kuelkamp, 2002[67]			X	X	X	X	X			
Landolina, 2011[60]					X					
Theuns,2005[63]								X		
Bossard,2014[58]							X	X		
Massoudi, 2014[70]	X				X					
Gopalamurugan,2014[71]								X		
Ricci, 2014[73]								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 1 week
Haugaa,2014[69]								X		
Vado,2014[72]							X			
Nian-Sang,2010[61]								X		
Strimel, 2011[62]						X	X		X	X
Van Boven,2012[68]								X	X	
Van Boven,2013[66]									X	
Adelstein, 2016[88]			X	X	X	X	X		X	X
friedman, 2015[83]	X		X	X	X	X				X
Hoke, 2014[86]	X		X	X	X	X	X			
Looi, 2017[76]	X			X	X	X	X	X		
Zue, 2016[81]								X		
Ziacchi, 2018[74]					X		X			
Killu, 2017[78]									X	
Echouffo-Tcheugui, 2016[87]	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 1 week
Su, 2018[91]								X	X	
Khazanie, 2016[89]	X									
Sardu, 2017[79]								X		

MADIT CRT Trial= Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy; MIRACLE=Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD II=Multicenter InSync ICD Randomized Clinical Evaluation II; RAFT= Resynchronization–Defibrillation for Ambulatory Heart Failure Trial; RCTs=randomized controlled trials

Harms Outcomes

A list of harms reported in the included studies is shown in Table 11.

Procedure-related Complications

Nine studies (7 from our updated search) reported on procedure-related harms in general[45, 70, 76, 83, 84, 86, 87, 89, 90] In the RAFT trial, 147 out of 904 (16.4%) participants in the ICD group and 126 out of 894 (13.9%) participants in the CRT-D group were hospitalized for "device-related events" over the course of the study (mean followup in the ICD group was 39.2±19.4 months and mean followup in the CRT-D group was 41.2±19.6 months, p=0.031).[45] 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 participants and 2.3 percent of CRT-D participants (p=0.049) at 3 years followup.[70] In the study by Looi et al. (2017), device complications were categorized as follows from device implantation: within 24 hours (acute), 24 hours to 2 weeks (early), and 2 weeks and over (late).[76] The study found that acute complications occurred more commonly in the CRT-D group than the ICD group (6.9% vs. 1.5%; p=0.01). For early (0.9% vs. 1.5%; p=0.62) and late (5.2% versus 4.1%; p=0.64) complications, there was no significant difference for the CRT-D group compared with the ICD group. Khazanie et al. (2016) compared complications rates for those with heart failure and AF using registry and Medicare claims data.[89] The in-hospital complication rate was 4% in the CRT-D group as compared with 2% in the ICD group (p=0.08). However, by 90 days, the CRT-D group did not have a significant increase in complications compared with those with ICD alone (3.0% vs. 2.7%; p=0.41).

Essebag et al. (2015) provided data on participants receiving a *de novo* CRT-D device or an upgrade during the study and found acute complications occurred in 26.2 percent of *de novo* participants compared with 18.8 percent of upgrades (p<0.001).[90] "Minor complications," including those not requiring hospitalization or intervention, were higher in the *de novo* group, 12.9 percent versus 8.8 percent. The authors suggested that increases in operator and site experience as well as advances in the devices during the RAFT trial may account for the difference. Interestingly, Steffel et al. (2015) compared the effect of CRT itself in CRT-ON to CRT-OFF participants and found more frequent CRT-D complications in the CRT-ON group (12.31% vs. 6.76%) in patients with a QRS duration of 120-130 ms. Complications in this study were defined as events that required additional invasive surgical interventions to resolve and were related to the CRT-D system or implantation.

For specific subgroups, several studies were completed for procedure-related complications. Echouffo-Tcheugui et al. (2016) assessed the risk of device-related complications, a composite of mechanical complications requiring revision by 90 days, in participants based on diabetic status, and found no significant difference in patients with diabetes compared with patients without diabetes (OR: 0.90, 95% CI: 0.77 to 1.06; p=0.20).[87] Friedman et al. (2015) compared ICD to CRT-D in participants with moderate to severe CKD and found no significant difference in the in-hospital (5.8% vs. 6.0% ; p=0.51), 30-day (4.7% vs. 5.0%; p=0.57), and 90-day (0.4% vs. 0.3% ; p=0.84) complications, respectively.[83] Hoke et al. (2014) compared complications in participants over and under 75 years of age, within 24 hours and between 24 hours to 30 days.[86] They found those 75 years of age and over had similar 24 hour (3.4% vs. 2.7%; p=0.552) and monthly (2.4% vs. 2.5%; p=0.984) adverse events to those under 75 years of age.

In general, complications are slightly more common with a CRT-D device compared with an ICD alone, especially within the first 24 hours.

Length of Hospital Stay

Only one study reported length of hospital stay.[45] 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 days vs. 14,896 days).[45] 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 days; p= 0.005). Further studies are needed to confirm this finding.

Pneumothorax

Ten studies[6, 7, 38, 57, 65, 67, 83, 86, 88, 90] (4 from an updated search) reported on the incidence of pneumothorax, two compared rates in participants receiving a CRT-D device with those receiving an ICD alone[6, 83] and two examined rates in the elderly.[86, 88]

The incidence of pneumothorax among patients receiving a CRT-D device ranged from 0 percent to 2.8 percent. In the MADIT-CRT trial, pneumothorax was slightly more common in patients receiving a CRT-D device (1.7%) compared with an ICD alone (0.85%).[6] Men had a lower incidence of pneumothorax or hemothorax compared with women (0.9% vs. 3.3%; p<0.001).[38] In the moderate-sized MIRACLE-ICD trial, there was an incidence of pneumothorax or hemothorax of 0.8 percent, but the study did not break down the incidence of pneumothorax further.[7]. In the study by Essebag et al. (2014), no pneumothorax was reported in participants in the RAFT trial who were upgraded to CRT after presentation of the RAFT trial results.[90] Friedman et al. (2016) examined the incidence of pneumothorax/hemothorax in moderate-to-severe renal disease participants (CKD stages 3-5) at both initial hospitalization and within 30 days.[83]. They found that CRT-D compared with ICD did not result in a statistically significant increased risk of pneumothorax/hemothorax at index hospitalization (0.9% vs. 1.1% respectively; p=0.54) or within 30 days (1.1% vs. 1.2% respectively; p=0.51).

In the older population, according to the study by Hoke et al. (2014), those 75 years of age and older experienced similar rates of pneumothorax compared with those younger than 75 years of age (1.4% vs. 0.5% respectively; p=0.158).[86] Similarly, in the study by Adelstein et al. (2016), there were similar rates of pneumothorax in those 80 years of age and older compared with the younger cohort (0% vs. 0.7%, respectively).[88]

Pneumothorax is an uncommon complication of CRT-D device implant. The incidence of pneumothorax appears to be similar in individuals receiving a CRT-D device compared with an ICD alone.

Pocket Hematoma

Eleven studies (5 from the updated search) reported on the incidence of pocket hematoma.[6, 38, 45, 57, 65, 67, 76, 83, 86, 88, 90] Four studies directly compared CRT-D with ICD alone, including two from the updated search.[6, 45, 76, 83] Overall, the incidence of pocket hematoma in patients receiving a CRT-D device ranged from 0 percent[90] to 3.2 percent[83].

In the studies by Gills et al. (2014)[45] and Moss et al. (2009),[6] the incidence of pocket hematoma in patients receiving a CRT-D 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). In a study of participants with moderate-to-severe chronic kidney disease, Friedman et al. (2015)

found that, in those with CRT-D compared with ICD, similar incidence of hematomas occurred within the index hospitalization (2.5% vs. 2.3%; p=0.23) and at 30 days (3.2% vs. 3.0%; p=0.53).[83] Looi et al. (2017) found that by 2 weeks followup, the incidence of pocket hematoma in CRT-D and ICD participants was low and similar (0% vs. 0.7%; no p-value reported).[76]

Two new studies from the updated search examined the incidence of hematoma based on age. Adelstein et al. (2016) found that hematomas requiring evacuation occurred at similar rates for those 80 years of age and older compared with younger participants (0.8% vs. 0.9%).[88]. Similarly, Hoke et al. (2014), comparing those 75 years of age and older with younger participants, found no statistically significant difference in incidence of hematoma within 24 hours (1% vs. 0.3%; p=0.250) and within 30 days (0.5% vs. 0.2%; p=0.418).[86] In the study by Essebag et al. (2014), no hematoma requiring intervention was reported in participants in the RAFT trial who were upgraded to CRT after presentation of the RAFT trial results.[90]

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 similar in patients receiving CRT-D and ICD devices.

Device Infection

Fifteen studies (6 from an updated search) reported on the incidence of device infections.[6, 38, 45, 57, 59, 60, 65, 67, 70, 74, 76, 83, 86, 88, 90] Six articles compared infection rates between a CRT-D and an ICD-alone arm. [6, 38, 45, 70, 76, 83]

The other studies were cohorts of CRT-D patients only. The rate of CRT-D device infections ranged from 0 percent[90] to 3.7 percent[88] over a highly variable followup time. At 30 days, both the RAFT[45] and MADIT-CRT[6] trials showed a slightly higher incidence of device infection with CRT-D compared with 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 with men (2.0% vs. 0.8%; p=0.019).[38] In the study by Massoudi et al. (2014), there was a higher incidence of device infection in the CRT-D arm (1.9%) compared with the ICD arm (1.0%) (p=0.002).[70]

From the updated search, two studies directly compared the infection incidence of the devices. In a study by Looi et al. (2017), of participants undergoing primary prevention ICD/CRT-D implantation, after 2 weeks of followup, the incidence of pocket infections was similar for CRT-D (0.9%) and ICD (1.5%) (p=0.62).[76] Similarly, in participants with moderate-to-severe kidney disease, by 90 days followup, device-related infections were similar for the CRT-D (0.3%) and ICD (0.4%) cohorts (p=0.84).[83]

Additional studies from the updated search assessed incidence of infection based on participant age, device upgrade, or LV lead type. Adelstein et al. (2016) found that device infection requiring explantation occurred at lower, but not statistically significant, rates for those 80 years of age and older compared with younger participants (2.3% vs. 3.7%; p≥0.05).[88] Similarly, Hoke et al. (2014), comparing those 75 years of age and older with younger participants, found no statistically significant difference in incidence of device infections/explantations within 30 days (0.5% vs. 0.5%; p=0.995).[86] In the study by Essebag et al. (2014), no pocket infection requiring intervention was reported in participants in the RAFT trial who were upgraded to CRT after presentation of the RAFT trial results.[90] These authors further divided infections into those requiring surgery, IV antibiotics, or oral antibiotics (although none occurred in the device upgrade group). The study by Ziacchi et al. (2018) compared LV bipolar, quadripolar, and active fixation leads.[74] Defining infection as requiring device removal within 12 months of followup, the authors found no significant difference in the

incidence of infection between bipolar (0.7%), quadripolar (1%) and active fixation (0%) LV leads (p=0.84).[74]

Device infection is an uncommon complication of CRT-D device implantation. The incidence of device infection appears similar in participants receiving a CRT-D device compared with an ICD alone.

Cardiac Perforation/Tamponade

Twelve studies (5 from the updated search) reported on cardiac perforation/tamponade.[7, 38, 42, 45, 62, 65, 67, 76, 83, 86, 88, 94] Five studies compared the incidence of cardiac perforation/tamponade in patients receiving CRT-D versus an ICD alone.[38, 45, 62, 76, 83] In the study by Gillis et al. (2014), the incidence of cardiac perforation/tamponade was the same (0.1%) in participants receiving CRT-D versus an ICD alone.[45] In the study by Strimel et al. (2011), one patient had perforation/tamponade in the CRT-D cohort compared with no patients in the ICD-alone cohort.[62] 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 percent and 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.[67]

From the updated search, we identified two new studies which directly compared the cardiac perforation/tamponade incidence between devices. In a study by Looi et al. (2017), of participants undergoing primary prevention ICD/CRT-D implantation, the incidence of cardiac tamponade within 24 hours of implantation was not statistically significantly different for CRT-D (0.9%) and ICD (0.4%) devices (p=0.28).[76] In a study of participants with moderate-to-severe chronic kidney disease, Friedman et al. (2015) found that in those with CRT-D compared with ICD, similar incidence of cardiac tamponade or pericardial effusion requiring pericardiocentesis (combined adverse event) occurred within the index hospitalization (0.6% vs. 0.9%; p=0.10) and by 30 days (0.9% vs. 1.1%; p=0.07).[83]

Additional studies from the updated search assessed incidence of cardiac perforation/tamponade based on participant age and device upgrade. Adelstein et al. (2016) distinguished between cardiac perforation and pericardial effusion with tamponade.[88] The authors found similar incidence of cardiac perforation and pericardial effusion with tamponade for those 80 years of age and older compared with younger participants (perforation: 0.4% vs. 0.5%; p≥0.05) (tamponade: 0.4% vs. 0%; p≥0.05).[88] Similarly, Hoke et al. (2014), comparing those 75 years of age and older with younger participants, found no statistically significant difference in incidence of coronary sinus dissection, lead perforation, or pericardial effusion (reported as a single adverse event category) within 24 hours of implantation (0.5% vs. 0.2%; p=0.563).[86] In the study by Essebag et al. (2014), no cardiac tamponade or coronary sinus dissection occurred in participants in the RAFT trial who were upgraded to CRT after presentation of the RAFT trial results.[90]

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 with an ICD alone.

Lead Dislodgement

Thirteen studies (6 from an updated search) reported on the incidence of lead dislodgement.[38, 42, 57, 58, 62, 67, 72, 74, 76, 85, 86, 88, 90] Two studies compared the incidence of lead

dislodgement in participants with a CRT-D with those with ICD alone.[62, 76] In the study by Strimel et al. (2011), one participant with CRT-D and one with a dual-lead ICD experienced a lead dislodgement over a mean followup of 34 months.[62] In the study by Looi et al. (2017), there were more lead dislodgments in the CRT-D (5.2%) compared with the ICD (1.5%) cohort within 24 hours of device implantation (p=0.02).[76] After 24 hours but less than 2 weeks from device implantation, however, there was no statistically significant difference in lead dislodgement between the CRT-D (0.9%) and ICD (0.7%) cohorts (p=0.9). After 2 weeks or more post-implantation, Looi et al. (2017) reported no significant difference in "lead issues" between the CRT-D (4.3%) and ICD (2.2%) cohorts (p=0.38).[76]

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 remaining studies were cohorts containing patients with CRT-D devices only. The incidence of lead dislodgement ranged from 0 percent to 15 percent.[74] Of note, from MADIT-CRT, there was no difference in the incidence of lead dislodgement between men and women receiving CRT (4.5% vs. 3.2%; p=0.23)

Additional studies from the updated search assessed incidence of lead dislodgment based on participant age, device upgrade, or lead type. Adelstein et al. (2016) found that any lead dislodgment occurred at a similar incidence for those 80 years of age and older compared with younger participants (6.2% vs. 5.5%; $p \geq 0.05$).[88] The authors further delineated the location of the lead dislodgement, right atrium or ventricle, or left ventricle. Left ventricular lead dislodgment occurred at a similar incidence for those 80 years of age and older compared with younger participants (5.4% vs. 3.9%; $p \geq 0.05$). Similarly, Hoke et al. (2014), comparing those 75 years of age and older with younger participants, found no statistically significant difference in incidence of LV lead dislodgement within 24 hours (0.5% vs. 1.7%; p=0.218) and within 30 days (1.4% vs. 1.9%; p=0.748).[86] In the study by Essebag et al. (2014), one participant (1.7%) in the RAFT trial who was upgraded to CRT after presentation of the RAFT trial results had a LV lead dislodgement requiring intervention.[90]

The study by Ziacchi et al. (2018) compared LV bipolar, quadripolar, and active fixation leads.[74] Defining LV lead dislodgement as correctable with pacing vector re-programming or requiring a re-operation within 12 months of followup, the authors found a significant difference in the incidence of lead dislodgement between bipolar (15%), quadripolar (5%) and active fixation (0%) LV leads (p=0.003).[74] For lead dislodgement requiring a re-operation within 12 months of followup, the authors found a significant difference in the incidence of lead dislodgement between bipolar (7.4%), quadripolar (4.1%) and active fixation (0%) LV leads (p=0.005). The authors noted that newer quadripolar leads allow for broader possibilities to reach the target stimulation site and may require less intervention. The observational study by Crossley et al. (2015) assessed a novel LV lead type (family of Attain Performa Quadripolar LV leads) with a short bipolar spacing between two of the four lead electrodes and found that the "straight" lead had a relatively lower dislodgement rate compared to the other leads (0.3% model 4398 lead vs. 2.0% model 4298 lead vs. 1.7% model 4598 lead).[85]

The data are insufficient to conclusively determine whether there is a difference in lead dislodgement rates between participants receiving a CRT-D device versus an ICD alone, but there may be an increased risk of dislodgement for CRT-D devices within 24 hours post-implantation. Largely due to the added requirement for insertion of an additional lead for LV

pacing to facilitate CRT, newer LV lead types, such as quadripolar or active fixation leads, may mitigate this potential risk.

Ventricular Arrhythmias

Twenty-three studies (8 from the updated search) assessed ventricular arrhythmia (VA) outcomes in participants receiving CRT-D devices.[7, 34, 38, 39, 42, 50, 53, 58, 61, 63, 64, 68, 69, 71, 73, 75-77, 79-82, 91] Ten articles compared VA between participants with a CRT-D device versus an ICD alone.[7, 34, 38, 39, 42, 50, 53, 76, 80, 82] Ouellet analyzed data from 1,820 patients in the MADIT-CRT trial and found that 327 participants (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, 0.89; p=0.003). This effect was noted only in participants with an LBBB morphology with no difference seen between those with a non-LBBB morphology (RBBB or NSIVCD) with or without CRT (HR: 1.05; 95% CI, 0.71 to 1.54; p=0.82). Once a participant 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; p=0.05).[34] In addition, acute procedure-related VAs were similar in men and women receiving both CRT-D and ICD-alone devices from this trial.[38] Sabbag et al. (2016) analyzed the ethnic differences in the risk of VA in a MADIT-CRT sub-study.[82] At 4 years followup, they reported that black participants compared with white had a higher risk of first VA, defined as any type of therapy delivered for ventricular tachycardia (VT)/ventricular fibrillation (VF) (HR: 1.69, 95% CI, 1.20 to 2.38; p=0.002).[82]. The relationship held for the first fast VA, defined as a rate greater than 200 beats per minute (HR: 1.93, 95% CI, 1.26 to 2.93; p=0.002). When CRT-D was compared with ICD in white participants with LBBB and adjusted for age, renal function, sex, LVESV, QRS duration, prior vascularization, and history of obesity, arrhythmia, or myocardial infarction, the risk of VA was significantly reduced for those with CRT-D versus ICD alone (HR: 0.66, 95% CI, 0.51 to 0.85; p=0.002); this same comparison in black participants did not reach level of significance (HR: 0.59, 95% CI, 0.27 to1.27; p=0.174). The authors noted that this may be the result of a limitation in sample size since the treatment-by-race interaction term was not statistically significant, suggesting a similar protective effect for both races by CRT-D compared with ICD.

Biton et al. (2018) examined the effect of adverse electrical modeling, measured as sum absolute QRST integral (SAI QRST) divided in tertiles, and risk of VA in participants receiving CRT-D devices in the MADIT-CRT trial.[75] The highest tertiles, Tertiles 2 and 3, were associated with a lower risk of the outcome of VT (Tertile 2: HR 0.65, 95% CI, 0.45 to 0.92; p=0.016 and Tertile 3: HR 0.45, 95% CI, 0.30 to 0.69; p<0.001). The same relationship was also seen for the combined outcome of VT and VF (Tertile 2: HR 0.67, 95% CI, 0.47 to 0.93; p=0.018 and Tertile 3: HR 0.45, 95% CI, 0.30 to 0.67; p<0.001). These models were adjusted for African American race, age ≥65 years, smoking, female sex, prior VA, relative wall thickness and LBBB. Ruwald et al. (2014) reported on the incidence of VAs based on EF response from MADIT-CRT. Five percent of participants in whom the LVEF improved to greater than 50 percent experienced a VA following CRT over a mean followup of 2.2±0.8 years (following a 1-year post implant period) compared with 13 percent in the 36 percent to 50 percent LVEF group, and 30 percent in the LVEF <35 percent group.[39]

Higgins et al. (2003) randomized 490 participants with symptomatic CHF and VA to have their CRT-D devices programmed with CRT-ON versus CRT-OFF.[50] Of the 245 participants

randomized to CRT-ON, 15 percent received appropriate treatment of VA compared with 16 percent of those with CRT-OFF.

In the RAFT trial, 1,798 participants were randomized to CRT-D versus ICD and showed a reduction in the rate of VAs in those with CRT-D (45.3%) as compared with an ICD (49.6%) in participants with a primary prevention indication for implantation (HR: 0.86, 95% CI, 0.74 to 0.99; p=0.044).[80] In participants with secondary prevention indications, the effect was not seen. The rate of VAs was 65.3 percent in the CRT-D group and 58 percent in the ICD group (HR: 1.14, 95% CI, 0.82 to 1.58; p=0.45).

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 VT and VF (p= 0.61).[42]

In the study by Young et al. (2003), 26 percent in the ICD alone group versus 22 percent in the CRT group experienced at least one VA (p=0.47).[7]

In a study by Looi et al. (2017) in New Zealand comparing the outcomes of heart failure participants receiving a primary prevention ICD, there were fewer VA hospitalizations in the CRT-D (23.3%) compared with the ICD group (76.7%) after a mean followup of 3.64 years, but this did not reach statistical significance (p=0.07).[76] No difference was found in mean duration from implant to first VA hospitalization (p=0.08).

In the study by Pinter et al. (2009), over a 6-month followup, 19.4 percent of participants had a VA requiring therapy in the CRT-ON arm compared with 16.7 percent in the CRT-OFF arm, a difference that was not statistically significant.[53] In the study by Gopalamurugan et al. (2014), there was no difference in the incidence of VAs in participants receiving a CRT-D device compared with an ICD alone over a mean followup of 23.9±9.8 months.[71] Theuns et al. (2005) compared CRT-D participants with primary or secondary ICD indications and found that VA occurred in only seven out of 38 participants with a primary prophylactic indication, compared with 29 out of 48 participants with a secondary prophylactic indication (p<0.001).[63]

Other studies reported the incidence of VA in a cohort of CRT-D patients alone.[58, 61, 64, 69, 73, 75, 79, 81] The study by Gasparini et al. (2009) found that 126 participants had 621 appropriately detected VAs over a mean followup period of 14 months.[64] The study by Bossard et al. (2014) evaluated outcomes of 49 participants in a CRT-D registry who survived at least 5 years after implant.[58] Fourteen of these (28.6%) experienced VA.[58] Nian-sang et al. (2010) examined the potential pro-arrhythmic effect of CRT during the perioperative period in 54 participants newly implanted with CRT-D devices.[61] Except for one with a history of frequent premature ventricular contractions but without paroxysmal or sustained VT before implantation, the others had no previous history of VA. In total, four participants (7.4%) experienced VT/VF within 3 days of implantation. They did not experience any additional VA over the 12 months of followup.[61] Ricci et al. (2014) followed 1,404 CRT-D participants over a median followup of 31 months; 36 percent experienced a VA. Haugaa and colleagues (2014) followed 201 participants who had received a CRT-D device; 14 percent experienced a VA over a followup of 2 years. Kronborg et al. (2018) assessed the association between ICD therapy and different lead positions in participants with CRT and found that after a mean of 2 years of followup, 20 percent received appropriate VA therapy.[77]. Su et al. (2018) assessed the influence of different right ventricular lead locations on ventricular arrhythmias, following 352 patients over 2 years.[91] When the left ventricular lead location was not considered, right ventricular middle septum (RVMS) and right ventricular apical (RVA) locations did not affect ventricular arrhythmias. However, when the left ventricular lead was positioned at the anterolateral cardiac vein, the RVMS group had increased

risk of ventricular arrhythmias (HR 3.29, 95% CI, 1.33-8.16; p=0.01). In contrast, when the left ventricular lead was at the posterolateral cardiac vein, the risk of ventricular arrhythmias in the RVMS group decreased (HR 0.49, 95% CI, 0.26-0.90; p=0.02). Finally, when the left ventricular lead was at the lateral cardiac vein, there was no difference between the two groups (HR 0.93, 95% CI, 0.58-1.51; p=0.78).

van Boven et al. (2013) followed a cohort of participants primarily receiving CRT-D devices (96.5%) and separated them into responders and non-responders (response was defined as an LVEF ≥35 percent on followup echocardiogram).[68] Over a 3-year followup period, 12 percent of participants experienced ≥1 appropriate shocks, all of whom were deemed non-responders by echocardiography.

A study by Sardu et al. (2017) assessed the effect of CRT-D in heart failure participants with metabolic syndrome.[79] They found that, by 12 months of followup, the number of VT events was similar in the metabolic syndrome (7%) and non-metabolic syndrome (9%) participants (p=0.405).

A study by Xue et al. (2016) examined CRT's acute (immediate) and chronic (1-year) effects on repolarization dispersion as measured by the prolongation of the T-peak minus T-end (TpTe) interval.[81] The authors found that the TpTe at 1-year shorten group had a lower rate of VA compared with the TpTe at 1-year non-shorten group (p = 0.001). The TpTe immediate shorten and non-shorten groups, however, had similar VT/VF episodes rates (p=0.449). After multivariate adjustment, however, TpTe immediately after CRT-D implantation was independently associated with the risk of VA (HR: 1.030, 95% CI, 1.020 to 1.040; p=0.001). The effect of CRT on TpTe is time dependent.

Overall, there is conflicting evidence as to whether CRT-D is protective against VA compared with an ICD alone. The data, however, are consistent that CRT-D does not appear to increase the rate of VA compared with an ICD alone, and may confer protection against first VA. More data are needed to confirm this finding.

Death Within One Week

Four studies (2 from the updated search) reported on death within 1 week of implantation.[62, 65, 83, 88] The two cohort studies[62, 65] from the prior review and one from the update[88] reported zero deaths. Friedman et al. (2015) reported 0.1 percent of chronic kidney disease (CKD stages 3-5) participants with ICD, compared with 0.2 percent of participants with CRT-D, experienced in-hospital death at time of implant (p=0.75).[83]

Inappropriate Implantable Cardioverter Defibrillator Shocks

Twelve studies (4 from the updated search) reported on inappropriate defibrillator shocks.[7, 39, 42, 45, 62, 66, 68, 73, 77, 78, 88, 91] Only three studies compared the incidence of inappropriate shocks in participants 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 with those receiving an ICD alone[42]; 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 participants in the CRT-D group were hospitalized for inappropriate shocks versus 3.3 percent in the ICD-only group.[45] 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.

In the retrospective cohort study by Van Boven et al. (2013), 33 participants (6.1%) experienced an inappropriate shock over a mean followup time of 3.2 $\pm$ 1.8 years.[66] In a second study by van Boven et al. (2013),[68] the incidence of inappropriate shock was 8.5 percent. Ricci et al. (2014) reported an incidence of 7 percent of inappropriate shocks in a cohort of 1,404 CRT-D patients over a median followup of 31 months.[73]

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.[62] Adelstein et al. (2016) compared the incidence of inappropriate shocks in those 80 years of age and older with the younger cohort and found that 6 percent of the older participants received at least one inappropriate shock (the younger cohort's number of shocks was not reported), comprising 41 percent of all older adults who received at least one shock for any reason. Forty percent of these inappropriate shocks were related to high-power lead issues.[88]

Ruwald et al. (2014), in an analysis from MADIT-CRT, demonstrated no significant difference in inappropriate shocks to participants based on level of LVEF improvement.[39] A study by Killu et al. (2018) assessed defibrillator therapy for super and non-super CRT responders (super-responder being defined as a post-CRT ejection fraction of ≥50% measured 2 months or more post-implantation).[78] They found no difference in the 5-year inappropriate defibrillator delivery rate in super (7%) and non-super (5.3%) responders (p=0.46). Subgroup analysis found dilated cardiomyopathy (HR 2.49, 95% CI, 1.20 to 5.17) and non-LBBB morphology at baseline (HR 2.94, 95% CI, 1.36 to 6.35) to be associated with higher likelihood of inappropriate ICD shock.

Kronborg et al. (2018) examined the impact of different right and left ventricular lead positions on the risk of defibrillator therapy in participants with a CRT-D device.[77] After a mean followup of 2 years, two percent of participants received an inappropriate shock, with no significant association based on lead position or ischemic heart disease status. Su et al. (2018) also assessed the influence of different right ventricular lead locations on inappropriate shock, following 352 patients over 2 years.[91] Combinations of right ventricular middle septum, right ventricular apical, anterolateral cardiac vein, and posterolateral cardiac vein leads did not have a significant difference between groups for inappropriate defibrillation (p>0.05).

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

Effectiveness of Cardiac Resynchronization Therapy With Pacemaker (CRT-P) Versus Optimal Medical Therapy (OMT)

Key Points

- There remains moderate evidence that CRT-P, versus OMT, is effective in improving survival and reducing hospitalizations for heart failure.
- We found insufficient evidence about the effect of CRT-P on quality of life.

Study Characteristics

Five trials [1-4, 51] addressed the effectiveness of CRT-P (reported in 14 articles). [1-3, 8, 20, 22, 23, 25-29, 41, 51] We did not identify any new trials comparing CRT-P therapy to OMT alone but did identify one additional secondary analysis of the COMPANION trial, relevant to some of the pre-specified subgroups of interest.[29]

Five of the articles reported re-analyses from the CARE-HF clinical trial,[20, 22, 23, 25, 26] two reported secondary analyses of the COMPANION trial,[27, 28] and one presented a secondary analysis of the MIRACLE trial.[41] Three trials were RCTs[1-3] and two were randomized crossover trials.[4, 51] All five trials reported the manufacturers of the device used. The planned length of followup ranged from 3 months to 18 months. One study did not report followup time.[20] One study also assessed effectiveness at the end of the study (followup at 29 months).[23]

In general, the trials were heterogeneous in the OMT used as the comparison group. Three trials compared CRT-P to medical therapy.[1-3] One trial compared biventricular (BiV) pacing to no pacing using a crossover design.[4] Another trial compared BiV pacing to right ventricular (RV) pacing alone using a crossover model.[51] Three trials (published in 12 articles) were industry funded.[1-3] One trial, published in two articles, was partially industry funded.[4, 8]

Table 12. Study characteristics of trials assessing effectiveness of CRT-P

Author, year	Length of followup (months)	Study design	Number of participants	Comparison	Device model name	NYHA class	Funding source
CARE-HF							
Cleland, 2004[1]	18	RCT	809	CRT-P vs. OMT	InSync or InSync III, Medtronic	III-IV	Industry
Cleland, 2009[22]	18	RCT	809	CRT-P vs. OMT	InSync or InSync III, Medtronic	III-IV	Industry
Cleland, 2006[20]	18	RCT	812	CRT-P vs. OMT	InSync or InSync III, Medtronic	III-IV	Industry
Cleland, 2012[26]	18	RCT	809 (309 with re-consent)	CRT-P vs. OMT	InSync or InSync III, Medtronic	III-IV	Industry
Cleland, 2008[21]	NR	Post Hoc Analysis	813	CRT-P vs. OMT	InSync or InSync III, Medtronic	I-IV	Industry
Ghio, 2009[23]	18	RCT	735	CRT-P vs. OMT	InSync or InSync III, Medtronic	III-IV	Industry
Wikstrom,2009[25]	18	RCT	813	CRT-P vs. OMT	InSync or InSync III, Medtronic	III-IV	Industry
COMPANION							
Anand 2009[27]	Hospitalization endpoint OMT arm:11.9 months CRT-P arm: 16.2 months	RCT	1,520	CRT-P vs. OMT	Contak TR 1241	III-IV	Industry
Bristow, 2004[2]	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[28]	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
Kalscheur, 2017[29]	33	RCT	1,180	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 participants	Comparison	Device model name	NYHA class	Funding source
St. John Sutton, 2003[41]	6	RCT	323	CRT-P vs. OMT	InSync 8040, Medtronic	III-IV	Industry
MUSTIC							
Cazeau, 2001[4]	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 [8]	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[51]	6	RCT cross-over	56	CRT-P vs. RV pacing	Chorum MSP 7336, Ela Medical	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 participants in the five trials ranged from 56 to 1,520 and were not impacted by the newly identified report from COMPANION. The percentage of women in the trials ranged from 9.1 percent in Leclerq et al. (2007)[51] (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.[2] The mean age in the trials ranged from 63 years of age to 73 years of age. Two trials reported median rather than mean age (median, 66-69 years of age).[1, 4] One study reported racial distribution of subjects (90 percent of the subjects were white).[3, 41] The proportion of participants with ICM ranged from 32 percent to 59 percent. One trial did not report on the proportion of ICM.[41] Only one trial reported the prevalence of AF (21%).[51] Three trials excluded participants with any history of AF.[1, 2, 4] One trial excluded participants with a history of AF within one month of enrollment.[3]

All five trials reported NYHA class of study participants, with four of the five enrolling participants having NYHA class III–IV symptoms. Enrollment of NYHA class IV participants ranged from 6 percent in the CRT-P arm of CARE-HF[1] to 18 percent in the OMT arm of the COMPANION trial.[2] Of note, in the large CARE-HF trial, 21.5 percent of participants assessed themselves to be NYHA class I–II (in contradiction to physician assessment).[20] The trial by Cazeau et al. (2001) only enrolled participants with NYHA class III symptoms.[4]

Three of the primary trials reported the mean LVEF.[3, 4, 51] Two large trials reported median LVEF, ranging from 20 percent in the OMT arm of the COMPANION trial[2] to 25 percent in both arms of the CARE-HF trial.[1]

Three of the trials reported the mean QRS duration,[3, 4, 51] including one in which all participants had permanent RV pacing prior to CRT-P upgrade.[51] Two trials reported median QRS duration, ranging from 158 ms in the OMT arm of the COMPANION trial[2] to 160 ms in both arms of the CARE-HF trial.[1] Four of the trials reported the incidence of native LBBB prior to CRT-P. The study by Leclercq et al. (2007)[51] enrolled only participants with permanent RV pacing and the MIRACLE[3] and CARE-HF[1] trials did not report on QRS morphology. The incidence of LBBB ranged from 69 percent in the CRT-P arm of the COMPANION trial[2] to 87 percent in the MUSTIC trial.[4] Only the COMPANION trial reported the incidence of RBBB[2] (9% in the OMT arm and 12% in the CRT-P arm). No trials reported on participants with non-specific intraventricular conduction delay (NSIVCD). The trial by Leclercq et al. (2007) was the only trial to include RV-paced participants (100% in this trial).[51]

In general, these trials comprised homogeneous patient populations with regard to LVEF, NYHA class, and QRS duration. The proportions of female participants varied between studies, and only one reported race; thus, sex and racial makeup of these populations might not be generalizable.

Risk of Bias

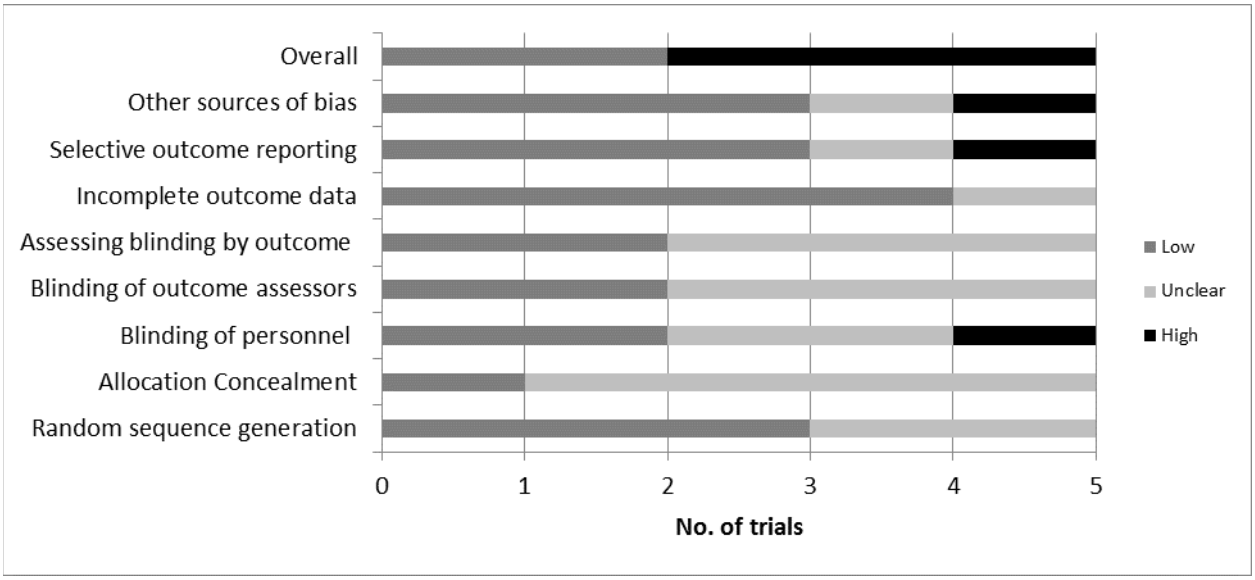
Several types of risk of bias were present in these trials. The most common potential cause of bias was lack of allocation concealment and blinding; details of allocation and blinding were not reported in the majority of studies.

Table 13. 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[1] Cleland, 2012[26] Cleland, 2006[20] Cleland, 2009[22] Wikstrom, 2009[25] Ghio, 2009[23]	-	?	?	?	?	-	+	?	+
COMPANION									
Bristow, 2004[2] Anand, 2009[27] Carson, 2005[28] Kalscheur, 2017[29]	?	?	+	-	-	-	-	+	+
MIRACLE									
Abraham, 2002[3] Sutton, 2003[41]	-	-	-	-	-	-	-	-	-
MUSTIC									
Cazeau, 2001[4] Leclercq, 2002, [8]	?	?	-	?	?	?	?	-	+
Other Trials									
Leclercq, 2007[51]	-	?	?	?	?	-	-	-	-

+=high; -=low; ?=unclear; CARE HF=Cardiac Resynchronization-Heart Failure ; COMPANION=Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; MIRACLE=Multicenter InSync Randomized Clinical Evaluation; MUSTIC=Multisite Stimulation in Cardiomyopathy

Figure 11. Summary of risk of bias for trials assessing effectiveness of CRT-P



Effectiveness Outcomes

The five trials addressed various outcomes, the most common of which were all-cause mortality and changes in QOL as measured by the MLHFQ (in 4 trials). No trials used the KCCQ to assess QOL. Five trials assessed changes in 6MHWD and heart failure hospitalizations; four studies assessed changes in LVEF, left ventricle end-systolic volume (LVESV), and left ventricle end-diastolic volume (LVEDV). No trials assessed changes in Packer (clinical composite) score.

Table 14. Outcomes reported in trials assessing effectiveness of CRT-P

Author, year	All-cause mortality	Heart failure hospitalizations	LVESV	LVEDV	QOL (MLHFQ score)	Change in LVEF	Clinical composite score	6MHWD
CARE-HF								
Cleland, 2004[1]	X	X			X			
Cleland, 2009[22]	X							
Ghio[23]			X	X				
Wikstrom[25]	X		X		X	X		
Cleland, 2006[20]								
Cleland, 2012[26]	X							
Cleland, 2008[21]	X				X			
COMPANION								
Bristow, 2004[2]	X				X			X
Carson, 2005[28]								
Anand, 2009[27]		X						
Kalscheur, 2017[29]	X							
MIRACLE								
Abraham, 2002[3]	X	X			X	X		X
St. John Sutton, 2003[41]			X	X		X		
MUSTIC								
Cazeau, 2001[4]		X			X			X
Leclercq, 2002[8]		X			X			X
Other trials								
Leclercq, 2007[51]		X						X

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; 6MHWD=6-minute hall walk distance; CARE HF=Cardiac Resynchronization-Heart Failure; COMPANION=Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; LVEDV=left ventricle end diastolic volume; LVEF=left ventricle ejection fraction; LVESV=left ventricle end systolic volume; MACLE=Multicenter InSync Randomized Clinical Evaluation; MLHFQ=Minnesota Living with Heart Failure Questionnaire; MUSTIC=Multisite Stimulation in Cardiomyopathy; QOL=quality of life

All-cause Mortality

Five trials (published in 8 articles) assessed all-cause mortality and were not impacted by any newly identified sub-study reports.[1-3, 20, 22, 25, 26, 51]

In the trial by Cleland et al. (2004) comparing CRT-P to OMT, 120 of 404 participants (30%) died of any cause in the OMT group, compared with 82 of 409 participants (20%) in the CRT-P group (HR: 0.64, 95% CI, 0.48 to 0.85, p<0.002).[1, 22] In Cleland et al. (2006), after 1,600 days of followup (mean followup 36.4 months), the mortality rate was 154 of 404 (38%) in the OMT group, compared with 101 of 409 (25%) in the CRT-P group (HR: 0.6, 95% CI, 0.47 to 0.77, p<0.001).[20, 26 20]

Abraham et al. (2002) compared an OMT group to a CRT-P group.[3] At 6 months, the number of participants who died from any cause was 16 of 225 (7.1%) in the OMT group, compared with 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.[51] During the crossover phase, two participants died from sudden cardiac death during biventricular pacing and two participants died from CHF during right ventricular pacing. Two other participants died from a pulmonary embolism and respiratory failure during right ventricular pacing. The overall mortality was 13.5 percent at 6 months followup; however, the study did not report analyses of comparisons of mortality between pacing groups.

Wikstrom et al. (2009) compared all-cause mortality between CRT-P and OMT in two separate groups, those with and without ICM, at 18 months. CRT-P had a significant beneficial 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 ICM and NICM, respectively).[25]

In the COMPANION trial, 77 of 308 participants in the OMT 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% (131 of 617 participants) during the entire study period. The study reported an association between CRT-P implementation and a statistical trend towards reduction in the risk of death from any cause (HR: 0.76, 95% CI, 0.58 to 1.01, p=0.059).[2, 28] This trial also reported that congestive heart failure was the predominant mode of death and that it was reduced by CRT-P, but that sudden cardiac death was not reduced by CRT-P compared with OMT.

Two trials with longer followup times (reported in 3 articles) showed statistically significant differences in mortality favoring CRT-P.[1, 2, 25] Two additional trials reported on all-cause mortality but had shorter followup times (3 or 6 months), which might explain their lack of statistically significant differences between CRT-P and OMT.[3, 51] There is moderate strength of evidence favoring CRT-P versus OMT in mortality.

The study results described are derived from NYHA class III-IV participants. Future studies should seek to reproduce this mortality finding in CRT-P for NYHA class I–II participants with consistent comparators and methodology.

Heart Failure Hospitalizations

Five trials (reported in 6 articles) assessed heart failure hospitalization outcome and were not impacted by any newly identified sub-study report.[1, 3, 4, 8, 27, 51] Cleland et al. assessed hospitalizations for heart failure at 18 months.[1] Of the 404 participants in the OMT group, 184 (46%) had been hospitalized by the end of followup, compared with 125 (31%) of the 409 participants in the CRT-P group (HR: 0.61, 95% CI, 0.49 to 0.77, p<0.001).

Abraham et al. (2002) compared an OMT group, N=225, to a CRT-P group, N=228, at 6 months.[3] There were 34 hospitalizations (15.1%) in the control group and 18 hospitalizations (7.9%) in the CRT-P group (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 their crossover study.[51] At 3 months, there was one hospitalization in the biventricular (BiV) pacing-first group versus nine hospitalizations in the right ventricular (RV) pacing-first group. Compared with the RV pacing-first group, the BiV pacing-first group had significantly fewer hospitalizations (p=0.01).

The MUSTIC trial[4] used a crossover model to randomize participants to receive either CRT-P (CRT-on) or RV pacing (CRT-off) first. Three hospitalizations for heart failure occurred during CRT pacing, and nine during RV pacing (p<0.05). Among one of the subgroups specified for the current review, specifically participants with AF, Leclercq et al. (2002) conducted a secondary analysis of the MUSTIC trial and found a total of three hospitalizations during the first 3 months of the crossover study (the number of hospitalizations in each group was not reported).[8] During the entire 6 months of this crossover study, 10 of 44 participants (23%) were hospitalized for heart failure during the RV pacing period, for a total of 11 hospitalizations, compared to three (7%) during the CRT-P period.

In a secondary analysis of the COMPANION trial and after adjustment for length of followup, Anand et al. (2009) showed an association between CRT-P and a 44 percent reduction in heart failure hospital admissions per patient-year compared with the OMT group (HR from 0.7 to 0.4, no p-value specified).[27]

In summary, the five trials addressing heart failure hospitalization outcome reported fewer hospitalizations in the CRT-P group compared with OMT. One study found fewer hospitalizations in a subgroup of participants with AF.[8] There is moderate strength of evidence indicating fewer hospitalizations for CRT-P compared with OMT.

These results are derived from NYHA class III–IV participants and applicability to NYHA class I and II will have to be addressed in future studies.

Left Ventricular End-systolic Volume

Three trials assessed LVESV in comparing CRT-P with OMT.[23, 25, 41]

St John Sutton et al. (2003) compared CRT-P with OMT at 3 months and 6 months and found a statistically significant decrease in LVESV in the CRT-P group but not in the OMT group.[41] In within-arm comparisons, the LVESV decreased a median of 21.8 mL in the CRT-P group (95% CI, -29.7 to -13.9), compared with a median increase of 0.6 mL in the OMT group (95% CI, -8.7 to 8.7, p<0.05). Similar changes were reported at 6 months, with the median decrease of 25.6 mL in the CRT-P group (95% CI, -37.4 to -17.7, p<0.05).

Ghio et al. (2009) compared CRT-P with OMT in the CARE-HF trial.[23] The decrease in LVESV at 18 months from baseline was 55.1 mL more in the CRT-P group than in the OMT group (95% CI, -67.2 to -42.9. p<0.0001).

Wikstrom et al. (2009) compared LVESV between CRT-P and OMT in two separate groups, those with and without ICM, at 3 months.[25] In those with ICM, the mean LVESV was significantly smaller at study end at 193.99cm^3 (SD 69.36) in the CRT-P group and 231.54cm^3 (SD 86.05) in the OMT group. In those with NICM, the mean LVESV was significantly smaller at study end at 194.01cm^3 (SD 104.74) in the CRT-P group and 233.18cm^3 (SD 98.36) in the OMT group (p=0.0354).

Left Ventricular End-diastolic Volume

Two trials assessed LVEDV in comparing CRT-P with OMT.[23, 41]

St. John Sutton et al. (2003) compared CRT-P to control at 3 months and 6 months and found a statistically significant decrease in LVEDV in the CRT-P group but not in the OMT group.[41] In within-arm comparisons, the LVEDV decreased a median of 22.6 mL in the CRT-P group (95% CI, -33.3 to -5.8), compared to a median increase of 2.8 mL in the OMT group (95% CI, -3.8 to 12.3, $p<0.05$). The study also reported similar changes at 6 months, with a median decrease of 27.2 mL in the CRT-P group (95% CI, -37.1 to -16.9, $p<0.05$

Ghio et al. (2009) compared CRT-P to OMT in the CARE-HF trial.[23] For LVEDV at 18 months, the reduction from baseline was greater in the CRT-P group than the OMT group, -57.6 mL (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 OMT.[23, 25, 41].

In summary, it is likely that LVEDV is improved by CRT-P compared with OMT although evidence for this is of low strength as it is based on only 2 unblinded trials.

Left Ventricular Ejection Fraction

Four trials assessed the change in LVEF, including two reports of the MIRACLE trial.[3, 25, 41, 51]

St. John Sutton et al. (2003) compared CRT-P to control at 3 months and 6 months.[41] In within-arm comparisons, the LVEF increased a median of 10.6 percent in the CRT-P group (95% CI, -0.4 to 1.8) compared with a median increase of 2.3 percent in the OMT group (95% CI, 1.5 to 3.2), which was significant ($p<0.05$). Similar changes were noticed at 6 months, with the median increase of 13.6 percent in the CRT-P group (95% CI, 2.5 to 5.8, $p<0.05$).

Abraham et al. (2002) compared an OMT group to a CRT-P group.[3] At 6 months, median change in the LVEF from baseline was -0.2 percent in the OMT group (95% CI, -1 to 1.5), and +4.6 percent in the CRT-P group (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)[41] 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 participants, the LVEF was 29.5 percent (SD ±11%) at baseline and 29 percent (SD ±11%) at 3 months.[51] For the group receiving biventricular pacing first, the LVEF was 32 percent (SD ±11%)) at baseline and 34 percent (SD ±12%) at 3 months; for the group receiving right ventricular pacing first the LVEF was 32 percent (SD ±13%) at baseline and 37 percent (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 OMT in two separate groups, those with and without ICM, at 3 months and found no significant difference between CRT-P and OMT.[25] In those with ICM, the mean LVEF at 3 months was 29.1 percent (SD ±6.9%) in the CRT-P group and 26.3 percent (SD ±6.5%) in the OMT group; in those with NICM, the LVEF was 30.6 percent (SD ±8.2%) in the CRT-P group and 26.6 percent (SD ±6.9%) in the OMT group ($p=0.3550$).

In summary, three of these four trials showed improved LVEF with CRT-P compared with OMT, although comparison time points and lengths of followup were different between trials. Thus, the absolute difference in LVEF is not comparable from study to study.

6-Minute Hall Walk Distance

Four trials (reported in 5 articles) assessed 6MHWD in comparing CRT-P with OMT.[2-4, 8, 51]

Abraham et al. (2002) compared an OMT group to a CRT-P group.[3] At 6 months, the median change of walk distance from baseline was +10m in the OMT 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: participants receiving biventricular pacing first, participants receiving right ventricular pacing first, and all participants.[51] For the group receiving right ventricular pacing first, the walk distance was 316m (SD ±25m) at baseline and 358m (SD ±88m) at 3 months. For the group receiving biventricular pacing first, the distance was 332m (SD ±173m) at baseline and 414m (SD ±110m) at 3 months. For all participants, the distance was 324m (SD ±149m) at baseline and 386m (SD ±99m) 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 OMT with CRT-P.[2] At 3 months, the change in 6MHWD was 33±99m in the CRT-P group compared with 9±84m in the OMT group (p<0.001). Results were similar at 6 months.

In the MUSTIC trial the mean distance walked was 375±83m during the RV pacing (CRT-off) period, compared with a significantly longer distance of 424±83m during the CRT-P (CRT-on) period (p<0.004).[4]

Among one of the subgroups specified for the current review, participants with AF, Leclercq et al. (2002) conducted a secondary analysis of the MUSTIC trial.[8] For the group receiving biventricular pacing first, the walk distance was 338m (SD ±95m) at randomization. For the group receiving RV pacing first, the distance was 317m (SD ±71m) at randomization. At 6 months, the walk distance was 341m (SD ±100m) in the RV pacing group, and 359m (SD ±121m) in the biventricular pacing group, which was not statistically significantly different.

In summary, although these five trials considered different comparisons, they all showed effectiveness in improving 6MHWD when comparing CRT-P with another treatment (OMT or RV pacing).

These results are derived from NYHA class III–IV participants and applicability to NYHA class I and II will require future studies. One study showed no difference in the AF subgroup of the MUSTIC trial.[8]

Quality of Life

Four trials (published in 7 articles) assessed QOL using MLHFQ in comparing CRT-P with OMT.[1-4, 8, 21, 25] No trials reported use of KCCQ to assess QOL.

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

Cleland et al. (2004) comparing CRT-P with OMT found that the mean difference between groups in MLHFQ score at 90 days was -10 (95% CI, -8 to -12, p<0.001) in favor of CRT-P.[1] Wikstrom et al. (2009), also from the CARE-HF trial, compared MLHFQ between CRT-P and

OMT at 3 months in two separate groups, those with and without ICM.[25] CRT-P had no significant effect versus OMT on MLHFQ in either cardiomyopathy subtype. 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 OMT group, compared with 213 (52%) in the CRT-P group (HR: 0.64, 95% CI, 0.48 to 0.86, p=0.002).[20]

Bristow et al. (2004) compared MLHFQ between CRT-P and OMT 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), favoring CRT-P. A similar, statistically significant difference existed at 6 months (p<0.001).[2]

In the MUSTIC trial those with CRT-P (CRT-on) had a MLHFQ score of 29.6+/-21.3, while those on RV pacing (CRT-off) had a significantly higher score of 43.2+/22.8 (p<0.001), favoring CRT-P.[4]

For one of the subgroups specified for the current review, participants with AF, Leclercq et al. (2002) conducted a secondary analysis of the MUSTIC trial.[8] For the group receiving biventricular pacing first, the score was 40 (SD ±23) at randomization. For the group receiving RV pacing first, the score was 50 (SD ±20) at randomization. At 6 months, the score was 38.5 (SD ±21.4) in the RV pacing group, and 34.1 (SD ±20.6) in the biventricular pacing group, showing no statistically significant difference.

These trials assessed this outcome at different endpoints and with different comparisons (insufficient strength of evidence).

Summary of Findings for Specific Subgroups of Interest

Two trials[1, 2] demonstrated benefit of CRT-P compared with OMT in the significant reduction of both hospitalizations and total mortality in women as well as men when analyzed separately (Table 15). The same trials demonstrated benefit from CRT-P compared with OMT in both significant reduction of hospitalizations and total mortality in participants >66.4 years of age (mean age in CARE-HF trial) and ≥65 years of age (COMPANION) as compared to younger participants.[1, 2]

Two trials[1, 25] demonstrated benefit of CRT-P compared with OMT in the significant reduction of both hospitalizations and total mortality in participants with ICM as well as NICM when analyzed separately.

One trial by Bristow et al.[2] demonstrated significant benefit from CRT-P compared with OMT in participants with LBBB morphology as well as those with non-LBBB morphology when analyzed separately for reduction of hospitalizations and total mortality.

Identified in this update, a recent COMPANION secondary analysis, Kalscheur et al. (2017),[29] compared participants with intermittent AF/atrial flutter to participants with normal sinus rhythm at enrollment. It demonstrated no significant benefit with CRT-P versus OMT in either risk of hospitalization or total mortality in those with a history of intermittent AF/atrial flutter.

There are generally limited and/or conflicting results as to the effect of CRT-P in different subgroups of interest, including those with AF.

Table 15. Summary of CRT-P effectiveness outcomes reported by subgroup

Gender (no. of trial)	Age (no. of trial)	Left ventricular ejection fraction (no. of trial)	NYHA class (no. of trial)	LBBB (no. of trial)	QRS duration >150 ms (no. of trial)	Non-ischemic cardiac conditions/ Cardiomyopathy subtype (no. of trial)	AF (no. of trial)
All-cause mortality							
2 trials	2 trials	NR	NR	1 trial	NR	2 trials	1 trial
Heart failure hospitalizations							
2 trials	2 trials	NR	NR	1 trial Benefit seen in those with LBBB and non-LBBB	NR	2 trials	2 trials Conflicting results
Quality of Life							
NR	NR	NR	NR	NR	NR	NR	NR
6-minute hall walk distance							
NR	NR	NR	NR	NR	NR	NR	1 trial No difference in outcome
Left ventricular ejection fraction							
NR	NR	NR	NR	NR	NR	1 trial No difference in outcome	NR
Left ventricular end-systolic volume/volume index							
NR	NR	NR	NR	NR	NR	NR	NR
Left ventricular end-diastolic volume/volume index							
NR	NR	NR	NR	NR	NR	NR	NR
Packer score							
NR	NR	NR	NR	NR	NR	NR	NR

LBBB=left bundle brunch block; No.=number of; NR=not reported; NYHA=New York Heart Association; QRS=QRS complex

Table 16. Strength of evidence for key effectiveness outcomes of CRT-P

Key Outcomes	No. Studies (number of participants)	Study limitation	Directness	Consistency	Precision	Reporting bias	Strength of evidence Finding
All-cause mortality	6 (2,635)	Low	Direct	Inconsistent	Precise	Undetected	Moderate Lower mortality in CRT-P
Hospitalizations for heart failure	5 (1,666)	Low	Direct	Consistent	Precise	Undetected	Moderate Fewer hospitalizations in CRT-P
MLHFQ	4 (2,445)	Low	Direct	Inconsistent	Precise	Undetected	Insufficient Outcome assessed at different endpoints and with different comparisons

CRT-P=cardiac resynchronization therapy with pacemaker; NA=not applicable

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

Key Points

- No additional studies or analyses were identified in the update.
- The limited number and size of studies precluded any definitive conclusions for procedure-related complications, length of hospital stay, pneumothorax, and pocket hematoma.
- Studies heterogeneous in participant populations and followup time (which affects incidence) prevented conclusions for device infections, cardiac perforation/tamponade, lead dislodgement, and death within one week.

Study Characteristics

No additional studies were identified during the systematic review update. From our prior systematic review, we identified ten studies (reported in 12 articles) that assessed harms associated with CRT-P.[1, 2, 4, 22, 24, 49, 95-100] Five were RCTs[1, 2, 22, 24, 49], three were secondary analyses of CARE-HF trial[1, 22, 24] one was a crossover study,[4] and the rest were prospective cohort studies. Followup ranged from 185 days to 36 months.

The studies used various devices. Two studies reported the use of only a single type of CRT-P device.[95, 97] Three studies used the InSync model 8040,[95, 96, 99] two studies used the InSync III,[97, 99] one study used the InSync 7272,[96] and four studies used other devices.[96, 98-100] Two studies did not report the device type they used.[1, 49]

Two studies explicitly reported funding from industry.[1, 95] One study had non-profit organization funding.[96] 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 percent[98] to 28.6 percent.[100] One study did not report the mean age.[1] Mean age in the other studies ranged from 53 years of age to 68 years of age. No studies assessing harms reported the racial makeup of their participants.

The proportion of participants with ICM ranged from 36 to 48 percent. Two studies did not report on the proportion of ICM.[99, 100] Two studies reported the prevalence of AF among their participants, which ranged from 6 percent to 33 percent[96, 98] Two studies reported the NYHA class of the participants[96, 97] and included participants in all NYHA classes.

Three studies did not report either the mean or the median LVEF.[49, 99, 100] Of those studies reporting this characteristic, the mean LVEF ranged from 19 percent to 30 percent.

In general, these studies were heterogeneous in patient population and frequently did not report proportions of female participants or racial categories of participants.

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 participants 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 (Figure 12 and Figure 13).

Table 17. 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[2]	?	?	+	-	-	-	-	+	+
CARE HF									
Cleland, 2009[22] Gras, 2007[24] Cleland, 2004[1]	-	?	?	?	?	-	+	?	+
MUSTIC TRIAL									
Cazeau, 2001[4]	?	?	-	?	?	?	?	-	+
Other trials									
Garikipati, 2014[49]	-	?	+	-	-	?	?	?	-

+=high; -=low; ?=unclear; CARE HF=Cardiac Resynchronization-Heart Failure ; COMPANION=Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; MUSTIC=Multisite Stimulation in Cardiomyopathy

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

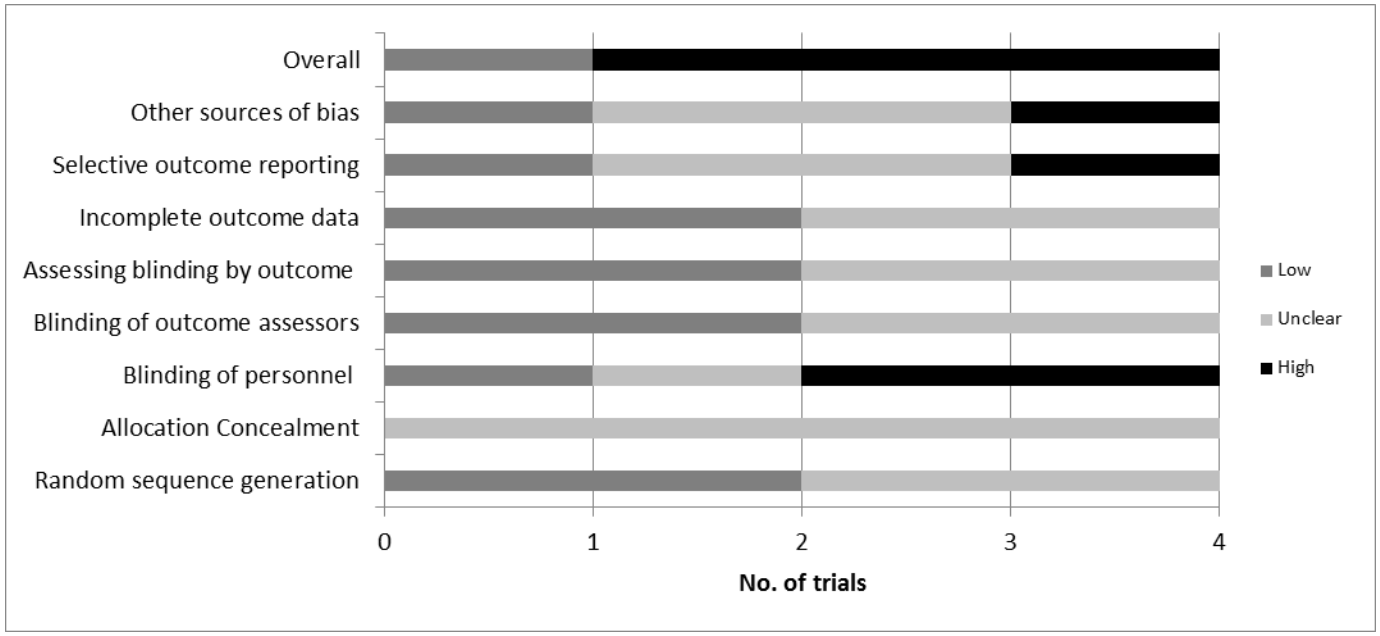
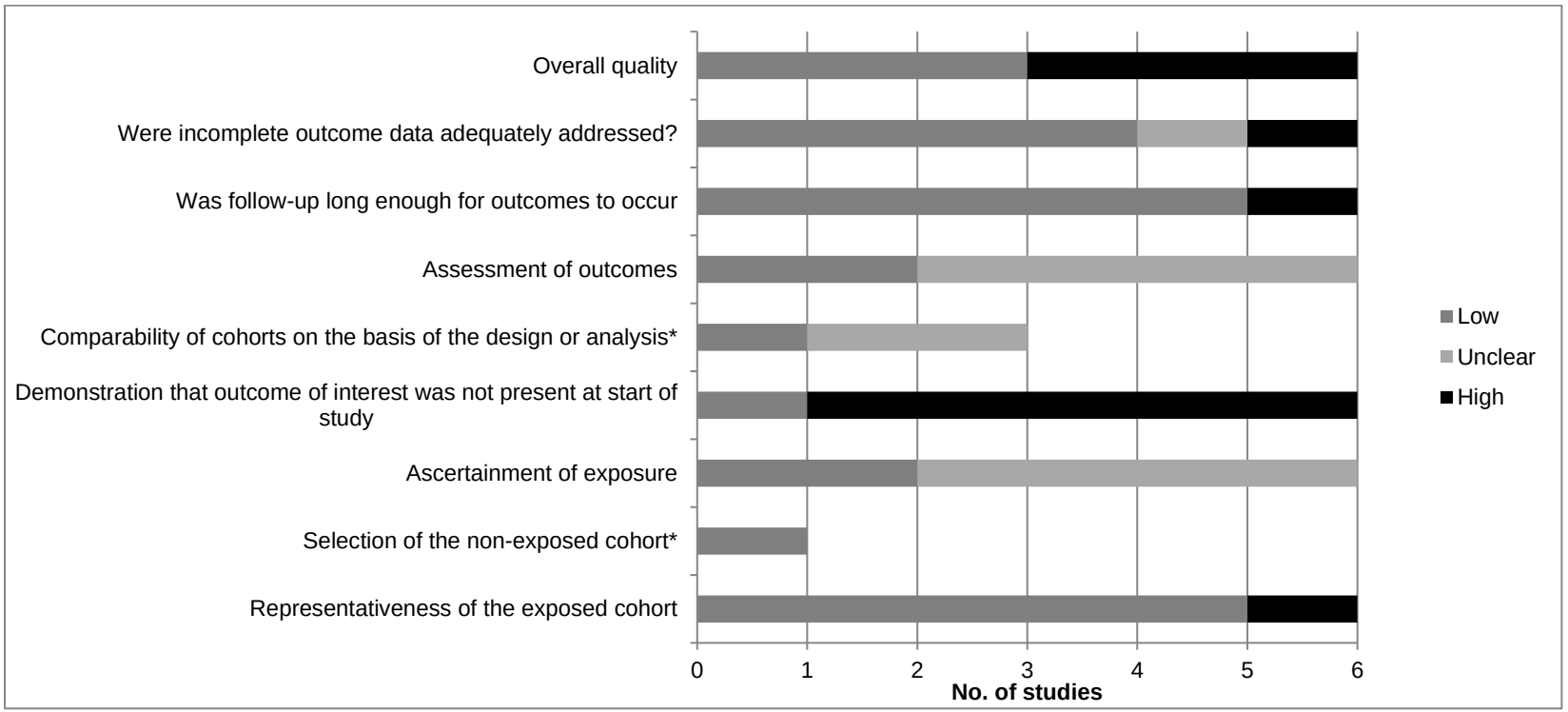


Table 18. Summary of risk of bias for cohort studies assessing harms of CRT-P

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[96]	+		?	-	?	?	-	?	+
Hong-xia, 2006[99]	-		?	+	?	?	+	+	+
Gras, 2002[95]	-	-	?	+	-	?	-	-	+
Mortensen, 2004[97]	-		-	+		-	-	-	-
Stahlberg, 2005[98]	-		-	+		-	-	-	-
Cock, 2003[100]	-		?	+		?	-	-	-

+=high; -=low; ?=unclear
*Only applicable to studies with control groups

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



*Only applicable to studies with control groups.

Table 19. 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 dislodgement	Death within 1 week
COMPANION									
Bristow, 2004[2]	RCT						X		
CARE-HF									
Cleland, 2004[1]	RCT			X		X		X	
Cleland, 2009 [22]	RCT		X						
Gras, 2007[24]	RCT			X	X	X		X	
MUSTIC									
Cazeau, 2001[4]	Randomized crossover								X
Other trials									
Garikipati, 2014[49]	RCT	X	X		X	X			
Cock, 2003[100]	Prospective cohort						X		
Gras, 2002[95]	Prospective cohort					X	X	X	
Hong-xia, 2006[99]	Prospective cohort							X	
Krahn, 2002[96]	Prospective cohort	X						X	X
Mortensen, 2004[97]	Prospective cohort				X			X	
Stahlberg, 2005[98]	Prospective cohort							X	

CARE HF=Cardiac Resynchronization-Heart Failure ; COMPANION=Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; MUSTIC=Multisite Stimulation in Cardiomyopathy; RCT=randomized controlled trail

Harms Outcomes

List of harms reported in the included studies is shown in Table 19.

Procedure-related Complications

Two studies reported miscellaneous procedure-related complications, both reporting a 33.3 percent proportion of participants with this outcome. The small sample sizes and the small number of studies mean that we cannot draw a conclusion other than that more data are needed.

Length of Hospital Stay

Garikipati et al. (2014) reported that, among 21 participants, the participants 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).[49]

Cleland et al. (2009) reported from the CARE-HF trial that, as a result of the implantation procedure, participants 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).[22] Participants with CRT-P spent fewer days in the hospital (384 in the control group vs. 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 with 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 2 articles) assessed pneumothorax.[1, 24] 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.[1] As is the case with other harms, we could not draw a conclusion based on limited data.

Pocket Hematoma

Three studies assessed pocket hematoma.[24, 49, 97] The percentage of participants 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.

Device Infection

Three studies (reported in 4 articles), assessed device infection, with heterogeneous population sizes and followup.[1, 24, 49, 95] Followup time in these studies ranged from 30 days to 18 months, and the proportion of device infection ranged from 0.7 percent to 4.8 percent. The percentage of participants with this outcome varied by approximately an order of magnitude, and the heterogeneity of these studies means that we cannot draw conclusions.

Cardiac Perforation/Tamponade

Three studies assessed cardiac perforation/tamponade,[2, 95, 100] assessing harm at varying time points, with the percentage ranging from 0 percent 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. These studies seem to indicate that this risk is prevalent.

Lead Dislodgement

Seven studies assessed lead dislodgement.[1, 24, 95-99] The proportion of participants experiencing this harm ranged from 1.71 percent to 17 percent for those studies that assessed the proportion over the entire population, which comprised all except one study.[1] Two studies reported lead dislodgement rates for only part of their study population. Cleland et al. (2004)[1] reported the proportion of participants with lead dislodgement only in the CRT-P arm as 5.9 percent; and Gras et al. (2007) reported a proportion of participants with lead dislodgement in the CRT-P arm as 2.7 percent.[24] 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.

Death Within One Week

Two studies assessed death within 1 week.[4, 96] Krahn et al. (2002) found one death within 1 week, as a result of sequelae from stroke, among 45 participants for a prevalence of 2.2 percent.[96] 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.[4] 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.

Effectiveness of Cardiac Resynchronization Therapy With Pacemaker Versus Cardiac Resynchronization Therapy With Defibrillator (CRT-P vs. CRT-D)

Key Points

- There is insufficient evidence, including no new definitive evidence since the 2015 report, that CRT-D improves health outcomes compared to CRT-P in patients with heart failure, LVEF ≤35% and QRS duration ≥120 ms, on optimal medical therapy.
- One additional study (a COMPANION sub-study examining LV end diastolic dimension index (LVEDDI) as a predictor) was identified in the update.
- There is low strength of evidence that CRT-P and CRT-D equally reduced heart failure hospitalizations compared with OMT.

Study Characteristics

One RCT (reported in four articles) compared the effectiveness of CRT-P versus OMT and CRT-D versus OMT but did not provide direct statistical analysis of the CRT-P arm versus the CRT-D arm. [2, 27, 28, 101] The COMPANION trial reported initial results in 2004,[2] with subsequent additional analyses for mortality[28] and hospitalizations.[27] The trial included 1,520 subjects with NYHA class III or IV heart failure and ICM or dilated NICM with a QRS duration of greater than 120 ms, randomized in a 1:2:2 ratio to OMT alone, or in combination with CRT-P (Contak TR model 1241, Guidant) or CRT-D (Contak CD model 1823, Guidant). The planned length of follow-up was 12 months. The study was industry sponsored (Guidant).

We identified one new report [101], a COMPANION sub-study examining LVEDDI as a predictor, comparing effectiveness of CRT-D and CRT-P therapy in the interim four year period (Table 20).

Participant Characteristics

The COMPANION trial included 308 participants in the OMT-alone arm, 617 in the CRT-P plus OMT arm and 595 in the CRT-D plus OMT arm.[2] The median age of participants in the trial arm ranged from 66 years of age to 68 years of age, and the majority of participants were male (67-69%). Most participants were NYHA class III (67-68%), had ICM (54-59%), and a median LVEF ranging from 20% to 22%. Median QRS duration was 160 ms in the CRT-P and CRT-D arms, and 158 ms in the OMT arm. Over two-thirds of participants had an LBBB (range, 69-73%). None of the articles reported racial distribution, history of AF, or glomerular filtration rates of the participants.

Table 20. Study characteristics of trial assessing effectiveness of CRT-P vs. CRT-D

Author, year	Number of participants	Length of followup	Device manufacturer name/ device model	Comparison	Funding source
COMPANION Bristow, 2004[2] Anand, 2009[27] Carson, 2005[28] Shamoun, 2019[101]	OMT: 308 CRT-P: 617 CRT-D: 595	12 months	CRT-P (Contak TR model 1241, Guidant) or CRT-D (Contak CD model 1823, Guidant)	OMT CRT-P CRT-D	Industry

COMPANION=Comparison of Medical Therapy; CRT-D=cardiac resynchronization therapy with defibrillator; CRT-P=cardiac resynchronization therapy with pacemaker; OMT=optimal medical therapy

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 6MHWD and MLHFQ. While the study masked the steering and endpoints committee to treatment assignment, it did not mask physicians, participants, and members of the data management and analysis team, raising concerns for potential bias. Similarly, the randomization technique and allocation concealment were unclear. Despite having both CRT-P and CRT-D arms, direct comparisons between the two arms have not been published, suggesting reporting bias. Accordingly, we judged the COMPANION trial to be at high risk of bias (Table 21).

Table 21. 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[2] Anand, 2009[27] Carson, 2005[28] Shamoun, 2019[101]	?	?	+	-	-	-	+	+	+

+=high; -=low; ?=unclear; COMPANION=Comparison of Medical Therapy

Effectiveness Outcomes

The COMPANION trial did not report change in LVEF, 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

Three articles reported all-cause mortality from the COMPANION trial.[2, 28, 101] Carson et al. (2005) examined the time to cause-specific death, including sudden cardiac death and "pump failure" (congestive heart failure).[28] The study did not specify follow-up time, but provided 3 years of data. Overall, 313 participants died, 78 percent from a cardiac cause, of which heart 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 regard to non-cardiac mortality, there was no significant difference between the treatment groups. The all-cause mortality for the OMT, CRT-P, and CRT-D arms were 25 percent, 21.2 percent, and 17.6 percent, respectively, suggesting the added benefit in mortality is from CRT-D in attenuating mortality from sudden cardiac death. Compared to OMT, 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.[2] The 1-year mortality rate in the OMT group was 19 percent. Compared to OMT, 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 significant mortality reduction of 36 percent (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 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 OMT, 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 only trended towards significance (24%; p=0.059). Primarily owing to high risk of bias and lack of direct comparison, there is insufficient strength of evidence for this outcome.

Hospitalization for Heart Failure

One article reported the impact of CRT-P and CRT-D on hospitalization from the COMPANION trial.[27] Median follow-up ranged from 11.9 months to 16.2 months. Overall, of the 1,520 participants, 959 were hospitalized at least once. Of the total 2,428 hospitalizations, 1,596 (66%) were for cardiac causes. OMT, CRT-P, and CRT-D arms accounted for 388, 628, and 580 cardiac hospitalizations, respectively. CRT resulted in a lower number of cardiac hospital admissions per patient-year: 1.2 for OMT, 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 OMT arm versus 16 percent for the CRT-P and CRT-D arms. Hospital admissions specific to heart failure were also higher in the OMT 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 with the OMT arm (OMT: 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 OMT, CRT-P and CRT-D resulted in a 44 percent and 41 percent reduction, respectively, in heart failure hospitalizations. No statistically significant differences were found when CRT-P was directly compared with CRT-D for the hospitalization endpoints. We graded this finding as low strength of evidence primarily owing to the high risk of bias (Table 23).

Left Ventricular End-systolic Volume and Left Ventricular End-diastolic Volume/Index

The COMPANION trial did not initially report on change in left ventricular end-systolic volume and left ventricular end-diastolic volume. Nevertheless, in 2019 it did provide a retrospective analysis of the baseline LV end diastolic dimension index (LVEDDI) as a predictor for mortality as well as mortality and heart failure hospitalization in 1260 of the enrolled 1520 participants. [101]The 614 participants with a LVEDDI ≥ 35mm/m2 experienced a significantly lower mortality rate in the CRT-P and CRT-D groups as compared to the OMT group ($p = 0.012$ and $p = 0.002$, respectively). Additionally, the CRT-P/CRT-D participants with LVEDDI ≥ 35 mm/m2 also demonstrated a lower rate for the combination of mortality and hospitalization as compared to the OMT group ($p = < 0.001$). These findings were in contrast to the 646 participants with a LVEDDI < 35 mm/m^2 in whom no difference in mortality nor the combination of mortality and hospitalization was observed between the CRT-P/CRT-D groups as compared to the OMT group.

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 6MHWD outcome for the COMPANION trial.[2] At baseline, there was no statistically significant difference in median distance walked between the OMT, CRT-P, and CRT-D arms (244m, 274m, 258m, respectively). We assessed the outcome at 3 months and 6 months post-intervention with the OMT arm as the only reference. For the OMT arm, the distance walked increased by 9±84m and 1±93m at 3 months and 6 months, respectively. In contrast, compared with OMT, the median distance walked significantly increased: 33±99m and 40±96m versus 44±109m and 46±98m at 3 months 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 quite similar.

Quality of Life

One article from the COMPANION trial reported on the change in MLHFQ score for CRT-P and CRT-D at 3 months and 6 months with the OMT arm as reference from the COMAPNION trial.[2] For the OMT arm, the MLHFQ median score decreased by -9±21 and -12±23 at 3 months and 6 months, respectively. In contrast, compared to OMT, the MLHFQ score decreased by over two-fold for both the CRT-P and CRT-D arms: -24±27 and -25±26 versus -24±28 and -26±28 at 3 months 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 the 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 23).

Summary of Findings for Specific Subgroups of Interest

Subgroup analyses suggested that those with NICM experience a greater mortality benefit than those with ICM with CRT-D whereas those with ICM may experience a greater mortality benefit than those with NICM from CRT-P.[2] It should be emphasized that the ability to draw conclusions regarding CRT-D versus CRT-P therapy for COMPANION subgroups is markedly limited by the fact that no direct comparison of these device populations was provided (Table 22).

Table 22. Summary of effectiveness outcomes reported in the trial of CRT-P versus CRT-D, by subgroup

Gender (no. of trial)	Age (no. of trial)	Left ventricular ejection fraction (no. of trial)	NYHA class (no. of trial)	LBBB (no. of trial)	QRS duration >150 ms (no. of trial)	Non-ischemic cardiac conditions/ Cardiomyopathy subtype (no. of trial)	AF (no. of trial)
All-cause mortality							
NR	NR	NR	NR	NR	NR	1 trial Participants with NICM benefit more with CRT-D vs. OMT whereas those with ICM benefit more from CRT-P vs. OMT	NR
Heart failure hospitalizations							
NR	NR	NR	NR	NR	NR	NR	NR
Minnesota Living with Heart Failure Questionnaire							
NR	NR	NR	NR	NR	NR	NR	NR
6-minute hall walk distance							
NR	NR	NR	NR	NR	NR	NR	NR
Left ventricular end-systolic volume/volume index							
NR	NR	NR	NR	NR	NR	NR	NR
Left ventricular ejection fraction							
NR	NR	NR	NR	NR	NR	NR	NR
Left ventricular end-diastolic volume/volume index							
NR	NR	NR	NR	NR	NR	NR	NR
Packer score							
NR	NR	NR	NR	NR	NR	NR	NR

CRT-D=cardiac resynchronization therapy with defibrillator; CRT-D=cardiac resynchronization therapy with pacemaker; ICM=ischaemic; LBBB=left bundle branch block; NYHA=New York Heart Association; OMT=optimal medical therapy; QRS=QRS complex

Table 23. Strength of evidence for key effectiveness outcomes of CRT-P vs. CRT-D

Key outcomes	No. Studies (number of participants)	Risk of bias	Directness	Consistency	Precision	Reporting bias	Strength of evidence Finding
All-cause mortality	1 (1520)	High	Indirect	Unknown (Single study)	Precise	Undetected	Insufficient
Hospitalizations for heart failure	1 (1,520)	High	Direct	Unknown (Single study)	Precise	Undetected	Low Compared with OMT, CRT-P and CRT-D were equally associated with reduction in heart failure hospitalizations (44% and 41%, not statistically significantly different).
Quality of Life (Minnesota Living with Heart Failure Score)	1 (1,520)	High	Direct	Unknown (Single study)	Imprecise	Undetected	Insufficient

NA=not applicable

Harms of Cardiac Resynchronization Therapy With Pacemaker Versus Defibrillator (CRT-P vs. CRT-D)

Key Points

- Analyzing the harms data continues to be a challenge owing to study-created, non-standardized definitions of harms, a large range of followup times, no specific time of the harms' occurrence, and limited direct CRT-P to CRT-D comparisons.
- No conclusions could be made for length of stay, pneumothorax, pocket hematomas, cardiac perforation/tamponade, ventricular arrhythmias, inappropriate shocks by CRT-D devices, and death within one week.
- Procedure-related complication rates are generally higher for CRT-D versus CRT-P devices.
- CRT-D is associated with higher risk of device infections and more dislodgment, but additional studies are needed to confirm this finding.

Study Characteristics

Fifteen studies (reported in 17 articles) assessed harms comparing CRT-P with CRT-D, including three RCTs.[2, 27, 28, 43, 47, 102-112] We identified six new studies in the updated search[47, 109-113], one of which was an RCT.[47] 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 participants.[43] Treating clinicians selected CRT-P versus CRT-D devices. Harms were assessed as a post-hoc analysis (Evidence Table 1). The second RCT, COMPANION, was a single-blinded trial that assigned participants in a 1:2:2 ratio to treatment with OPT alone, OPT plus CRT-P, or OPT plus CRT-D.[2, 27, 28] The primary outcome was a composite of all-cause mortality and all-cause hospitalization, and the secondary endpoint was all-cause mortality. The third RCT, identified in our update, is the Danish Study to Assess the Efficacy of ICDs in Participants with Non-Ischemic Systolic Heart Failure on Mortality (DANISH), an investigator-initiated, multicenter, randomized, unmasked controlled trial performed at all centers in Denmark that implanted ICDs.[47] Primary outcome was death from any cause; secondary outcomes included sudden cardiac death, cardiovascular death, cardiac arrest or sustained ventricular tachycardia, and change from baseline of various QOL outcomes. Participants were seen at 2 months and then subsequent 6-month intervals. Only those with a non-ischemic cause of heart failure, as determined by coronary angiography or nuclear perfusion, were included. Participants were randomly assigned in a 1:1 ratio to either the ICD group or the control group, with a decision for cardiac resynchronization before randomization, and thus included CRT-P and CRT-D devices. In both arms of the study, 58 percent of participants received CRT.

Of the non-randomized studies, seven were prospective[103, 106, 108-111, 113] and five were retrospective.[102, 104, 105, 107, 112] We identified four prospective cohort studies[109-111, 113] and one retrospective cohort study in the updated search.[112]

Followup ranged from approximately 6 months[103] to 7 years.[47] Only three studies specified the device names,[2, 27, 28] none of the studies identified in the update did so.

Six studies (reported in 8 articles) reported funding.[2, 27, 28, 43, 107 47, 109, 110] The three RCTs were industry funded.[2, 27, 28, 43, 47] Four studies explicitly specified no funding.[104, 106, 109, 110]

Population Characteristics

The number of participants in the studies ranged from 40[103] to 26,887.[107] The percentage of women among participants in the study arms ranged from 16 percent[104] to 44 percent,[110] excluding a study separated by sex.[112] Only one study from the prior review[107] and one in the update[113] reported the racial makeup of its participants. Mean age in the study arms ranged from 58 years of age[103] to 74 years of age[104] in the initial systematic review and was older in the update, ranging from 61.5 years of age[113] to 83 years of age[110].

Twelve studies (reported in 14 articles) reported the percentage of participants with ICM,[2, 27, 28, 47, 103-111, 113] ranging from 19 percent[103] to 70 percent[105] per study arm. All[47, 109-112] but one[112] of the five studies in the update reported the percentage of participants with ICM. The DANISH RCT specifically excluded ischemic heart failure.[47] All but two studies reported mean ejection fraction,[104, 107] ranging from 20 percent[2, 27, 28] to 33.7 percent,[113]. One study in the update reported median rather them mean ejection fraction, a median value of 25% (IQR: 20-30).[47] All but two studies (which were in the original review) reported history of AF,[2, 27, 28, 107] ranging from 11 percent[114] to 41.8 percent per study arm,[113]. One study separated by sex had 65 percent of males and 12 percent of females with AF.[112]

Mean QRS duration ranged from 147 ms to 185 ms but four studies did not report it.[102-104, 107] One study, separated by sex, reported on males versus females with mean QRS duration of 146 ms and 148 ms, respectively.[112] Another study reported median QRS duration, with the narrowest median QRS duration in the arm being 145 ms (IQR: 110, 164) versus 146 ms (IQR: 114-166).[47] Only six studies, two from the prior review[2, 28, 106] and four from the update,[110-113] specified QRS morphology, with the predominance being LBBB, ranging from 27.9 percent[113] to 84 percent[106] per arm. Only seven studies (reported in 9 articles) specified NYHA classification,[2, 27, 28, 43, 47, 102, 106, 109, 113] with the majority of participants in class II or III, ranging from 10 percent[102] to 54 percent[47] for class II and from 40.8 percent[113] to 87 percent[2, 27, 28] for class III per arm. Renal function was inconsistently reported. Seven studies reported baseline renal function.[47, 104-106, 108, 109, 111] Three studies reported eGFR,[47, 104, 106] with a mean range of 52ml/min/1.73m^2 to 72ml/min/1.73m^2 per arm.[106] Two studies reported median glomerular filtration rate (GFR), similar within study arms, as 74ml/min/1.73m^2 (IQR: 58-91) and 60ml/min/1.73m^2 (IQR reported as 51).[47, 113] Three studies[105, 108, 111] reported creatinine, ranging from a median of 1.2mg/dL[108] to a mean level of 1.6mg/dL.[105] Two studies reported dichotomized estimates of renal function with cut-points of GFR <30ml/min/1.73m^2[109] or creatinine ≥1.4mg/dL.[111]

Risk of Bias

The MASCOT and COMPANION trials were included in our prior review; the DANISH trial was identified during the update. The COMPANION trial had high risk of bias because it did not mask participants, 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 endpoints committee, and the sponsor were unaware of the treatment assignments). Similarly, a very high percentage (26%) of participants changed from medical therapy to receive device implants. Random sequence generation and allocation

concealment for the trial were also unclear. Finally, reporting bias is suggested, because COMPANION articles rarely reported direct comparisons of CRT-P versus CRT-D.

The MASCOT trial was also at high risk of bias because device type was not randomized but was 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 with CRT-P participants, CRT-D recipients were more likely to be male ($p < 0.0001$) and have ICM ($p < 0.001$) and shorter QRS duration ($p < 0.0005$), and were less likely to receive spironolactone ($p < 0.0001$) and anti-arrhythmic medications ($p < 0.0222$). The study made no adjustment for these factors.

In the DANISH trial, the overall risk of bias was low including low risk of bias intervention assignment and concealment.[47] Randomization was performed with the use of a Web-based system, in permuted blocks, and was stratified according to center and according to whether participants were scheduled to receive CRT. The decision to implant a CRT device had to be made before randomization. Also, an endpoint classification committee, the members of which were unaware of treatment assignments, used pre-specified criteria to assess clinical outcomes. For harms, we do not expect un-masking of participants to affect harms reporting by the participants, nor physicians to alter harms when knowing allocation given the objective criteria used by the masked endpoint classification committee. Similarly, attrition and outcomes were appropriately reported (Table 24 and Figure 14).

For the cohort studies,[102-113] the main concerns for bias included unclear description of the cohort,[102] concern for the representativeness of the cohort of the heart failure population,[110, 111, 113] comparability of the study arms,[109, 110] self-reported outcomes in the main study,[106] incomplete outcome data,[111] and no standardized followup time.[107] One study included only participants with AF,[111] another included only those 75 years of age or older,[110] and an additional study had over 75 percent of participants from New Zealand/Europe per study arm.[113] Two studies had significant differences between baseline characteristics, including age, EF, QRS, and medications.[109, 110] One study did not quantify how participants were excluded.[111] However, all of the following were adequate: selection of the cohort, ascertainment of exposure, outcome of interest not being present on study initiation, pre-specified outcomes and assessment (typically registry or medical records linkage), and followup long enough for outcomes to occur.

Five of the 11 cohort studies had low risk of bias;[102, 104, 105, 108, 112] seven cohort studies had high risk of bias (Table 25 and Figure 15).[103, 107-111, 113]

Table 24. 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[2] COMPANION Sub-Study Anand, 2009[27] Carson, 2005[28]	?	?	+	-	-	-	-	+	+
DANISH Kober, 2016[47]	-	-	-	-	-	-	-	-	-
Schuchert, 2013[43]	-	?	?	?	?	-	-	-	+

+=high; -=low; ?=unclear; COMPANION=Comparison of Medical Therapy; DANISH=The Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality

Figure 14. Summary of risk of bias for trials assessing harms of CRT-P vs. CRT-D

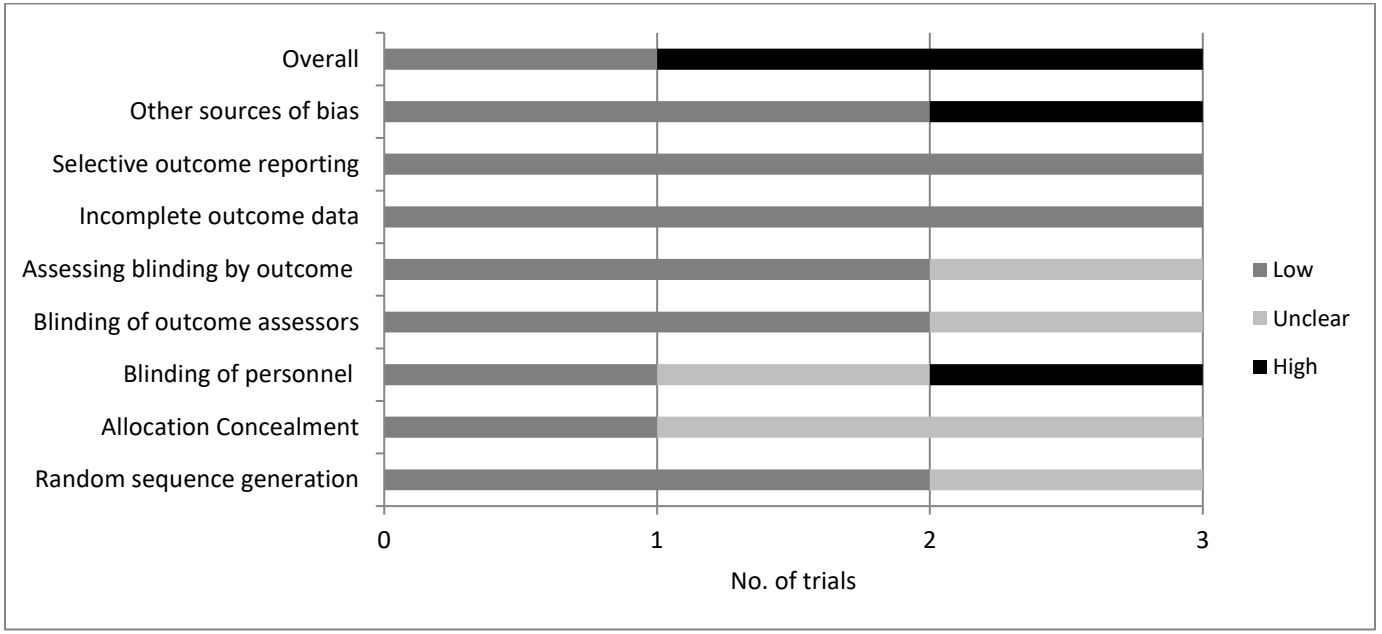
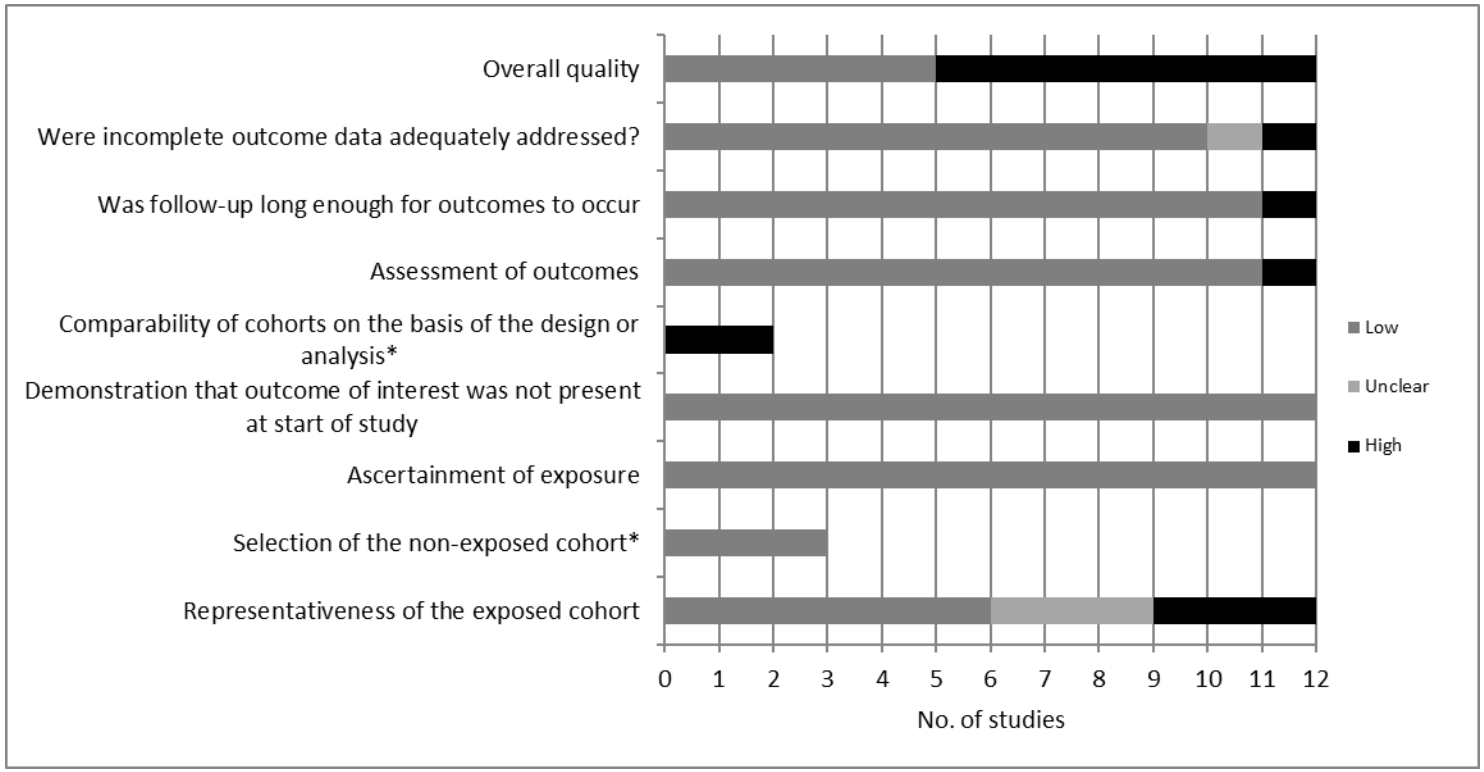


Table 25. Summary of risk of bias for cohort studies assessing harms of CRT-P vs. CRT-D

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[102]	?		-	-		-	-	-	-
Barra, 2018[109]	-	-	-	-	+	-	-	-	+
Doring, 2018[110]	+	-	-	-	+	-	-	-	+
Killu, 2013[105]	-		-	-		-	-	-	-
Looi, 2018[113]	+	-	-	-		-	-	-	+
Nakajima, 2018[111]	+		-	-		-	-	+	+
Nezorov, 2018[112]	-		-	-		-	-	-	-
Romeyer-Bouchard, 2010[108]	-		-	-		-	-	-	-
Swindle, 2010[107]	?		-	-		-	+	-	+
Takaya, 2013[103]	?		-	-		-	-	?	+
Verbrugge, 2013[104]	-		-	-		-	-	-	-
Verbrugge, 2013[106]	-		-	-		+	-	-	+

+=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



*Only applicable to studies with control groups

Table 26. 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[27]		X[1]								
MASCOT Schuchert, 2013[43]*						X				
Bristow, 2004[2]	X				X					
Carson, 2005[28]								X[5]		
Kober, 2016[47]			X			X			X	X
Prospective Cohorts										
Barra, 2018[109]	X		X	X	X	X	X			
Doring, 2018[110]	X			X		X	X			
Looi, 2018[113]	X	X		X	X	X	X			X
Nakajima, 2018[111]										X
Romeyer-Bouchard, 2010[108]			X	X		X	X			
Takaya, 2013[103]								X		
Verbrugge, 2013[106]		X	X		X	X[2]	X			
Verbrugge, 2013[104]										X
Retrospective Studies										
Azizi, 2006[102]			X		X	X	X	X	X	
Killu, 2013[105]			X	X	X	X	X	X[4]		X
Nezorov, 2018[112]	X		X	X		X				
Swindle, 2010[107]	X	X						X[3]		

CRT-D=cardiac resynchronization therapy with defibrillator; RCT=randomized controlled trial

*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 participants undergoing device procedures.
4. 30-day Mortality was reported.
5. Exact timing of death was not specified.

Harms Outcomes

Overall, the harms most commonly reported were device infections,[43, 47, 102, 105, 106, 108, 109, 112, 113, 115] pneumothorax,[47, 102, 105, 106, 108, 109, 112] and lead dislodgement.[102, 105, 106, 108-110, 113] Studies rarely reported VA[47, 102] and length of hospital stay.[27, 106, 107, 113] For most adverse events, the studies used study-defined, non-standardized definitions, did not report the exact time of the harm, 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.

In the update, the harm most commonly reported continued to be device infections, in five of the six new studies,[47, 109, 110, 112, 113] followed by procedure-related complications,[109, 110, 112, 113] pneumothorax,[47, 109, 112] and pocket hematomas.[109, 110, 112, 113] The newer studies rarely reported cardiac perforation/tamponade.[109, 113] Three studies each reported lead dislodgement[109, 110, 113] and inappropriate ICD shocks (CRT-D only).[47, 111, 113] In contrast to the original systematic review, only one study specifically reported length of hospital stay (combining all groups)[113] and none reported death within 1 week. Also, four of the six new studies did differentiate by device type, CRT-P versus CRT-D;[47, 109, 110, 113] two of these studies did not.[111, 112] The first of these studies defined harms by sex but did not specify the differential of harms in CRT-P and CRT-D participants;[112] 63 percent of males and 35 percent of females had a CRT-D device. The other study defined harms by AF status (sinus rhythm, or intermittent or permanent AF) but did not specify the differential of harms in CRT-P and CRT-D participants.[111] The challenges in the newer studies remained the same: study-created definitions of harms, a large range of followup times, and no specific time of the harms' occurrence. List of harms reported in the included studies is shown in Table 26.

Procedure-related Complications

Six total studies reported on procedure-related complications,[2, 107, 109, 110, 112] four from the update.[109, 110, 112, 113] Swindle et al. (2005) used 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.[107] For CRT-P compared with CRT-D, 94.2 percent versus 95.0 percent of participants had no complications, 5.2 percent versus 4.6 percent had one complication, and 0.6 percent versus 0.4 percent had greater than one complication.[107] 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 participants, those under 80 years of age (p=0.03). Another study, COMPANION, reported that 10 percent of CRT-P and eight percent of CRT-D participants experienced moderate or severe adverse events related to the implantation procedure.[2] There was no statistically significant difference in complications between CRT-P and CRT-D (p=0.42), consistent with the first study.

In the update, we identified four additional studies reporting procedure-related complications.[109, 110, 112, 113] Followup in all studies exceeded 1 year. Barra et al. (2018) explicitly defined complications with respect to timing as either acute or late.[109] "Acute" was defined as occurring during the procedure or diagnosed prior to the initial hospital discharge. "Late" was defined as occurring or being diagnosed after the initial hospital discharge. The authors further delineated complications as access-related (related to vascular access, such as a pneumothorax), lead-related (related directly to the lead, such as dislodgement), generator-related (related directly to the generator, such as a pocket hematoma, but excluding infection), infection

(requiring surgical explanation or revision of the device), and device-related death (device complication considered to have contributed to the death of the patient, such as through systemic infection but also including all death from the initial hospitalization). After adjustment for age, sex, heart failure etiology, upgrade of device versus de novo implantation, Barra et al. (2018) found overall acute complications to be higher in CRT-D participants (16.9% vs. 14%), but not statistically significant (OR 1.2, 95% CI, 0.72 to 2.0; p=0.47). After propensity-matching, the same non-statistically significant relationship was found (OR 1.29, 95% CI, 0.81 to 2.05; p=0.29). In contrast, for late complications, after similar adjustment, Barra et al. (2018) found a significant increase in late complications for CRT-D versus CRT-P (11.4% vs. 8.9%, HR: 1.68, 95% CI, 1.27 to 2.23; p=0.001). After propensity-matching, the same significant relationship was found (HR 1.73, 95% CI, 1.11 to 2.68; p=0.013).[109]

Looi et al. (2018) used a similar definition for complications of acute (within 24 hours of implant), early (>24 hours to 2 weeks after implant) and late (≥2 weeks after device implantation).[113] In this observational study in New Zealand, 200 patients undergoing CRT were followed for a median of 4 years. There were 5.7 percent acute (within 24 hours of implant) perioperative complications in the CRT-D as compared to 4.7 percent in the CRT-P group (p=0.78). There was no significant difference in the occurrence of early (>24 hours to 2 weeks after implant; 1.3% versus 0%, no p value) and late (≥2 weeks after device implantation; 5.7% versus 9.3%, p=0.4) complications for the CRT-D and CRT-P groups respectively.

Doring et al. (2018) reported a study on participants at least 75 years of age who had been implanted with CRT-D or CRT-P and provided an overall complication rate as well as separate procedure-related adverse events, such as infections and hematomas.[110] The study found procedure-related complications in general occurred more in CRT-D participants but was not statistically significant: 9.3 percent in CRT-D participants versus 5.0 percent in CRT-P participants (p=0.458). Pericardial effusion only occurred in CRT-P participants (2.5%).

Nevzorov et al. (2018) examined sex differences in CRT participants and provided overall complication rates by sex but did not distinguish between device types.[112] Complication rates were higher for females (14.7%) compared with males (5.6%), but not statistically significant (p=0.09). Similarly, pericardial effusion was more common in females (2.9%) compared with males (0.7%), but not statistically significantly (p=0.2).

Complication rates were generally higher for CRT-P versus CRT-D devices.

Length of Hospital Stay

Two studies reported the length of hospital stay,[106, 107] finding that the presence of a device complication or an elevated comorbidity score resulted in increased length of stay and total cost of hospitalization, as would be expected. We identified no new studies providing direct comparison of CRT-P and CRT-D for length of hospital stay for the initial device implantation. In the update, the study by Looi et al. (2018) examined CRT devices in New Zealand and only reported a median length of stay of 4 (IQR: 2) days, not separated by device group.[113]

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 participants undergoing a CRT-D procedure. 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 device type.[106] The COMPANION trial

excluded initial implantation and elective implantation of CRT-P and CRT-D devices from its hospitalization and length of stay analyses.[27]

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

Pneumothorax

Seven total studies reported on pneumothorax,[47, 102, 105, 106, 108, 109, 112] three of which we identified in the update.[47, 109, 112] The studies reported a pneumothorax prevalence of 0, 0.3, 0.6, 0.7, 1, 1.1-2.0, and 1.4 percent respectively.[47, 102, 105, 106, 108, 109, 112] One study noted no difference by age, comparing participants aged ≤80 years (1.3%) versus >80 years (2.2%) (p=0.36).[105] In the prior review, no study directly compared pneumothorax by CRT type. In the update, only one study showed pneumothorax to be less common among CRT-D (0.5%) when directly compared with CRT-P (0.9%) (no p value given).[109] The other study from the update[47] did not distinguish between device type and the final study had no pneumothoraxes.[112] Pneumothorax is an uncommon device complication.

Pocket Hematoma

Six total studies reported on pocket hematoma,[105, 108-110, 112, 113] four of which we identified in the update.[109, 110, 112, 113] The two studies from the initial review had very specific definitions for pocket hematomas. 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."[105] Among those participants aged ≤80 years versus >80 years, 0.5 percent and 1.1 percent, respectively, experienced a hematoma requiring intervention (p=0.41), but this was not separated by device type.[105] The second study by Romeyer-Bouchard et al. (2007) required two investigators to agree on a "palpable mass that protruded 2cm anterior to the pulse generator and lead(s)."[108] Twenty-nine participants (9.5%) experienced a large hematoma, with five (1.66%) requiring re-intervention due to the size of the hematoma but, again, device type was not specified. One of the newer studies, Nevzorov et al. (2018) also did not specify the device type and reported more hematomas in males (0.7%) compared with females (0) (p=1).[112]

Three of the newer studies reported pocket hematomas by device type. Barra et al. (2018) specified by device type and distinguished acute (initial hospitalization) from late (after discharge from index hospitalization) hematomas, finding a similar overall occurrence of hematoma for CRT-D (1%) and CRT-P (0.7%) devices (no p value specified), as well as for late hematomas for CRT-D (0.05%) and CRT-P (0.08%) devices (no p value specified).[109] Doring et al. (2018) found higher prevalence of pocket hematoma among those older than 75 years of age for CRT-D (1%) versus CRT-P (0%).[110] Looi et al.

(2018) found that device/pocket issues requiring intervention occurred more frequently with CRT-D (0.6%) as compared to CRT-P (0%) devices (no p value specified).[113] Larger pockets from the larger leads, connectors, and size of the CRT-D devices may predispose for hematoma, but the newer studies suggest only a slightly increased risk for CRT-D.

Device Infection

Ten studies reported on device infection,[43, 102, 105, 106, 108, 113] including five we identified in the update.[47, 109, 110, 112, 113] Killu et al. (2008) reported a prevalence of 0.3 percent with no statistically significant difference among participants older versus younger than the age of 80

years (p >0.99).[105] Verbrugge et al. (2011) report a prevalence of 0.5 percent infections.[106] Azizi et al. (2005) reported infection in only 0.8 percent of participants.[102] When they separated by sex, Nevzorov et al. (2018) found a higher percentage of pocket infections in female participants compared with male participants (11.8% vs. 2.8%, p=0.045), although only 34 women were in the study.[112] However, none of these studies distinguished infection by CRT device type or provided specific definitions of, or timing criteria for, infections.

In contrast, one study from the prior review[43] and four studies from the update[47, 109, 110, 113] provided data by device type. Schuchert et al. (2010) reported a CRT-specific rate of infection of 1.7 percent for CRT-P and 2.1 percent for CRT-D (p=0.88)[43] but did not provide a specific definition for infection. In contrast, Romeyer-Bouchard et al. (2007) defined device-related infection (DRI) in detail 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)."[108] This was also categorized by timing 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; 1.6 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. The authors suggest that technical factors, such as larger leads, connectors, size, and pocket size, may predispose to infection and stretch the skin relatively thinner. Also, lead materials and size may affect bacterial adhesion.

Barra et al. (2018) explicitly defined infection as "any device-related infection requiring surgical intervention, either extraction or pocket/wound revision, but not causing the death of the patient."[109] Overall, infection occurred in 3.1 percent of CRT-D and 1.9 percent of CRT-P participants (no p value reported). In this study, an infection occurring during the index hospitalization of implantation was classified as an "acute" complication. In contrast, infections that were diagnosed or occurred after the initial hospitalization were classified as "late" complications and occurred more frequently in CRT-D (3.4%) compared with CRT-P (2.1%) participants. The mean annual cause-specific incidence of infection was 9 (95% CI, 3 to 14) and 5 (95% CI, 1 to 9) infections per 1000 patient-years in CRT-D and CRT-P participants, respectively. Adjusting for all predictors of complications from univariate analysis, CRT-D was associated with a significantly increased hazard of infection (HR 2.1, 95% CI, 1.18 to 3.45; p=0.004). Further confirmed by propensity score matching, infection was more frequent with CRT-D devices (HR 2.58, 95% CI, 1.36 to 5.1; p=0.009). Both upgrade to CRT and having an acute infection were associated with an increased hazard of a late infection. In the majority of cases (56.7%), the infection occurred during the first 12 months. Subgroup analysis showed participants younger than 65 years of age and receiving a CRT-D upgrade were at a high risk of infection (10.7%). The authors note several possible explanations for the increased risk, including the higher likelihood of needing a generator replacement due to shorter battery life, unanticipated intervention due to lead dysfunction and wound issues, having a higher mean number of leads, and a patient population that is more likely to be male and younger. The authors recommended development of smaller devices with thinner leads to reduce the size of the pocket, longer battery life, and use of subpectoral implants or antibacterial coatings.

A subset of non-ischemic systolic heart failure participants in the new DANISH trial received CRT devices.[47] Kober et al. (2016) examined both device and serious device infections (serious device infection was defined as "infection requiring lead extraction or life-long antibiotic treatment or causing death").[47] Comparing CRT-D with CRT-P participants, the odds of a device infection were lower (OR: 0.83, 95% CI, 0.38 to 1.78; p=0.60) but not statistically significant, occurring in 4.7 percent of CRT-D participants and 5.6 percent of CRT-P participants. Serious device infections showed a similar trend. Comparing CRT-D with CRT-P participants, the odds of a serious device infection were lower (OR: 0.82, 95% CI, 0.29 to 2.20; p=0.65) but not statistically significant, occurring in 2.8 percent of CRT-D participants and 3.4 percent of CRT-P participants.

Using a definition for device infection of "device pocket infection needing extraction", Looi et al. (2018) found no significant difference for CRT-D (0.6%) versus CRT-P (2.3%) devices ≥2 weeks after device implantation (p=0.97).[113]

When examining CRT devices in participants older than 75 years of age, Doring et al. (2018) found a higher percentage of infection needing device removal with CRT-D devices: 3.1 percent of CRT-D participants compared with none of CRT-P participants.[110]CRT-D is generally associated with higher risk of device infections, but additional studies are needed to confirm this finding.

Cardiac Perforation/Tamponade

Six studies reported on cardiac perforation (including coronary sinus perforation) or cardiac tamponade.[2, 102, 105, 106, 109, 113] Three studies did not report which CRT type experienced the event.[102, 105, 106] Azizi et al. (2005) only reported one coronary sinus perforation for 244 participants (0.4%).[102] Verbrugge et al. (2011) reported cardiac tamponade in only one case of 220 participants (0.5%), occurring in the cohort of participants 70 to 79 years of age.[106] Killu et al. (2008) compared coronary sinus perforation among those participants ≤80 years of age (0.2%) versus >80 years (0%) and found no significant difference (p >0.99).[105]

In the COMPANION trial, device types were compared and coronary venous perforation and tamponade were 1.1 percent and 0.5 percent, respectively, for the CRT-P and 0.8 percent and 0.3 percent, respectively, for the CRT-D groups (no p value specified).[2] We identified two new studies reporting this outcome. Barra et al. (2018) found cardiac perforation with tamponade occurred in 0 percent of CRT-P participants and 0.3 percent of CRT-D participants (no p value reported).[109] As a "late" complication, after the initial hospital discharge, cardiac perforation with tamponade occurred in 0 percent of CRT-P participants and 0.1 percent of CRT-D participants.

Using a definition of "cardiac tamponade needing intervention", Looi et al. (2018) found a similar incidence for CRT-D (0.6%) versus CRT-P (0%) devices within 24 hours of implant (p value not reported).[113] Coronary sinus dissection was reported separately but showed no significant difference (CRT-D (0.6%) versus CRT-P (2.3%); p=0.97).

A conclusion regarding the comparative risk for CRT-P versus CRT-D for cardiac perforation/tamponade cannot be made.

Lead Dislodgement

Seven studies reported on lead dislodgement,[102, 105, 106, 108-110, 113] including three studies we identified during the update.[109, 110, 113] 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.[105] Verbrugge et al. (2011) reported multiple reasons for lead replacement (5.4% dislodgement), including dislocation, microperforation, and diaphragmatic stimulation.[106] However, the study reported this complication by age category and did not separate by device type. Similarly, Romeyer-Bouchard et al. (2007) reported dislodgement in 6.9 percent of cases but did not specify by device type.[108] The study also correlated lead dislodgement with re-intervention (r =0.8; p<0.001).[108] Azizi et al. (2005) reported 2.9 percent dislodgment[102] and Kilu et al. (2008) reported 7.1 percent lead revisions,[105] but neither study specified dislodgement by device type. Two studies found no difference in lead replacement with increasing age (≤80 years of age vs. >80 years of age; 7.3% vs. 5.6%, p=0.66)[105] or dislodgment (<70 years of age, 70 to 79 years of age, and ≥80 years of age; 3% vs. 1% vs. 2%, respectively; no p-value).[106]

In contrast to the prior studies, the studies we identified during the update separated results for lead dislodgement by device type. Doring et al. (2018) noted that lead dislodgment requiring a revision procedure was the most common major complication for CRT devices, occurring in 2.5 percent of CRT-P participants and 5.2 percent of CRT-D participants (no p value reported).[110]

Using the definition of acute and late complications, Barra et al. (2018) found similar rates among the devices.[109] Overall, dislodgement occurred in 4.2 percent of CRT-P devices and 4.4 percent of CRT-D devices . As a late complication, dislodgement occurred in 2.3 percent of CRT-P devices and 3.1 percent of CRT-D devices. Other types of lead dysfunction were also reported, including lead dysfunction, diaphragmatic pacing without macro-displacement, and "loose set screw."

A study by Looi et al. (2018) used a similar definition for complications of acute (within 24 hours of implant) and early (>24 hours to 2 weeks after implant) "lead displacement/ remanipulation".[113] There was an increased but not statistically significant different increase in lead displacement/remanipulation for CRT-D (4.5%) versus CRT-P (2.3%) devices within 24 hours of implant (p=0.53) and within 2 weeks of implant for CRT-D (1.3%) versus CRT-P (0%) devices (p value not reported). Using a definition of "lead issues needing intervention", late lead complications (≥2 weeks after device implantation) were lower for CRT-D (4.5%) versus CRT-P (6.9%) devices (p=0.5).

In general, CRT-D devices had more dislodgment but further studies are needed.

Ventricular Arrhythmia

Two studies reported on VA, one[102] from the prior review and the other from the update.[47] Only one study reported on VA perioperatively.[102] In the study by Azizi et al. (2005), perioperative VT requiring defibrillation occurred in four of 285 procedures (1.3%).[102] However, this study did not report results by device type.

In the other study, VA was classified as resuscitated cardiac arrest or sustained VT versus sustained VT requiring medical intervention or electrical conversion.[47] However, this study included the harm as a clinical outcome and not necessarily as a perioperative complication. Similarly, the study arms had multiple devices combined, such as ICD and CRT-D or bradycardia pacemaker and CRT-P. Incidence between the device categories for resuscitated cardiac arrest or sustained VT was 4 percent for pacing device and 4.7 percent for defibrillator devices. Incidence between the device categories for sustained VT requiring medical intervention or electrical conversion was 2.5 percent for pacing devices and 2.9 percent for defibrillator devices. Overall, there was no statistically significant difference between these device categories

(defibrillator vs. pacing) for resuscitated cardiac arrest or sustained VT (HR 1.03, 95% CI, 0.59 to 1.79; p=0.91) or sustained VT requiring medical intervention or electrical conversion (HR 1.12, 95% CI, 0.54 to 2.30; p=0.76). However, no direct comparison of VA was made for CRT-P versus CRT-D and no definitive conclusion can be made.

Inappropriate Shocks Cardiac Resynchronization Therapy With Defibrillator Only

Five studies reported inappropriate shocks.[47, 104, 105, 111, 113] Three of the studies were identified during the update.[47, 111, 113] Killu et al. (2008) reported an incidence of 4.3 percent over the duration of the study, a median 3.1 years.[105] Younger participants (≤80 years of age) received a higher percentage of inappropriate therapy (5.1%) as compared with those older than 80 years of age (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 these events occurred.[104] Looi et al. (2018) reported an observational study in New Zealand of 200 patients undergoing CRT, followed for a median of 4 years, in which 10 (6.4%) of the patients had inappropriate shocks, most commonly because of atrial fibrillation (60%) or supraventricular tachycardia (30%).[113]

In the DANISH trial, an endpoint classification committee assessed inappropriate shocks.[47] The overall incidence of inappropriate shocks in defibrillator devices (CRT-D and ICD) was reported as 5.9 percent during a median of 5.6 years followup but not reported by device type (CRT-D versus ICD). In a cohort assessing the response of cardiac synchronization therapy in AF participants, during a median followup of 2.6 years, inappropriate shocks occurred significantly more frequently in intermittent AF participants (24%) than in those with sinus rhythm (3%) (HR: 7.9, 95% CI, 2.5 to 35.0), after adjustment for age, sex, NYHA functional class, proportion of LBBB morphology, ejection fraction, QRS duration, left atrial volume, serum creatinine ≥ 1.4mg/dL, and use of beta blockers.[111] Although not significant, the results for those with permanent AF (2%) was in the opposite direction (HR 0.7, 95% CI, 0.1 to 6.2).

In general, studies have variation in reporting and followup duration, including number of inappropriate shocks versus number of participants with inappropriate shocks and time to first inappropriate shock. This variation, in addition to failure to specify inappropriate shocks by CRT-D, preclude any conclusion.

Death Within 1 Week

Two studies reported death within 1 week,[102, 103] one study reported in-hospital mortality,[107] one study reported 30-day mortality,[105] and in one study the exact timing was not specified.[28] In the study by Takaya et al. (2010), no events occurred during 6-month followup for either the five CRT-P participants or the thirty-five CRT-D participants.[103] The study by Azizi et al. (2005) reported no perioperative mortality.[102] The study by Killu et al. (2008) specified a 30-day mortality, with six deaths among participants ≤80 years of age (1.0%) versus zero among participants >80 years of age (0%) (p >0.99).[105] Mortality was not specified by CRT device type. 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 comparison.[107] The authors did find that among participants undergoing CRT-D placement, the odds of death were over 30-fold greater for those using inotropes and having at least one complication versus those with no complications (OR: 35.51, 95% CI, 14.44 to 87.32, p<0.001).[107] However, this study, too, made no direct CRT

comparison. The COMPANION trial did not specify the timing of deaths in its study nor did it directly compare mortality between CRT-P and CRT-D.[28] Consequently, although five studies reported on mortality, the studies rarely specified the exact timing or cause of death and used Kaplan-Meyer survival curves for mortality.[28, 105] These included studies are not comparable in their definition of mortality and followup, and no definitive conclusion can be made.

Effectiveness of Alternative CRT Techniques Versus Conventional CRT Techniques

Key Points

- There are fewer HF hospitalizations with quadripolar LV leads compared with bipolar LV leads (low strength of evidence) but insufficient evidence to draw conclusions about other outcomes.
- MultiPoint Pacing (MPP) with a quadripolar LV lead does not appear to confer additional clinical benefits compared with CRT with a quadripolar LV lead alone.
- There is insufficient evidence to determine the effectiveness of other alternative CRT techniques compared with conventional CRT techniques.

Study Characteristics

We identified three trials assessing the effectiveness of alternative cardiac resynchronization therapy techniques.[54, 55, 116] Two trials randomized patients to CRT-D insertion using a transvenous (conventional) bipolar LV pacing lead versus CRT-D insertion using a transvenous quadripolar LV pacing lead (initially FDA approved for use in the United States in 2011). [54, 55] One trial [117] randomized patients to conventional CRT (incorporating one vector for LV pacing) versus MPP (incorporating two vectors for LV pacing). We identified no randomized control trials assessing adaptive CRT, or His bundle pacing compared with conventional CRT techniques.

Both quadripolar LV lead trials stipulated enrollment criteria consisting of LVEF ≤35%, NYHA class II–IV, and QRS duration ≥130 ms with LBBB morphology. One was a small single center RCT[54] with 46 participants with primary efficacy endpoints of change in LVEF and NYHA class after 3 months follow-up. The other was a multicenter RCT[55] with 195 participants (199 enrolled) with primary endpoints of heart failure hospitalizations and total mortality and a secondary efficacy endpoint of change in NYHA class after 12 months follow-up (Table 27).

The MPP trial prospectively enrolled patients meeting ESC or ACC/AHA/HRS guideline criteria for CRT therapy (95.9% received CRT-D therapy) consisting of LVEF ≤35%, NYHA class II–IV, and QRS duration ≥120 - 130 ms. Following 6 months follow-up a total of 544 participants were determined to be echocardiographic "non-responders" (reduction in LVESV < 15%) and 467 participants were both randomized and completed 6 months of additional follow-up in a 1:1 ratio to MPP (236 participants had MPP activated) versus conventional CRT (231 participants) with reassessment for echocardiographic response (Table 27). [117]

Participant Characteristics

Both quadripolar LV lead versus bipolar LV lead trials used established clinical guideline criteria for CRT-D insertion (see above). They enrolled a predominantly male population (74% to 86% male) with a similar mean age (68 to 69 years) and included participants with non-ischemic as well as ICM (51% to 66%). There were no significant differences in baseline characteristics including mean LVEF (25% to 28%), cardiomyopathy subtype, and medical therapy. [54, 55]

The MPP trial also used established clinical guideline criteria for CRT-D insertion (only 4.1% received CRT-P therapy). It enrolled a predominantly male population (78.4% - 80.9%) with a similar mean age (68 years) and included participants with non-ischemic as well as ICM

(51.5% to 56.4%). There were no significant differences in baseline characteristics including mean LVEF (26%), cardiomyopathy subtype, and medical therapy.[117]

Table 27. Study characteristics of trials assessing effectiveness of CRT-D with Quadripolar LV Lead versus Bipolar LV Lead or MultiPoint LV Pacing

Author, year	Number of patients	Length of followup	Device manufacturer name/ device model	Comparison	NYHA class	Funding source
Sardu, 2017[55]	195	12 months	St. Jude Medical	Bipolar LV lead	NYHA II-III	Unknown
Bencardino, 2016[54]	43	3 months	St. Jude Medical	Bipolar LV lead	NYHA III-IV	Unknown
Leclercq, 2019[117]	467	6 months	Multipoint pacing	MultiPoint LV Pacing	NYHA II-IV	Industry

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

Risk of Bias

In the quadripolar LV lead trails, computerized randomization was used for LV lead selection. One trial stated that it was not double-blinded (high risk of bias) but did note blinding for outcome assessment. For the other trial, most of the risk of bias elements were unclear.

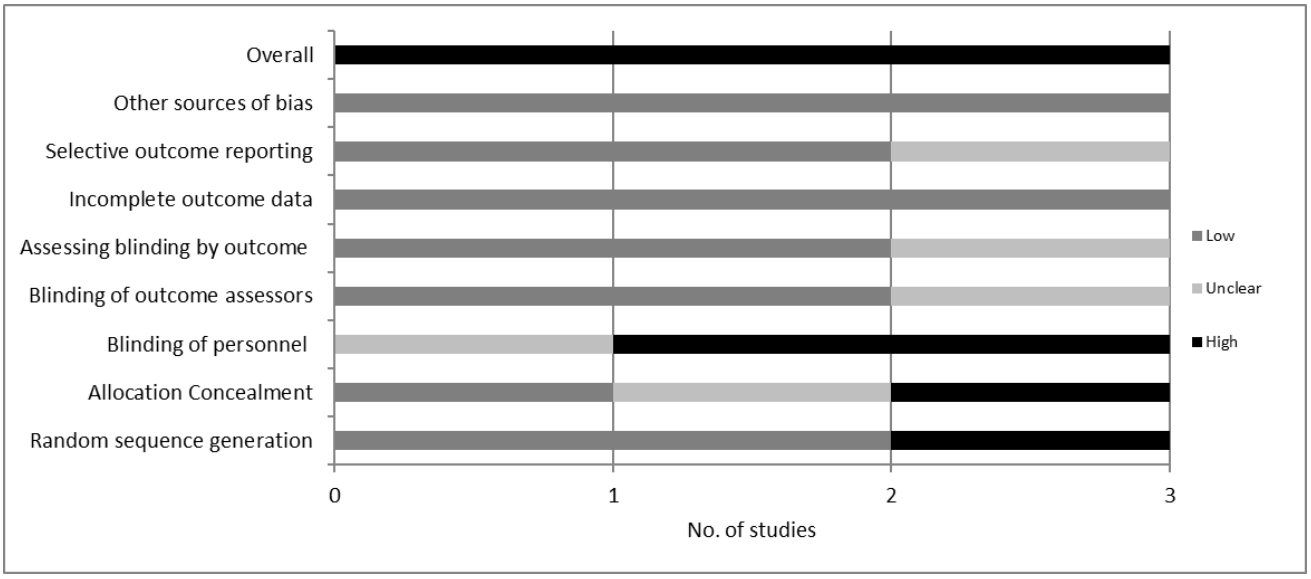
In the MPP trial there was blinding of both the patients and echocardiographic core laboratory although not the treating physician following randomization to conventional CRT programming versus activation of MPP programming. Of note, the authors reported an "on treatment" analysis as opposed to an "intention to treat" analysis (high risk of bias).

Table 28. Summary of risk of bias for trials assessing effectiveness of CRT-D with Quadripolar LV Lead versus CRT-D with Bipolar LV Lead or MultiPoint LV Pacing

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
Bencardino, 2016[54]	-	-	+	-	-	-	-	-	+
Sardu, 2017[55]	-	?	?	?	?	-	?	-	+
Leclercq, 2019[117]	+	+	+	-	-	-	-	-	+

+=high; -=low; ?=unknown

Figure 16. Summary of risk of bias for trials assessing effectiveness of quadripolar lead pacing vs. bundle pacing



Effectiveness Outcomes

One small quadripolar LV lead RCT[54] with 46 participants reported only change in LVEF after 3 months follow-up. The larger quadripolar LV lead RCT[55] (with 195 participants) included the primary endpoints of heart failure hospitalizations and total mortality after 12 months follow-up. The MPP trial [117] with 467 participants reported change in LVESV after 6 months follow-up as the primary end point, as well as mortality and heart failure events as secondary end points. None of the trials reported other outcomes of interest, such as QOL or Packer score.

Table 29. Outcomes reported in the trials assessing effectiveness of CRT-D with Quadripolar LV Lead versus CRT-D with Bipolar LV Lead

Author, year	All-cause mortality	HF hospitalization	LVEF	LVESV
Sardu, 2017[55]	X	X		
Bencardino, 2016[54]			X	
Leclercq, 2019[117]	X	X		X

HF= heart failure; LVEF=left ventricular ejection fraction; LVESV=left ventricular end systolic volume

All-cause Mortality

Sardu et al.[55] did not identify a significant difference in mortality between those with quadripolar LV leads (5%) versus those with bipolar LV leads (7%). The follow-up was limited to 12 months. There is insufficient evidence to draw a conclusion about the comparison of quadripolar LV leads with bipolar LV leads.

Leclercq et al.[117] did not identify a significant difference in mortality between the MPP arm (4 deaths) versus the conventional CRT arm (6 deaths) at 6 months follow-up, however, this study was not powered to examine this outcome as a primary endpoint.

Heart Failure (HF) Hospitalizations

Sardu et al.[55] reported a significant difference in heart failure hospitalizations between those with quadripolar LV leads (15.2%) versus those with bipolar LV leads (25%) after 12 months follow-up ($p = 0.035$). There were fewer HF hospitalizations with quadripolar LV leads compared with bipolar LV leads (low strength of evidence).

Leclercq et al. [117] reported no significant difference in heart failure hospitalizations between those with MPP (7.9%) versus those with conventional CRT (8.0%) after 6 months follow-up.

Left Ventricular Ejection Fraction

Bencardino et al.[54] reported a significant difference in the increase in LVEF between those with quadripolar LV leads (increased from 25% to 36%) versus those with bipolar LV leads (increased from 27% to 32%) after 3 months follow-up ($p < 0.01$).

Left Ventricular Ejection Systolic Volume

Leclercq et al. [117] reported no significant difference in those with at least 15% reduction in LVESV (CRT "responder") between those with MPP (31.8%) versus those with conventional CRT (33.8%) after 6 months follow-up.

Summary of Findings for Specific Subgroups of Interest

Comparative analyses of the pre-specified subgroups were not undertaken in these RCTs, likely due to their modest size.

Table 30. Strength of evidence for key effectiveness outcomes of CRT-D with Quadripolar LV Lead versus CRT-D with Bipolar LV Lead or MultiPoint LV Pacing

Key outcomes	No. Studies (number of patients)	Study limitations	Directness	Consistency	Precision	Reporting bias	Strength of evidence Findings
All-cause mortality	2 trials (662)	High	Direct	Unknown	Precise	Undetected	Insufficient
Heart failure hospitalizations	2 trials (662)	Low	Direct	Unknown	Precise	Undetected	Low Fewer HF hospitalizations with quadripolar LV leads compared with bipolar LV leads and no difference with addition of MPP

HF=heart failure; LV=left ventricular; No.=number of ; MPP=MultiPoint Pacing

Harms of Alternative CRT Techniques Versus Conventional CRT Techniques

Key Points

- We identified no studies reporting procedure related complications, length of hospital stay, cardiac perforation/tamponade, pneumothorax; and, for several harms, only one study provided data.
- Quadripolar lead pacing compared with bipolar leads has less lead dislodgment, likely owing to more stable positioning and greater sensing and pacing configurations.
- No definitive conclusion can be made regarding VAs, but incidence of VA appears similar by lead type.

Study Characteristics

Four studies addressed harms of alternative cardiac resynchronizations techniques: three studies assessed quadripolar lead pacing[55, 118, 119] and one study assessed multipoint pacing.[120] We identified no studies reporting harms for adaptive and His bundle pacing. One study on quadripolar leads was an RCT[55] and the others were prospective[119, 120] or retrospective cohorts.[118] The largest study had 230 participants in a study arm[119] and the smallest included only five participants, both prospective cohort studies.[120] Followup ranged from 6 months[119] to 30 months.[120] The multipoint study was conducted with the following devices: Medtronic (46%), Biotronik (23%), Guidant (Boston Scientific) (15.5%), and St. Jude Medical (15.5%).[120] One quadripolar study used bipolar LV pacing leads from St. Jude and Medtronic and quadripolar LV pacing leads from St. Jude (Quartet® model 1458Q and Promote Q®) and Medtronic (Attain Performa®).[55] LV pacing leads were connected to a bipolar CRT-D device (St. Jude, Medtronic) and/or to a quadripolar CRT-D device (St. Jude Quadra Assura®; Medtronic Viva® Quad XT and Viva® Quad S).[55] Another quadripolar lead pacing study used a Medtronic CRT-D device and a bipolar lead or a quadripolar Attain Performa® lead.[118] The last quadripolar lead pacing study was performed with the St. Jude Quartet 1458Q lead while the control arm used different market-released LV leads from five manufacturers (Boston Scientific, Medtronic, St. Jude, Sorin Group, and Biotronik).[119] Two studies reported no sponsor support,[55, 119] and the other two did not report the funding source.[118, 120]

Population Characteristics

In the multipoint study, the only arm which met inclusion criteria was composed of five participants with severe heart failure with reduced ejection fraction and wide QRS (≥150 ms) or those with failure of biventricular pacing to narrow QRS during implantation.[120] In all the studies of alternative cardiac resynchronizations techniques, the percentage of women in the study arms ranged from 0 percent[120] in the multipoint study to 28 percent in the quadripolar lead pacing arm of the study by Sardu et al. (2017).[55] The mean age ranged from 67 years of age[55] in the bipolar arm of the study by Sardu et al. (2017) to 75 years of age in the multipoint study by Laish-Farkash et al. (2018).[120] No studies reported the racial distribution of the participants.

Three of the four studies reported the proportion of participants with ICM,[55, 118, 120] which ranged from 47 percent[118] to 68 percent.[55] One study reported coronary artery disease, which ranged from 52 percent to 59 percent.[119] Only two studies[118, 120] reported AF, which ranged from 27 percent[118] to 80 percent[120].

Three studies reported individual NYHA classes,[55, 118, 120] which was predominantly class II with a range of 52 percent[55] to 100 percent[120] of study arm participants, or class III with a range of 0 percent (all participants were class II)[120] to 50 percent[55] of study arm participants. One study combined classes III and IV, which ranged from 62 percent to 72 percent.[118] Classes I and IV were either not directly reported[55, 118, 119] or had no participants with NYHA class I/IV symptoms.[120]

All four studies[55, 118-120] reported the mean LVEF, which ranged from 17 percent[120] to 28 percent[55]. Only one study reported LBBB, occurring in 68 percent to 71 percent of the participants in the study arms[118]; RBBB and left hemiblock ranged from 6 percent to 11 percent and approximately 6 percent, respectively.[118] The other three studies did not report LBBB, RBBB, or intraventricular conduction delay characteristics.[55, 119, 120]

All four studies reported QRS duration.[55, 118-120] The mean QRS duration ranged from 135 ms[55] to 172 ms[120] in the study arms.

No studies reported serum creatinine levels. Two studies reported renal function as either chronic kidney disease[118], ranging from 12 percent to 21 percent of participants per arm, or renal insufficiency,[55] ranging from 8 percent to 10 percent of study arm participants.

Risk of Bias

Of the four studies reporting harms for alternative cardiac resynchronizations techniques, three studies were cohort studies[118-120] and one was an RCT.[55] The single multipoint pacing study was a cohort study.[120] Two cohort studies had an overall low risk of bias[119, 120]; one cohort study had an unclear risk of bias because it did not assess reasons for study attrition.[118] Two cohort studies had non-differential lost to follow up[119] or included detailed outcomes, including cause of death.[120] In each study, the cohorts were representative of the heart failure population and the control groups, if applicable, were drawn from the same cohort as the comparison arm. The multipoint pacing study did not have a control arm, but was representative of those who would need multipoint pacing, including those with severe systolic heart failure, wide QRS, and failure of biventricular pacing to narrow the QRS during implantation.[120] In general, the harms were not present at the beginning of the study and appropriate baseline characteristics were assessed, including the use of beta blockers when assessing ventricular arrhythmias,[120] and not statistically significantly different. The three cohort studies assessed outcomes through records linkage, such as registry data or medical records, and followup was long enough for harms to be identified, from 6 months[119] to 30 months[120] (Table 31 and Table 32).

The single included RCT studied 195 people with type 2 diabetes who received CRT-D treatment, randomly assigned to either quadripolar lead pacing or bipolar LV lead pacing with 1 year of followup.[55] The overall risk of bias for the harms outcomes for this trial was low. Although it was not clear if there was blinding of personnel or for outcome assessment, the harms of lead dislodgement and VA would not be expected to be influenced by unmasking.

Table 31. Summary of risk of bias for trials assessing harms of alternative versus conventional cardiac resynchronization therapy techniques

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
Sardu, 2017[55]	-	?	?	?	?	-	?	-	-

+=high; -=low; ?=unclear

Figure 17. Summary of risk of bias for trials assessing harms of alternative versus conventional cardiac resynchronization therapy techniques

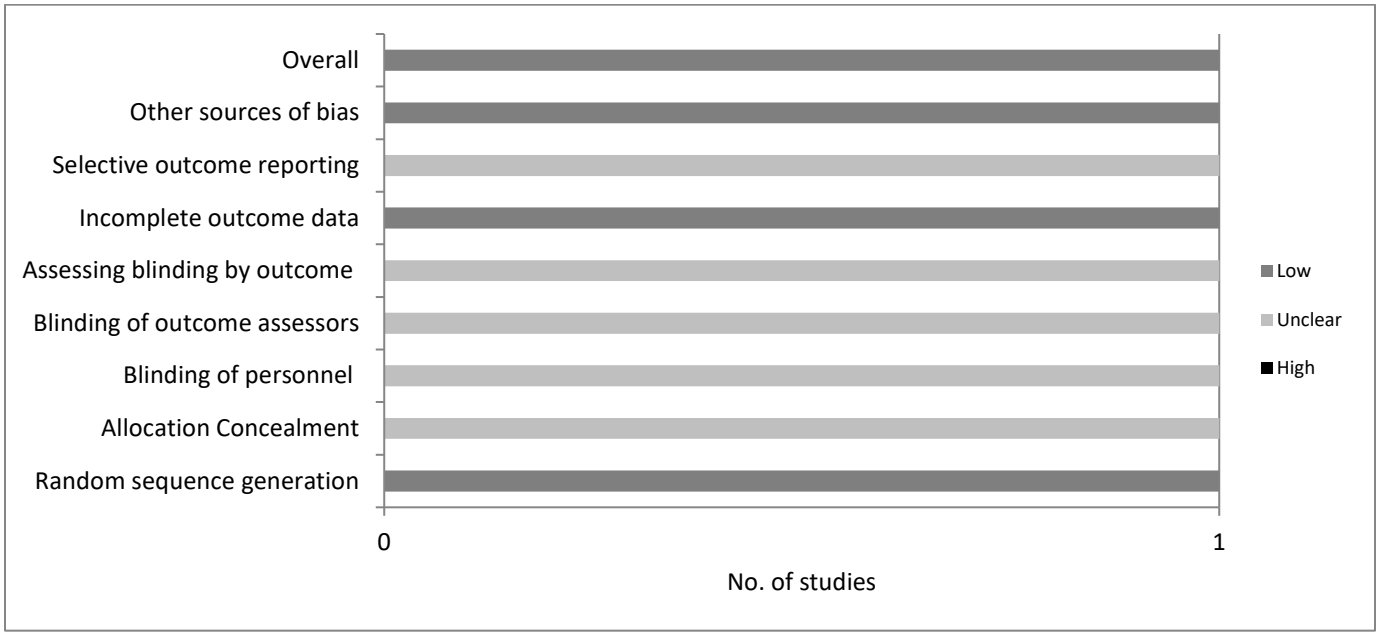
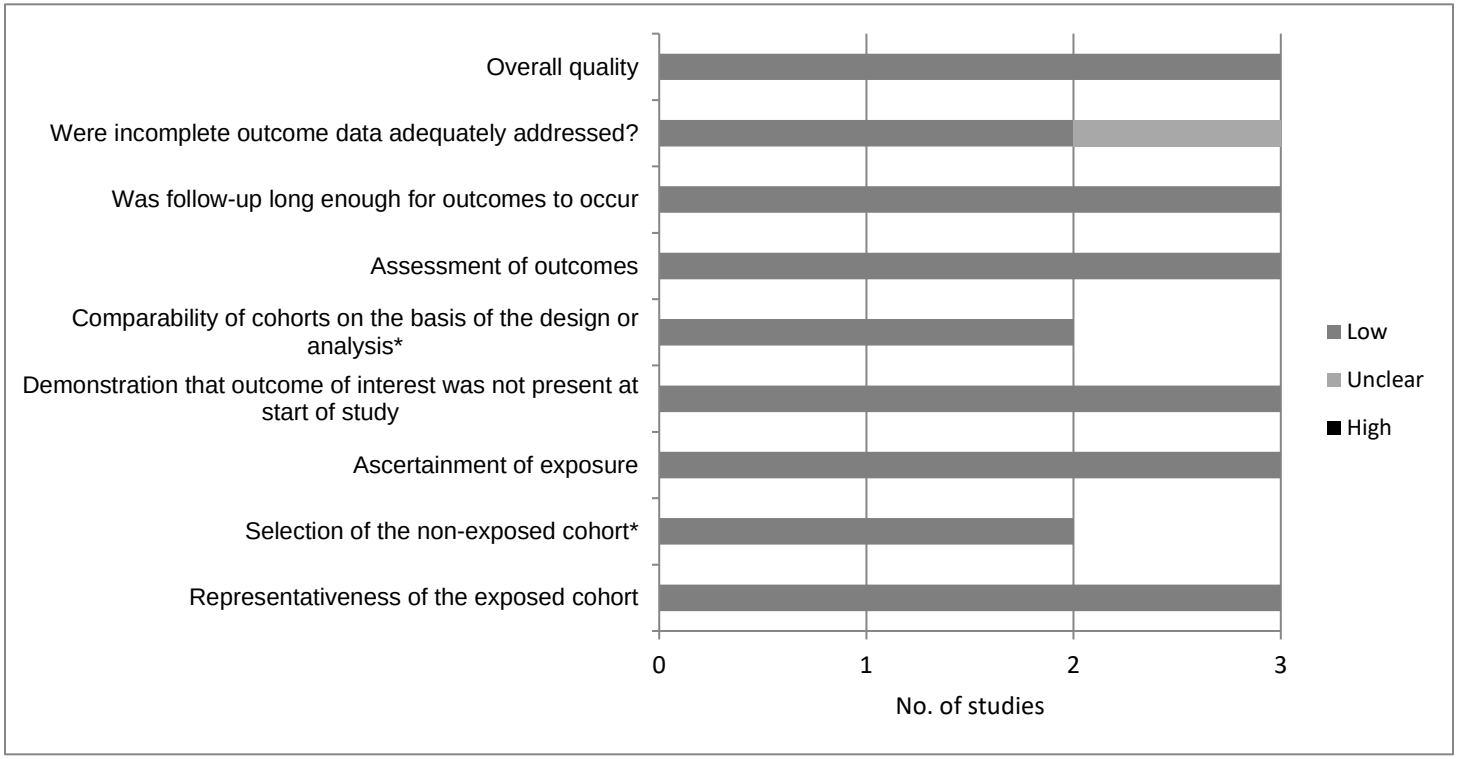


Table 32. Summary of risk of bias for cohort studies assessing harms of alternative versus conventional cardiac resynchronization therapy techniques

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
Forleo, 2015[119]	-	-	-	-	-	-	-	-	-
Laish-Farkash, 2018[120]	-	NA	-	-	NA	-	-	-	-
Ziacchi, 2018[118]	-	-	-	-	-	-	-	?	-

+=high; -=low; ?=unclear; NA=not available
*Only applicable to studies with control groups

Figure 18. Summary of risk of bias for cohort studies assessing harms of alternative versus conventional cardiac resynchronization therapy techniques



*Only applicable to studies with control groups

Table 33. List of harms reported in studies assessing harms of alternative versus conventional cardiac resynchronization therapy techniques

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 1 week
RCTs										
Sardu, 2017[55]							X	X	X*	
Prospective cohorts										
Forleo, 2015[119]				X	X		X			
Laish-Farkash, 2018[120]								X		X
Retrospective studies										
Ziacchi, 2018[118]							X			

*Study did not distinguish between appropriate and inappropriate shocks

Harms Outcomes

List of harms reported in the included studies is shown in Table 33. We identified no studies reporting procedure-related complications, length of hospital stay, cardiac perforation/tamponade, or pneumothorax.

Pocket Hematoma

Only one study reported this outcome, reporting an incidence of 0.7 percent of pocket hematomas in a single-center prospective registry study, but results were not provided by the bipolar or quadripolar lead study arms.[119]

Device Infection

Only one study reported device infection.[119] The study by Forleo et al. (2015)[119] was a single-center prospective cohort registry study, which compared outcomes and complications at 6 months after implantation of a CRT-D device with either quadripolar lead pacing or bipolar leads. The decision to implant a quadripolar lead was at the discretion of the electrophysiologist. The authors reported an infection rate of 1.1 percent in the bipolar arm compared with 0 percent in the quadripolar lead pacing arm, but this was not statistically significant (p=0.12).

Lead Dislodgement

Lead dislodgement was the primary harm reported in the studies of alternative cardiac resynchronization therapy techniques, described in three of the four studies, all with quadripolar leads.[55, 118, 119] The incidence of lead dislodgment for quadripolar leads was generally lower, 1 percent versus 9.4 percent (p=0.018),[55] 2 percent versus 2.5 percent (p value not reported),[118] and 2.7 percent versus 5.7 percent (p=0.16)[119] in quadripolar lead pacing compared with bipolar leads, respectively.

With only 6 months of followup, Forleo et al. (2015)[119] noted that the quadripolar LV leads increased implant flexibility and had lower rates of dislodgment and phrenic nerve stimulation.[119] By Kaplan-Meier analysis, the primary outcome of lead failure was significantly lower in the arm with quadripolar leads (p=0.02). Also, all cases of phrenic nerve stimulation were resolved by reprogramming in the quadripolar lead pacing arm, as compared with only 84 percent of the bipolar arm (p=0.75).

Ziacchi et al. (2018) similarly noted that the quadripolar leads allowed for more distal vein wedging, which allowed better lead stability but also the option of pacing at mid and basal rather than only apical sites.[118] Although the quadripolar lead was placed apically in 36 percent of participants in that study arm, only 12.5 percent of quadripolar lead pacing participants were paced apically, thus allowing for more pacing options. There was a low dislodgement rate of 2 percent at a longer, 14 months of followup, compared with the 6 months followup by Foreleo et al. (2015).[119] However, the authors note that minor dislodgements can be resolved with cathode reprogramming and, therefore, stability may be overestimated if dislodgment is defined as requiring surgical repair.[118]

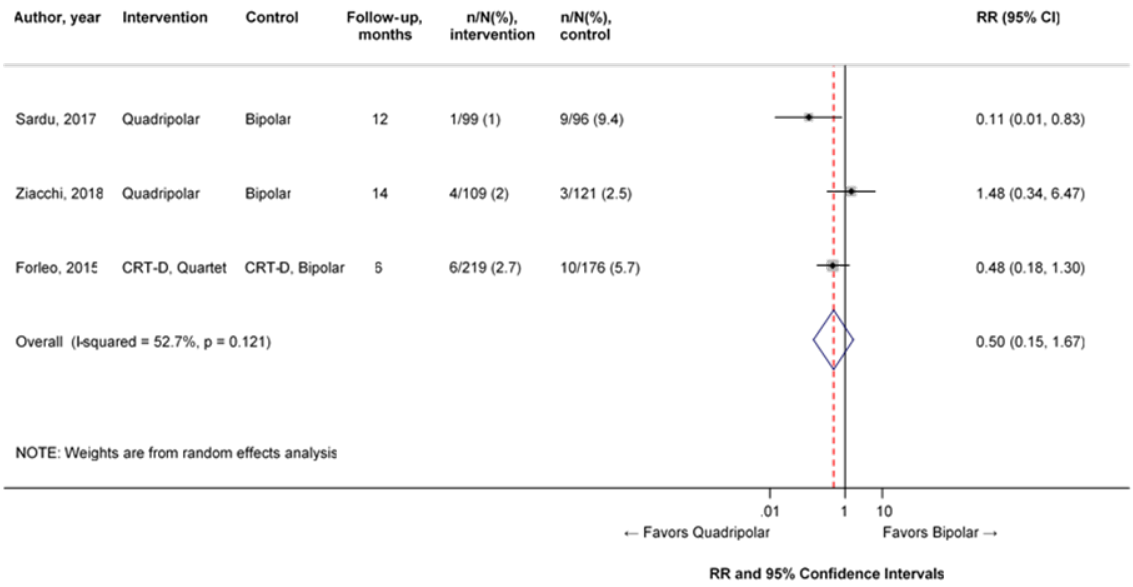
Sardu et al. (2017) defined catheter dislodgements based on symptoms, schedules, and device interrogation, confirmed by radiographic biplane projections assessment.[55] After adjustment for age, obesity, renal dysfunction, NYHA class III, QRS duration, and LVEF, quadripolar leads were associated with an 88 percent reduction in LV catheter dislodgements (HR 0.112, 95% CI, 0.014 to 0.893; p=0.039). Similar challenges in the anatomic target and lead location stability were noted. Again, the role of lead position stability, sensing and pacing thresholds, and programming was noted. Similarly, the authors noted quadripolar lead

pacing compared with bipolar lead pacing may offer more variety in sensing and pacing configurations from different sites, reducing LV dislodgements and need for interventions.[55]

A meta-analysis of these three studies showed a non-statistically significant relative risk reduction of lead dislodgement for quadripolar leads of 50% (RR: 0.50, 95% CI, 0.15 to 1.67; p=0.258) (Figure 19). There was moderate statistical heterogeneity (I^2=53%). One study included only participants with type 2 diabetes.[55] Given the small number of studies, participants, and events as well as variation in followup time, no definitive conclusion can be made.

Overall, quadripolar lead pacing compared with bipolar leads had less lead dislodgment, likely owing to more stable positioning and greater sensing and pacing configurations, which decreases the need for intervention.

Figure 19. Meta-analysis of lead dislodgement comparing quadripolar lead pacing with bipolar lead



Ventricular Arrhythmias

Two studies reported on VAs, one study compared quadripolar lead pacing to bipolar leads[55] and the other reported on multipoint pacing.[120] Sardu et al. (2017) found an incidence of VT in 27.1 percent of participants with quadripolar lead pacing compared with 25.2 percent of participants with bipolar lead pacing by 1 year of followup (p=0.5).[55] Although the study was small, with only five participants, Laish-Farkash et al. (2018) found a similar incidence of 20 percent of VAs by 1 year for multipoint cardiac resynchronization therapy.[120] No definitive conclusion can be made, although incidence of VA appears similar by lead type.

Inappropriate Implantable Cardioverter Defibrillator Shocks

Only one study reported on defibrillator shocks in participants with quadripolar lead pacing versus bipolar leads with 1 year followup, finding no statistically significant difference (13.1% vs. 14.6%; p=0.51).[55] However, the study did not distinguish between appropriate and inappropriate shocks, and no definitive conclusion can be made.

Death Within 1 Week

Only one study reported on death within 1 week of implantation in a small study of five participants receiving multipoint cardiac resynchronization therapy.[120] A single patient died post-implantation from a large LV thrombus, likely unrelated to the procedure.

Effectiveness and Harms of His Bundle Pacing or CRT Versus Right Ventricular Pacing for LVEF between 36% and 50% With AVB

Key Points

- The evidence is limited on effectiveness and harms of rapidly expanding CRT or His bundle pacing in eligible participants, with the completion of several ongoing RCTs expected in a few years.

Description of Included Studies

We identified a recent existing systematic review addressing His bundle pacing or CRT (biventricular pacing) versus right ventricular pacing in patients with LVEF between 36% and 50% and AVB requiring ventricular pacing. Slotwiner and colleagues (2018) conducted a systematic review to inform the 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients with Bradycardia and Cardiac Conduction Delay.[15] This review included eight studies (4 RCTs): four comparing biventricular pacing versus right ventricular pacing (N=438)[121-124] and four comparing His bundle pacing versus right ventricular pacing (N=241).[125-128]

We updated this review by conducting a search for additional primary studies (Figure 3). We identified two additional cohort studies of His bundle pacing versus right ventricular pacing reporting limited harms data (Table 34).[129, 130]

Mortality

The review identified two studies comparing biventricular pacing versus right ventricular pacing and two studies comparing His bundle pacing versus right ventricular pacing for assessment of mortality. The effects on mortality were not statistically significant in comparing biventricular pacing with right ventricular pacing (RR: 1.0758; 95% CI, 0.51 to 2.27; p=0.848).[125, 128]

Additionally, no significant effect was also reported when biventricular pacing and His bundle pacing patients were pooled and compared with right ventricular pacing patients (RR: 0.926; 95% CI, 0.55 to1.57; p=0.773; I2=0%) (30-33).[123-125, 128]

Heart Failure Hospitalizations

No study was included in the review or found in our updated search that reported data on hospitalizations for heart failure.

Left Ventricular End-systolic Volume

The review identified three studies assessing LVESV in comparing biventricular pacing with right ventricular pacing. The authors conducted a meta-analysis and reported a significant decrease in end-systolic volume with biventricular pacing compared with right ventricular pacing (MD: –7.2039 mL; 95% CI, –11.95 to –2.46 mL; p=0.003; I^2=12.31%).[121, 123, 124]

The review authors also reported a significant reduction in LVESV when both biventricular pacing and His bundle pacing patients were pooled (5 studies) and compared with patients receiving right ventricular pacing (–7.09 mL; 95% CI, –11.27 to –2.91 mL; p=0.0009).[121, 123-126]

Left Ventricular End-diastolic Volume

The review identified three studies assessing LVEDV comparing biventricular pacing with right ventricular pacing. The authors conducted a meta-analysis and reported a significant decrease in end-diastolic volume for biventricular pacing compared with right ventricular pacing (MD: –2.7027 mL; 95% CI, –4.35 to –1.06 mL; p=0.0013; I^2=0%).[121, 123, 124]

The review authors also reported a significant reduction in LVEDV when both biventricular pacing and His bundle pacing patients were pooled and compared with right ventricular pacing patients (–2.74 mL; 95% CI, –4.37 to –1.1; p=0.001; I^2=0%)[121, 123-126]

Left Ventricular Ejection Fraction

The review identified three studies assessing change in LVEF in comparing biventricular pacing with right ventricular pacing. The authors conducted a meta-analysis and reported significantly higher LVEF with biventricular pacing compared with right ventricular pacing (MD: 6.340%, 95% CI, 2.84 to 9.84%; p=0.0004; I^2=0%).[121, 123, 124]

The authors conducted a meta-analysis of three studies comparing His bundle pacing with right ventricular pacing and reported that His bundle pacing was associated with a significantly greater LVEF (MD: 4.33%; 95% CI, 0.85 to 7.81%; p<0.01; I^2= 0%; mean duration of followup: 8.36 months).[125-127]

The review authors also reported that LVEF, which declined with right ventricular pacing, remained preserved and, in some studies, increased (5.328%; 95% CI, 2.86 to 7.8; p<0.0001; I^2=39.11%) when both biventricular pacing and His bundle pacing patients were pooled and compared with right ventricular pacing patients.

6-Minute Hall Walk Distance

The review identified three studies reporting the effect of biventricular pacing on 6MHWD. The authors conducted a meta-analysis and concluded that there was no definitive difference with biventricular pacing compared with RV pacing (MD: 6.736 m; 95% CI, –2.82 to 16.29 m; p=0.167; I^2= 0%).[121-123]

The two studies assessing effect of His bundle pacing reported conflicting results.[125, 126]

Quality of Life

The review identified one study on QOL assessed by SF-36.[123] This study did not report any significant difference in SF-36 domains between the biventricular pacing and RV pacing groups.

The two studies assessing effect of His bundle pacing reported conflicting results (one showing improvement and the other showing no improvement); one using the SF-36 survey[125] and the other using the MLHFQ.[126]

Complications Associated With Pacemaker Implantation

Six of the eight studies reported complications requiring surgical revision. The review authors concluded that physiologic pacing with either biventricular pacing or His bundle pacing was associated with a slightly higher risk of re-operation for lead revision.

We identified two cohort studies assessing the harms of His bundle pacing in our updated search but these studies reported limited data.[129, 130]

Table 34. Number of studies addressing clinical outcomes and harms for His bundle pacing or CRT versus right ventricular pacing

Study, Year Design	Intervention	No. of Participants	Followup	Outcomes
Stockburger et al., 2011[124] RCT	BiVP	108	1 year	Complications of Physiologic Pacing
Yu et al., 2014[123] RCT	BiVP	177	>2 years (Mean duration 4.8±1.5 years)	• % Ventricular Paced • 6-Min Walk • QOL • Complications of Physiologic Pacing
Albertsen et al., 2011[121] RCT	BiVP	50	3 years	6-Min Walk
Doshi et al., 2005[122] RCT	BiVP	103	6 months	• % Ventricular Paced • QOL • Functional Status • Complications of Physiologic Pacing
Kronborg et al., 2014[125] Randomized crossover	HisBP	38	1 year	• % Ventricular Paced • QOL • Complications of Physiologic Pacing
Occhetta et al., 2006[126] Randomized crossover	HisBP	18	6 months	• 6-Min Walk • QOL • Functional Status • Complications of Physiologic Pacing
Sharma et al., 2015[128] Retrospective study	HisBP	173	2 years	• % Ventricular Paced • Complications of Physiologic Pacing
Zanon et al., 2008[127] Non-randomized controlled trial	HisBP	12	Crossover design: 3	• % Ventricular Paced
*Bhatt, 2018[129] Prospective cohort	HisBP	427	24 months	• Lead dislodgement • Pneumothorax
*Shan, 2018[130] Prospective cohort	HisBP	18	Mean 36.2 months	• Procedure related complications • Lead dislodgement

BiVP=biventricular pacing; HisBP=His bundle pacing; QOL=quality of life; RCT=randomized controlled trial

*Newly identified studies from updated search

Discussion

Key Findings and the Strength of Evidence

Effectiveness and Harms of CRT-D Versus ICD

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 participants with an LVEF ≤35% and a QRS duration ≥120 ms compared with therapy with an ICD alone. Specifically, we found moderate strength of evidence for benefit from CRT-D versus ICD alone for all-cause mortality in minimally symptomatic participants. This statement is derived from data looking primarily at NYHA class II participants. The applicability of this finding to NYHA class I participants, a population significantly under-represented in studies, remains 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). Our update did not identify any new trials comparing CRT-D and ICD therapy but did identify new secondary analyses from one trial relevant to some of the pre-specified subgroups of interest.

In terms of pre-specified subgroups, there is compelling evidence that in CRT-D participants (compared to an ICD alone), female sex, LBBB morphology, and NICM are associated with superior outcomes (i.e., reduced heart failure hospitalizations and total mortality) as validated in recent sub-study reports. Clinical efficacy was still consistently seen in male sex and ICM but not in non-LBBB morphology. Sinus rhythm (as opposed to a history of AF) and a wider QRS complex are also associated with superior outcomes in participants undergoing CRT-D compared to an ICD alone although the data for these are less compelling. Finally, being < 65 years of age or ≥ 65 years of age did not diminish improvement in clinical outcomes, but little efficacy data was available for participants ≥75 years of age.

We identified 40 studies assessing harms for CRT-D, but the limited numbers of studies assessing each specific harm, heterogeneous study design, variable definitions of the harms, and overall low rate of complications, limits our ability to make conclusions. No significant and consistent differences were seen in pneumothorax, pocket hematomas, device infection, ventricular arrhythmias, inappropriate shocks, or cardiac perforation/tamponade when CRT-D and ICD devices were compared. CRT-D devices may confer protection against first VA. Additional study is needed for length of hospitalization and death within 7 days of device implantation. Studies suggest a potential increase in the number of procedural complications and LV lead dislodgement within 24 hours of implantation for CRT-D compared with ICD devices.

Effectiveness and Harms of CRT-P Versus Optimal Medical Therapy

There is moderate evidence that CRT-P, compared with OMT, is effective in improving survival, and reducing hospitalizations for heart failure in participants with an LVEF ≤35% and a QRS duration ≥120 ms compared with OMT alone**.** These data are largely derived from participants with NYHA class III–IV heart failure. The applicability of these findings to patients with NYHA class I–II heart failure remains unclear. Our systematic update did not reveal new effectiveness studies comparing CRT-P therapy with OMT alone but did identify one recent sub-study relevant to the pre-specified subgroups of interest noted below.

In regard to pre-specified subgroups, CRT-P was associated with improved clinical outcomes across subgroups of interest: in both women and men, those with ICM and NICM, and for those age ≥ 65 – 66.4 years and younger age. Clinical efficacy was attenuated by history of intermittent AF but not QRS morphology (LBBB vs. non-LBBB), although the data for these group analyses were limited.

We identified no additional harms studies during the update. From our prior report, harms associated with CRT-P were: cardiac perforation/tamponade (0% to 1.6%), pocket hematoma (0.2% to 9.5%), pneumothorax (0.5% to 1.5%), device infection (0.7% to 4.8%), and lead dislodgement (1.7% to 17%). Death within 1 week of implantation was reported in only very small studies, making the true incidence unclear.

Effectiveness and Harms of CRT-P Versus CRT-D

There is insufficient evidence, including no new definitive evidence since the 2015 report, that CRT-D improves health outcomes compared to CRT-P in patients with heart failure, LVEF ≤35% and QRS duration ≥120 ms, on optimal medical therapy.

One RCT included 1,520 subjects with NYHA class III or IV heart failure and ICM or NICM with a QRS duration of greater than 120 ms, randomized in a 1:2:2 ratio to optimized medical therapy alone, or in combination with CRT-P or CRT-D. This was the only randomized clinical trial that contained both CRT-D and CRT-P arms, however, direct statistical comparisons between those arms in this industry funded study have never been reported. Therefore, there is insufficient evidence to determine the effectiveness of CRT-D compared to CRT-P. Our systematic update did not reveal new effectiveness studies directly comparing CRT-D and CRT-P therapy in the interim four year period in this same patient population.

Due to study created, non-standardized definitions of harms, a large range of followup times, no specific time of the harms' occurrence, and limited direct CRT-P to CRT-D comparisons, assessing the comparative harms of the device types was a challenge. No conclusions could be made for length of stay, pneumothorax, pocket hematomas, cardiac perforation/tamponade, ventricular arrhythmias, inappropriate shocks (CRT-D devices), and death within 1 week. Procedure-related complication rates tended to be higher for CRT-D versus CRT-P devices, but not statistically significant. CRT-D tended to be associated with higher risk of device infections (similar to our prior review) and more lead dislodgment, but additional studies are needed to confirm this finding.

Effectiveness and Harms of Alternative versus Conventional Cardiac Resynchronization Therapy Techniques

Our updated systematic review identified two recently published CRT-D trials [54, 55] randomizing patients to CRT-D insertion utilizing a transvenous (conventional) "bipolar" left ventricular (LV) pacing lead versus CRT-D insertion utilizing a transvenous "quadripolar" LV pacing lead (approved for use in the United States in 2011) and demonstrated improvement in NYHA class, LVEF, and hospitalizations during a limited 3 to 12 month followup period. Comparative analyses of the pre-specified subgroups were not undertaken in these RCTs. Due to the advantage of quadripolar leads in regard to LV pacing programming we anticipate that quadripolar LV lead technology will rapidly supplant bipolar LV lead technology in clinical practice despite the lack of large long-term randomized control trials.

There were no recent adaptive CRT or His bundle pacing RCTs identified. Only one study assessed multipoint LV pacing, providing limited data for the harms of VA and death within 1

week.[120]

We identified no studies of alternative CRT techniques reporting procedure-related complications, length of hospital stay, cardiac perforation/tamponade, and pneumothorax. For several harms, only one study provided data. Quadripolar compared with bipolar LV leads appear to have less lead dislodgment owing to more stable positioning and four-fold greater sensing and pacing configurations. A meta-analysis showed a non-statistically significant relative risk reduction of lead dislodgement for quadripolar leads of 50 percent (RR: 0.496, 95% CI, 0.147 to 1.672; p=0.258). No definitive conclusion could be made regarding VAs, but incidence of VA appeared similar with quadripolar and bipolar leads.

Effectiveness and Harms of His Bundle Pacing or CRT (BiVentricular Pacing) Versus RV Pacing

Of great relevance for CRT-pacemaker therapy, the recently issued 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients with Bradycardia and Cardiac Conduction Delay: Executive Summary,[14] recommended that "in patients with a left ventricular ejection fraction between 36 percent and 50 percent and AVB, who have an indication for permanent pacing and are expected to require ventricular pacing >40 percent of the time, techniques that provide more physiologic ventricular activation (e.g., cardiac resynchronization therapy, His bundle pacing) are preferred to right ventricular pacing to prevent heart failure." This recommendation was based on a systematic review commissioned by the ACC/AHA/HRS.[15] There have been no studies in the interim that have conflicted with findings from this report although two randomized clinical trials are currently underway and will likely provide more definitive data regarding clinical efficacy in a few years. Since AVB constitutes the second most common indication for conventional pacing therapy, this new recommendation will likely lead to a rapid expansion of CRT-pacemaker implantation and His bundle pacing leads in the U.S..

Table 35. Summary of the strength of evidence for key effectiveness outcomes

Comparisons	All-cause mortality	Hospitalizations for heart failure	Quality of Life
Cardiac resynchronization therapy with defibrillator (CRT-D) vs. ICD alone	Moderate CRT-D improves mortality in participants with minimally symptomatic CHF (primarily class NYHA class II) compared with ICD alone. There is insufficient evidence to determine the effect on mortality of CRT-D compared with an ICD alone in patients with NYHA class III-IV symptoms.	High Reduction in HF events for CRT-D compared with an ICD alone, primarily in participants with an LBBB morphology.	High CRT-D compared with ICD alone improves QOL in participants with NYHA class III-IV CHF [mean difference -10.91 (95% CI, -12.03 to 7.27)]. However, CRT-D does not improve QOL in minimally symptomatic participants compared with an ICD alone [mean difference -0.83 (95% CI, -9.27 to 5.30)].
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.	Insufficient
Cardiac resynchronization therapy with pacemaker vs. with defibrillator	Insufficient	Low Compared with OMT, CRT-P and CRT-D were associated with 44% and 41% reduction in heart failure hospitalizations (not significantly different).	Insufficient
CRT-D with Quadripolar LV Lead vs. CRT-D with Bipolar LV	Insufficient	Low Study showed statistically difference in mortality but was a single non-blinded study.	Not Reported

CHF=chronic heart failure; CI=confidence interval; CRT-D=cardiac resynchronization therapy with defibrillator; CRT-P=cardiac resynchronization therapy with pacemaker; ICD=implantable cardioverter defibrillator; LBBB=left bundle branch block; MADIT-CRT=Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy; NA=not available; NYHA=New York Heart Association; QOL=quality of life; RAFT=Resynchronization–Defibrillation for Ambulatory Heart Failure Trial

Relationship of Findings to Existing Literature

Several systematic reviews have focused on CRT (see Table 36). Our review differs from prior reviews in that only studies with participants 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 appropriate use criteria for CRT based on guidelines.[131] This eliminated the REVERSE, BLOCK-HF, and HOBIPACE trials which included participants with LVEFs >35%.[132-134] 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 OMT alone to assess the impact of cardiac resynchronization. We did not assess the comparison of CRT-D with OMT as we determined this to be an inappropriate comparison given the known improvements in mortality by ICD therapy. Also, in contrast to several previous reviews, we included only RCTs to assess the key questions regarding effectiveness.

In terms of minimally symptomatic participants, the results of our review largely agree with those of prior reviews, which focused on the same population. Similarly, the prior review was in agreement with the systematic review performed in 2007 by Mcallister et al., which included studies primarily involving an advanced heart failure population.[135] Our prior review arrived at somewhat different conclusions in terms of the efficacy of CRT-D versus CRT-P in comparison to those by Jiang et al., which purported significant superiority of the former over the latter.[136] 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.[2]

In our updated review, we identified only two RCTs assessing a newer LV lead technology (the quadripolar LV pacing lead). Nevertheless, our process did identify an update to the 2016 ESC Guidelines[13] for the diagnosis and treatment of acute and chronic heart failure which, consistent with our 2015 report, specified that a QRS duration ≥130 ms should be warranted for CRT, citing two meta-analyses indicating a lack of CRT efficacy with QRS duration <130 ms.[137, 138] We also identified a major update to the ACC/AHA/HRS Guidelines on the Management of Patients with Bradycardia and Cardiac Conduction Delay, published in 2018, which advocated "physiologic pacing" (defined as either CRT or His bundle pacing) for patients with AVB and LVEF between 36% and 50% expected to require ventricular pacing >40 percent of the time to prevent heart failure.[14] This new recommendation was drawn from the conclusions of the ACC/AHA/HRS appointed Evidence Review Committee report completed the year before.[15] We have summarized the findings of this systematic review in this report and have found the subsequent studies published in the interim to be congruent with their findings.

Table 36. Prior systematic reviews of cardiac resynchronization therapy

Author, year	Review scope	Number of studies	Findings	Key differences compared to current systematic review
Adabag, 2011[139]	Effectiveness of CRT in participants with minimally symptomatic heart failure	5	CRT decreases all-cause mortality, reduces HF hospitalizations, and improves LVEF in NYHA functional class I/II HF participants.	Focused on minimally symptomatic participants (NYHA I-II). Included LVEF ≤40%.
Bryant, 2013 [140]	CRT and QRS duration	44	The benefit of CRT appears restricted to those with a baseline QRS duration >150 ms.	Focused on the effect of QRS duration and response to CRT. Included studies with QRS duration <120 ms. Included studies enrolling participants with LVEF >35%.
Ganesan, 2012 [141]	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 participants with AF.
Garg, 2013 [142]	CRT and chronic kidney disease	18	CRT improves left ventricular and renal function in participants 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 ≥120 ms.
Hess, 2013 [143]	CRT and AF	12	The combined rate of conversion from persistent or permanent AF to sinus rhythm was 0.107 amongst CRT participants.	Focused on studies reporting the effect of CRT on AF. Note: Only 1 reviewer assessed studies.
Jiang, 2012 [136]	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 [144]	Effectiveness of CRT in participants with minimally symptomatic heart failure	2	CRT reduces heart failure events in participants with mild heart failure symptoms, left ventricular dysfunction, sinus rhythm, and a prolonged QRS duration.	Included only NYHA class I and II participants.
McAlister, 2004 [145]	Effectiveness and harms of CRT in participants 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 participants with NYHA class III-IV symptoms). Included trials of LV only pacing. Did not examine remodeling outcomes (changes in

Author, year	Review scope	Number of studies	Findings	Key differences compared to current systematic review
				LVEF, LVESV, or LVEDV).
McAlister, 2007 [135]	Effectiveness and harms of CRT	195	CRT reduces morbidity and mortality in participants with LV systolic dysfunction, prolonged QRS duration, and NYHA class III or IV when combined with OMT.	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 [146]	Effect of CRT in participants with RBBB	5	There is no benefit of participants with RBBB although more data are needed.	Examined RBBB population specifically.
Proietti, 2014 [147]	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 ≥120 ms.
Santangeli, 2011 [148]	Effectiveness of CRT in participants with minimally symptomatic heart failure	5	Among participants 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 participants (NYHA I-II). Included LVEF ≤40%.
Tu R, 2011 [149]	Effectiveness of CRT in participants with minimally symptomatic heart failure	8	CRT improves outcomes in participants with mild heart failure and ventricular dyssynchrony. The improvements are accompanied by more adverse events.	Focused on minimally symptomatic participants (NYHA I-II). Included LVEF ≤40%.
Van Rees, 2011 [150]	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 [151]	Effect of CRT in participants with AF	23	The benefits of CRT appear to be attenuated in participants with AF.	Focused exclusively on AF population.
Cleland, 2013[137]	Effectiveness of CRT in participants with symptomatic heart failure	5	The benefit of CRT correlated with QRS duration (especially at a duration of 140 ms and above).	Focused on 5 RCTs funded by Medtronic.
Zusterzeel, 2014[138]	Effectiveness of CRT in women versus men with LBBB	3	Neither women nor men benefited from CRT-D at QRS duration <130 ms	Focused on patients with predominantly mild heart failure (NYHA II).

Author, year	Review scope	Number of studies	Findings	Key differences compared to current systematic review
Slotwiner, 2018 [15]	Impact of Physiologic Pacing Versus Right Ventricular Pacing	8	The LVEF remained preserved or increased with either BiVP or HisBP compared with RVP.	Included studies with an LVEF of >35%. *Updated for our Key Questions 9-10.

AF=atrial fibrillation; AV=atrioventricular; BiVP=biventricular pacing; CKD=chronic kidney disease; CRT=cardiac resynchronization therapy; CRT-D=cardiac resynchronization therapy with defibrillator; CRT-P=cardiac resynchronization therapy with pacemaker; HisBP=His bundle pacing; ICD=implantable cardioverter defibrillator; LV=left ventricular; LVEDV=left ventricular end-diastolic volume; LVEF=left ventricular ejection fraction; LVESV=left ventricular end-systolic volume; ms=milliseconds; NYHA=New York Heart Association; QRS=QRS complex; RBBB=right bundle branch block; RCT=randomized controlled trial; RVP=right ventricular pacing

Applicability

The generalizability of our initial systematic review results was slightly limited. The majority of participants 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 participants included were in the age range of the Medicare population. There has not been an RCT that specifically enrolled Medicare-eligible participants. Also, data for older participants (>75 years of age) remain limited. In cohort studies and relevant pre-specified subgroup analyses from the RCTs, age was not found to be a differentiating factor in clinical 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. It should be noted that patients enrolled in trials (especially older patients) may not be representative of the "real world" adult population, who may have increased comorbidities, frailty, cognitive and/or functional impairment, limited life expectancy, or competing risks. Pragmatic trials which include these types of patients could provide insight in applying these interventions to an older, more complex population.

Our update identified two new RCTs using novel quadripolar LV lead technology versus older bipolar LV lead technology. While the evidence for improved efficacy with quadripolar leads was limited in these studies by their modest size and followup, this newer technology appears poised for rapid adoption due to the greater LV pacing programming options that they proffer (despite the absence of specific endorsement in current clinical guidelines). Quadripolar compared with bipolar LV leads appear to be more stable in placement and have greater programming pacing configurations, which can reduce lead LV dislodgement and requirement for subsequent reoperations and complications.

Since the majority of conventional pacemaker recipients are >65 years of age and because AVB is the second most common indication for pacemaker therapy in the United States, we do anticipate rapid expansion in CRT pacemaker implantation in Medicare participants. This follows the recent 2018 ACC/AHA/HRS recommendation to pursue CRT or His bundle pacing in individuals with an LVEF between 36% and 50% and AVB, who have an indication for permanent pacing and are expected to require ventricular pacing >40% of the time.

Implications for Clinical and Policy Decision making

Due to the advantage of quadripolar leads in regard to LV pacing programming for both CRT-D and CRT-P recipients, we anticipate that quadripolar lead technology will rapidly supplant bipolar lead technology in clinical practice despite the lack of large randomized trials with long-term followup or endorsement in clinical guidelines.

The recent 2018 ACC/AHA/HRS recommendation to pursue CRT or His bundle pacing in patients with an LVEF between 36% and 50% and AVB, who have an indication for permanent pacing and are expected to require ventricular pacing >40% of the time, will impact clinical practice. Since AVB constitutes the second most common indication for conventional pacing therapy, this new recommendation will likely lead to a rapid expansion of CRT-P implantation which has hitherto been an uncommon option, as opposed to conventional (RV pacing) pacemaker implantation, in the United States.

Limitations of the Review Process

In addressing the questions of efficacy, several studies potentially of interest (e.g., REVERSE, HOBI-PACE, BLOCK-HF) were excluded because outcomes were reported for mixed populations or for different types of CRT without device-specific results. We attempted to obtain population or device-specific data from the authors of such studies, but response was limited. Additionally, we also excluded the DANISH-ICD trial as it randomized ICD therapy de novo and not CRT. In fact, 13 percent to 15 percent of participants had pacemaker therapy (some with CRT) at baseline.

We did not consider non-randomized studies for the questions addressing efficacy due to concerns of potential residual confounding. A prior systematic review assessing the effectiveness of CRT-D versus CRT-P included both RCTs and non-randomized studies and purported superiority of the CRT-D.[136] However, the authors noted moderate selection bias of included studies, and that findings were driven by the observational studies due to their combined large size and longer followup compared to the sole RCT (COMPANION). They cautioned that the results should be considered preliminary, with a need for further RCTs, which our report also concludes.

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 participants enrolled in the clinical trials had NYHA class II–IV heart failure symptoms. The applicability of the current findings to class I participants is not clear. In contrast, for the comparison of CRT-D with CRT-P, only the COMPANION trial was found to include both CRT-D and CRT-P arms.[2] However, a direct comparison of the CRT-D with CRT-P arms was not reported for several outcomes. Also, for all comparisons, applicability of findings to patients typically seen in practice (i.e., older, with comorbidities) is not clear.

Research Recommendations

Important clinical questions remain regarding the long-term efficacy of quadripolar LV leads versus bipolar LV leads for CRT, as well as the long-term efficacy and harms of CRT-pacing versus His bundle pacing both in newly eligible participants with LVEF between 36% and 50% and AVB and for conventional criteria (LVEF ≤35% and QRS duration >120 ms). However, these new clinical questions are not likely to be definitively answered until the completion of several ongoing RCTs a few years from now. These include, among others soon to be underway, the His-SYNC trial (His Bundle Pacing versus Coronary Sinus Pacing for Cardiac Resynchronization Therapy; NCT02700425) and the HOPE-HF trial (His Optimized Pacing Evaluated for Heart Failure; NCT02671903). It is only when such trials provide key clinical outcomes data (such as heart failure hospitalizations and total mortality) in participants with long-term followup (beyond the 1 to 2 years in the current published literature) that definitive recommendations comparing these novel pacing techniques and indications can be derived.

There remains a paucity of RCT data directly comparing CRT-D with CRT-P in eligible participants. Some studies have also suggested that CRT-D compared with CRT-P devices are predisposed to increased complications owing to defibrillator lead dysfunction and wound issues. Also, currently, CRT-D is the standard therapy used in the Medicare population. Older participants deemed to be eligible for CRT with a strong likelihood of clinical response (e.g.,

LBBB morphology, QRS duration >130 ms, NICM) could be proffered enrollment in an RCT comparing CRT-P with CRT-D directly, considering participant preferences/outcomes and end-of-life and goals-of-care discussions.

The incidence of harms varies by duration of followup and some harms may occur primarily peri-procedurally (such as a pneumothorax) or both with short (<30 days) and longer (6 to 12 months) followup, therefore standardized intervals of followup are recommended. For example, peri-procedural (before index hospitalization discharge), 7 day, 30 day, 6 month, and 1 year followup could be considered. Similarly, standardized definitions for harms could be created. For example, a device infection could be defined 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)."[108] Alternatively, a simpler definition could be "any device-related infection requiring surgical intervention, either extraction or pocket/wound revision, but not causing the death of the patient."[109] The challenge of definition, timing, and attribution also remained in the update. By standardizing both harms definitions and timing of assessment, direct comparisons between studies could be made. One could consider formally including these *standardized* definitions into the registries which are available to track medical devices.

Some studies have also suggested that CRT-D compared with CRT-P devices are predisposed to increased complications owing to defibrillator lead dysfunction and wound issues. Development of smaller devices with thinner leads to reduce the size of the pocket, longer battery life, and use of sub-pectoral implants or antibacterial coatings could potentially mitigate these increased risks.

In harms studies, individual, non-standardized definitions of harms, a range of followup times, no specific time of the harms' occurrence, and limited direct comparison of devices makes assessing harms a challenge. More comparable studies, with the standardized definitions suggested above, are needed to assess harms, including peri-procedural complications and device infections, to form definitive conclusions.

In addition, patients enrolled in trials (especially older patients) may not be representative of the "real world" adult population, who may have increased comorbidities, frailty, cognitive and/or functional impairment, limited life expectancy, or competing risks. Pragmatic trials which include these types of patients could provide essential insight in applying these interventions to the older population. Similarly, differentiating true non-responders from the "non-progressors", those who had not clinically worsened but would have if not for the intervention, is an important area for further CRT research. Additional important areas of research are techniques or learnings (i.e., clinical, imaging, or other factors) to improve lead implant sites such as the role of non-invasive electrocardiographic mapping combined with radiographic data, CRT optimization such as device settings to maximize pacing, adjunctive medical therapy and follow-up algorithms, CRT device diagnostic capabilities, CRT device modifications (i.e., antibiotic envelope and better battery life), remote monitoring, and alternative pacing methods among patients who fail endovascular coronary sinus LV lead implantation.

Finally, it should be noted that, in 2018, a decision memo was issued mandating that "shared decision making" (SDM) using an evidence-based decision tool for participants should be undertaken (and documented) by health care providers prior to ICD surgery for primary prevention of sudden cardiac death. However, the efficacy of this mandatory policy in regard to clinical outcomes remains to be determined. Research in this arena will likely be of importance

to participants eligible for CRT-D therapy given the added complexity of educating participants on the risks and benefits of CRT itself, independent of ICD therapy.

Conclusion

There is insufficient evidence, including no new definitive evidence since the 2015 report, that CRT-D improves health outcomes compared to CRT-P in patients with heart failure, LVEF ≤35% and QRS duration ≥120 ms, on optimal medical therapy.

There remains convincing evidence that CRT-D is effective with regard to improvements in multiple outcomes compared to an ICD alone in participants with an LVEF ≤35% and a QRS duration ≥120 ms. These findings are based on participants primarily with NYHA class II–IV heart failure. The applicability of these findings to participants with NYHA class I symptoms remains unclear. Similarly, there remains convincing evidence that CRT-P is effective in improving multiple endpoints compared with OMT alone in the same population. These data are primarily derived from NYHA class III–IV participants; the applicability to participants with NYHA class I and II remains less clear. Female sex, LBBB, a widened QRS duration, sinus rhythm, and NICM are associated with improved outcomes following CRT-D, as validated in recent sub-study reports.

Although limited by study-defined harms and followup, procedure-related complication rates, infections, and lead dislodgement tended to be higher for CRT-D versus CRT-P devices, but additional studies are needed to confirm these findings. Similarly, although few studies were available for CRT alternative techniques, quadripolar compared with bipolar LV leads appear to have less lead dislodgment, likely owing to more stable positioning and greater sensing and pacing configurations, and similar incidence of VA.

Important questions remain regarding the long-term clinical efficacy of quadripolar leads for CRT as well as the long-term clinical efficacy and harms of CRT versus His bundle pacing in eligible patients, but those questions likely will not be definitively answered until completion of several ongoing RCTs a few years from now. Additionally, the clinical impact of the recently mandated shared decisionmaking process has yet to be determined in either ICD or CRT-D participants. Finally, pragmatic trials which include patients with complex comorbidities, frailty, cognitive and/or functional impairment, limited life expectancy, or competing risks could provide insight in applying these interventions to the older patient population typically seen in practice.

References

1. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005 2005 Apr 14;352(15):1539-49.

2. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004 2004 May 20;350(21):2140-50.

3. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002 2002 Jun 13;346(24):1845-53.

4. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med. 2001 2001 Mar 22;344(12):873-80.

5. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med. 2010 2010 Dec 16;363(25):2385-95.

6. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009 2009 Oct 1;361(14):1329-38.

7. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA. 2003 2003 May 28;289(20):2685-94.

8. Leclercq C, Walker S, Linde C, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J. 2002 2002 Nov;23(22):1780-7.

9. Birnie DH, Tang AS. The problem of non-response to cardiac resynchronization therapy. Curr Opin Cardiol. 2006 Jan;21(1):20-6. PMID: 16355025.

10. Tsai V, Goldstein MK, Hsia HH, et al. Influence of age on perioperative complications among patients undergoing implantable cardioverter-defibrillators for primary prevention in the United States. Circ Cardiovasc Qual Outcomes. 2011 2011 Sep;4(5):549-56.

11. Russo AM, Stainback RF, Bailey SR, et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation appropriate use criteria task force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2013 2013 Mar 26;61(12):1318-68.

12. Exner DV, Birnie DH, Moe G, et al. Canadian Cardiovascular Society Guidelines on the Use of Cardiac Resynchronization Therapy: Evidence and Patient Selection. Can. J. Cardiol. 2013 2013;29(2):182-95.

13. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129-200. doi: 10.1093/eurheartj/ehw128. PMID: 27206819.

14. Kusumoto FM, Bailey KR, Chaouki AS, et al. Systematic review for the 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A Report of the American College of

Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2018 Oct;15(10):e253-e74. doi: 10.1016/j.hrthm.2017.10.037. PMID: 29097318.

15. Slotwiner DJ, Raitt MH, Del-Carpio Munoz F, et al. Impact of Physiologic Pacing Versus Right Ventricular Pacing Among Patients With Left Ventricular Ejection Fraction Greater Than 35% A Systematic Review for the 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2018 Oct 31doi: 10.1016/j.hrthm.2018.10.035. PMID: 30412776.

16. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF Agency for Healthcare Research and Quality. Rockville, MD: 2014. www.effectivehealthcare.ahrq.gov

17. Rickard J, Michtalik H, Sharma R, et al. 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) Agency for Healthcare Research and Quality. Rockville, MD: 2015. www.effectivehealthcare.ahrq.gov.

18. Higgins JPT. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.Available from www.cochrane-handbook.org. 2011.

19. Wells GA. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Web Page]. Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. 2011.

20. Cleland JGF, Daubert J-C, Erdmann E, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. Eur. Heart J. 2006 2006;27(16):1928-32.

21. Cleland JG, Freemantle N, Daubert JC, et al. Long-term effect of cardiac resynchronisation in patients reporting mild symptoms of heart failure: a report from the CARE-HF study. Heart. 2008 2008 Mar;94(3):278-83.

22. Cleland JG, Calvert MJ, Verboven Y, et al. Effects of cardiac resynchronization therapy on long-term quality of life: an analysis from the CArdiac Resynchronisation-Heart Failure (CARE-HF) study. Am Heart J. 2009 2009 Mar;157(3):457-66.

23. Ghio S, Freemantle N, Scelsi L, et al. Long-term left ventricular reverse remodelling with cardiac resynchronization therapy: results from the CARE-HF trial. Eur J Heart Fail. 2009 2009 May;11(5):480-8.

24. Gras D, Bocker D, Lunati M, et al. Implantation of cardiac resynchronization therapy systems in the CARE-HF trial: procedural success rate and safety. Europace. 2007 2007 Jul;9(7):516-22.

25. Wikstrom G, Blomstrom-Lundqvist C, Andren B, et al. The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE-HF trial. Eur Heart J. 2009 2009 Apr;30(7):782-8.

26. Cleland JG, Freemantle N, Erdmann E, et al. Long-term mortality with cardiac resynchronization therapy in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial. Eur J Heart Fail. 2012 2012 Jun;14(6):628-34.

27. Anand IS, Carson P, Galle E, et al. Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure: results from the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial.

Circulation. 2009 2009 Feb 24;119(7):969-77.

28. Carson P, Anand I, O'Connor C, et al. Mode of death in advanced heart failure: the Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial. J Am Coll Cardiol. 2005 2005 Dec 20;46(12):2329-34.

29. Kalscheur MM, Saxon LA, Lee BK, et al. Outcomes of cardiac resynchronization therapy in patients with intermittent atrial fibrillation or atrial flutter in the COMPANION trial. Heart Rhythm. 2017 Jun;14(6):858-65. doi: 10.1016/j.hrthm.2017.03.024. PMID: 28323173.

30. Arshad A, Moss AJ, Foster E, et al. Cardiac resynchronization therapy is more effective in women than in men: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. J Am Coll Cardiol. 2011 2011 Feb 15;57(7):813-20.

31. Barsheshet A, Goldenberg I, Moss AJ, et al. Response to preventive cardiac resynchronization therapy in patients with ischaemic and nonischaemic cardiomyopathy in MADIT-CRT. Eur Heart J. 2011 2011 Jul;32(13):1622-30.

32. Stockburger M, Moss AJ, Klein HU, et al. Sustained clinical benefit of cardiac resynchronization therapy in non-LBBB patients with prolonged PR-interval: MADIT-CRT long-term follow-up. Clin Res Cardiol. 2016 Nov;105(11):944-52. doi: 10.1007/s00392-016-1003-z. PMID: 27318807.

33. Biton Y, Kutyifa V, Cygankiewicz I, et al. Relation of QRS Duration to Clinical Benefit of Cardiac Resynchronization Therapy in Mild Heart Failure Patients Without Left Bundle Branch Block: The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy Substudy. Circ Heart Fail. 2016 Feb;9(2):e002667. doi: 10.1161/circheartfailure.115.002667. PMID: 26823498.

34. Ouellet G, Huang DT, Moss AJ, et al. Effect of cardiac resynchronization therapy on the risk of first and recurrent ventricular tachyarrhythmic events in MADIT-CRT. J Am Coll Cardiol. 2012 2012 Oct 30;60(18):1809-16.

35. Solomon SD, Foster E, Bourgoun M, et al. Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome: multicenter automatic defibrillator implantation trial: cardiac resynchronization therapy. Circulation. 2010 2010 Sep 7;122(10):985-92.

36. Tompkins C, Kutyifa V, McNitt S, et al. Effect on cardiac function of cardiac resynchronization therapy in patients with right bundle branch block (from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy. Am J Cardiol. 2013 2013 Aug 15;112(4):525-9.

37. Zareba W, Klein H, Cygankiewicz I, et al. Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation. 2011 2011 Mar 15;123(10):1061-72.

38. Jamerson D, McNitt S, Polonsky S, et al. Early Procedure-Related Adverse Events by Gender in MADIT-CRT. J Cardiovasc Electrophysiol. 2014 2014 Sep;25(9):985-9.

39. Ruwald MH, Solomon SD, Foster E, et al. Left ventricular ejection fraction normalization in cardiac resynchronization therapy and risk of ventricular arrhythmias and clinical outcomes: results from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) trial. Circulation. 2014 Dec 23;130(25):2278-86. doi: 10.1161/circulationaha.114.011283. PMID: 25301831.

40. Goldenberg I, Kutyifa V, Klein HU, et al. Survival with cardiac-resynchronization therapy in mild heart failure. New England

Journal of Medicine. 2014;370(18):1694-701. doi: 10.1056/NEJMoa1401426.

41. St John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation. 2003 2003 Apr 22;107(15):1985-90.

42. Abraham WT, Young JB, Leon AR, et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. Circulation. 2004 2004 Nov 2;110(18):2864-8.

43. Schuchert A, Muto C, Maounis T, et al. Lead complications, device infections, and clinical outcomes in the first year after implantation of cardiac resynchronization therapy-defibrillator and cardiac resynchronization therapy-pacemaker. Europace. 2013 2013 Jan;15(1):71-6.

44. Birnie DH, Ha A, Higginson L, et al. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: Results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). Circ Heart Fail. 2013 2013 Nov;6(6):1190-8.

45. Gillis AM, Kerr CR, Philippon F, et al. Impact of Cardiac Resynchronization Therapy on Hospitalizations in the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial. Circulation. 2014 2014 Mar 7.

46. Healey JS, Hohnloser SH, Exner DV, et al. Cardiac resynchronization therapy in patients with permanent atrial fibrillation: results from the Resynchronization for Ambulatory Heart Failure Trial (RAFT). Circ Heart Fail. 2012 2012 Sep 1;5(5):566-70.

47. Kober L, Thune JJ, Nielsen JC, et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med. 2016 Sep 29;375(13):1221-30. doi: 10.1056/NEJMoa1608029. PMID: 27571011.

48. Diab IG, Hunter RJ, Kamdar R, et al. Does ventricular dyssynchrony on echocardiography predict response to cardiac resynchronisation therapy? A randomised controlled study. Heart. 2011 2011 Sep;97(17):1410-6.

49. Garikipati NV, Mittal S, Chaudhry F, et al. Comparison of endovascular versus epicardial lead placement for resynchronization therapy. Am J Cardiol. 2014 2014 Mar 1;113(5):840-4.

50. Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol. 2003 2003 Oct 15;42(8):1454-9.

51. Leclercq C, Cazeau S, Lellouche D, et al. Upgrading from single chamber right ventricular to biventricular pacing in permanently paced patients with worsening heart failure: The RD-CHF Study. Pacing Clin Electrophysiol. 2007 2007 Jan;30 Suppl 1:S23-30.

52. Lozano I, Bocchiardo M, Achtelik M, et al. Impact of biventricular pacing on mortality in a randomized crossover study of patients with heart failure and ventricular arrhythmias. Pacing Clin Electrophysiol. 2000 2000 Nov;23(11 Pt 2):1711-2.

53. Pinter A, Mangat I, Korley V, et al. Assessment of resynchronization therapy on functional status and quality of life in patients requiring an implantable defibrillator. Pacing Clin Electrophysiol. 2009 2009 Dec;32(12):1509-19.

54. Bencardino G, Di Monaco A, Russo E, et al. Outcome of Patients Treated by Cardiac Resynchronization Therapy Using a Quadripolar Left Ventricular Lead. Circ J. 2016;80(3):613-8. doi: 10.1253/circj.CJ-15-0932. PMID: 26821688.

55. Sardu C, Barbieri M, Santamaria M, et al. Multipolar pacing by cardiac

resynchronization therapy with a defibrillators treatment in type 2 diabetes mellitus failing heart patients: impact on responders rate, and clinical outcomes. Cardiovasc Diabetol. 2017 Jun 9;16(1):75. doi: 10.1186/s12933-017-0554-2. PMID: 28599667.

56. Biton Y, Zareba W, Goldenberg I, et al. Sex Differences in Long-Term Outcomes With Cardiac Resynchronization Therapy in Mild Heart Failure Patients With Left Bundle Branch Block. J Am Heart Assoc. 2015 Jun 29;4(7)doi: 10.1161/jaha.115.002013. PMID: 26124205.

57. Auricchio A, Gold MR, Brugada J, et al. Long-term effectiveness of the combined minute ventilation and patient activity sensors as predictor of heart failure events in patients treated with cardiac resynchronization therapy: Results of the Clinical Evaluation of the Physiological Diagnosis Function in the PARADYM CRT device Trial (CLEPSYDRA) study. Eur J Heart Fail. 2014;16(6):663-70. doi: 10.1002/ejhf.79.

58. Bossard M, Sticherling C, Kuhne M, et al. Outcome of patients with cardiac resynchronisation defibrillator therapy and a follow-up of at least five years after implant. Swiss Med Wkly. 2014 2014;144:w13938.

59. Knight BP, Desai A, Coman J, et al. Long-term retention of cardiac resynchronization therapy. J Am Coll Cardiol. 2004 2004 Jul 7;44(1):72-7.

60. Landolina M, Gasparini M, Lunati M, et al. Long-term complications related to biventricular defibrillator implantation: rate of surgical revisions and impact on survival: insights from the Italian Clinical Service Database. Circulation. 2011 2011 Jun 7;123(22):2526-35.

61. Luo NS, Yuan WL, Lin YQ, et al. Potential proarrhythmic effect of cardiac resynchronization therapy during perioperative period: data from a single cardiac center. Chin Med J (Engl). 2010 2010 Sep;123(17):2295-8.

62. Strimel W, Koplik S, Chen HR, et al. Safety and effectiveness of primary prevention cardioverter defibrillators in octogenarians. Pacing Clin Electrophysiol. 2011 2011 Jul;34(7):900-6.

63. Theuns DA, Thornton AS, Klootwijk AP, et al. Outcome in patients with an ICD incorporating cardiac resynchronisation therapy: differences between primary and secondary prophylaxis. Eur J Heart Fail. 2005 2005 Oct;7(6):1027-32.

64. Gasparini M, Menozzi C, Proclemer A, et al. A simplified biventricular defibrillator with fixed long detection intervals reduces implantable cardioverter defibrillator (ICD) interventions and heart failure hospitalizations in patients with non-ischaemic cardiomyopathy implanted for primary prevention: the RELEVANT. Eur Heart J. 2009 2009 Nov;30(22):2758-67.

65. Duray GZ, Israel CW, Pajitnev D, et al. Upgrading to biventricular pacing/defibrillation systems in right ventricular paced congestive heart failure patients: prospective assessment of procedural parameters and response rate. Europace. 2008 2008 Jan;10(1):48-52.

66. Boven NV, Theuns D, Bogaard K, et al. Atrial Fibrillation in Cardiac Resynchronization Therapy with a Defibrillator: A Risk Factor for Mortality, Appropriate and Inappropriate Shocks. J Cardiovasc Electrophysiol. 2013 2013 Jun 17.

67. Kuhlkamp V. Initial experience with an implantable cardioverter-defibrillator incorporating cardiac resynchronization therapy. J Am Coll Cardiol. 2002 2002 Mar 6;39(5):790-7.

68. Van Boven N, Bogaard K, Ruiter J, et al. Functional response to cardiac resynchronization therapy is associated with improved clinical outcome and absence of appropriate shocks. J Cardiovasc Electrophysiol. 2013 2013 Mar;24(3):316-22.

69. Haugaa KH, Marek JJ, Ahmed M, et al. Mechanical dyssynchrony after cardiac

resynchronization therapy for severely symptomatic heart failure is associated with risk for ventricular arrhythmias. J Am Soc Echocardiogr. 2014 2014 Aug;27(8):872-9.

70. Masoudi FA, Mi X, Curtis LH, et al. Comparative effectiveness of cardiac resynchronization therapy with an implantable cardioverter-defibrillator versus defibrillator therapy alone: a cohort study. Ann Intern Med. 2014 2014 May 6;160(9):603-11.

71. Gopalamurugan AB, Ganesha Babu G, Rogers DP, et al. Is CRT pro-arrhythmic? A comparative analysis of the occurrence of ventricular arrhythmias between patients implanted with CRTs and ICDs. Front Physiol. 2014 2014;5:334.

72. Vado A, Menardi E, Rossetti G, et al. Single-center experience of a quadripolar pacing lead for cardiac resynchronization therapy. J Interv Card Electrophysiol. 2014 2014 Mar;39(2):161-5.

73. Ricci RP, Pignalberi C, Landolina M, et al. Ventricular rate monitoring as a tool to predict and prevent atrial fibrillation-related inappropriate shocks in heart failure patients treated with cardiac resynchronisation therapy defibrillators. Heart. 2014 2014 Jun;100(11):848-54.

74. Ziacchi M, Diemberger I, Corzani A, et al. Cardiac resynchronization therapy: a comparison among left ventricular bipolar, quadripolar and active fixation leads. Sci Rep. 2018 Sep 5;8(1):13262. doi: 10.1038/s41598-018-31692-z. PMID: 30185834.

75. Biton Y, Ng CY, Xia X, et al. Baseline adverse electrical remodeling and the risk for ventricular arrhythmia in Cardiac Resynchronization Therapy Recipients (MADIT CRT). J Cardiovasc Electrophysiol. 2018 Jul;29(7):1017-23. doi: 10.1111/jce.13640. PMID: 29846992.

76. Looi KL, Sidhu K, Cooper L, et al. Long-term outcomes of heart failure patients who received primary prevention implantable cardioverter-defibrillator: An observational study. J Arrhythm. 2018 Feb;34(1):46-54. doi: 10.1002/joa3.12027. PMID: 29721113.

77. Kronborg MB, Johansen JB, Haarbo J, et al. Association between implantable cardioverter-defibrillator therapy and different lead positions in patients with cardiac resynchronization therapy. Europace. 2018 Sep 1;20(9):e133-e9. doi: 10.1093/europace/eux296. PMID: 29036292.

78. Killu AM, Mazo A, Grupper A, et al. Super-response to cardiac resynchronization therapy reduces appropriate implantable cardioverter defibrillator therapy. Europace. 2017 Aug 4doi: 10.1093/europace/eux235. PMID: 29016821.

79. Sardu C, Santamaria M, Funaro S, et al. Cardiac electrophysiological alterations and clinical response in cardiac resynchronization therapy with a defibrillator treated patients affected by metabolic syndrome. Medicine (Baltimore). 2017 Apr;96(14):e6558. doi: 10.1097/md.0000000000006558. PMID: 28383431.

80. Sapp JL, Parkash R, Wells GA, et al. Cardiac Resynchronization Therapy Reduces Ventricular Arrhythmias in Primary but Not Secondary Prophylactic Implantable Cardioverter Defibrillator Patients: Insight From the Resynchronization in Ambulatory Heart Failure Trial. Circ Arrhythm Electrophysiol. 2017 Mar;10(3)doi: 10.1161/circep.116.004875. PMID: 28292754.

81. Xue C, Hua W, Cai C, et al. Acute and Chronic Changes and Predictive Value of Tpeak-Tend for Ventricular Arrhythmia Risk in Cardiac Resynchronization Therapy Patients. Chin Med J (Engl). 2016 Sep 20;129(18):2204-11. doi: 10.4103/0366-6999.189916. PMID: 27625093.

82. Sabbag A, Goldenberg I, Moss AJ, et al. Predictors and Risk of Ventricular Tachyarrhythmias or Death in Black and White Cardiac Patients: A MADIT-CRT Trial Substudy. JACC Clin Electrophysiol. 2016 Aug;2(4):448-55. doi:

10.1016/j.jacep.2016.03.003. PMID: 29759864.

83. Friedman DJ, Singh JP, Curtis JP, et al. Comparative Effectiveness of CRT-D Versus Defibrillator Alone in HF Patients With Moderate-to-Severe Chronic Kidney Disease. J Am Coll Cardiol. 2015 Dec 15;66(23):2618-29. doi: 10.1016/j.jacc.2015.09.097. PMID: 26670062.

84. Steffel J, Robertson M, Singh JP, et al. The effect of QRS duration on cardiac resynchronization therapy in patients with a narrow QRS complex: a subgroup analysis of the EchoCRT trial. Eur Heart J. 2015 Aug 7;36(30):1983-9. doi: 10.1093/eurheartj/ehv242. PMID: 26009595.

85. Crossley GH, Biffi M, Johnson B, et al. Performance of a novel left ventricular lead with short bipolar spacing for cardiac resynchronization therapy: primary results of the Attain Performa quadripolar left ventricular lead study. Heart Rhythm. 2015 Apr;12(4):751-8. doi: 10.1016/j.hrthm.2014.12.019. PMID: 25533587.

86. Hoke U, Putter H, Van Der Velde ET, et al. Left ventricular reverse remodeling, device-related adverse events, and long-term outcome after cardiac resynchronization therapy in the elderly. Circ Cardiovasc Qual Outcomes. 2014 May;7(3):437-44. doi: 10.1161/circoutcomes.113.000821. PMID: 24823954.

87. Echouffo-Tcheugui JB, Masoudi FA, Bao H, et al. Diabetes Mellitus and Outcomes of Cardiac Resynchronization With Implantable Cardioverter-Defibrillator Therapy in Older Patients With Heart Failure. Circ Arrhythm Electrophysiol. 2016 Aug;9(8)doi: 10.1161/circep.116.004132. PMID: 27489243.

88. Adelstein EC, Liu J, Jain S, et al. Clinical outcomes in cardiac resynchronization therapy-defibrillator recipients 80 years of age and older. Europace. 2016 Mar;18(3):420-7. doi: 10.1093/europace/euv222. PMID: 26487669.

89. Khazanie P, Greiner MA, Al-Khatib SM, et al. Comparative Effectiveness of Cardiac Resynchronization Therapy Among Patients With Heart Failure and Atrial Fibrillation: Findings From the National Cardiovascular Data Registry's Implantable Cardioverter-Defibrillator Registry. Circ Heart Fail. 2016 Jun;9(6)doi: 10.1161/circheartfailure.115.002324. PMID: 27296396.

90. Essebag V, Joza J, Birnie DH, et al. Incidence, predictors, and procedural results of upgrade to resynchronization therapy: the RAFT upgrade substudy. Circ Arrhythm Electrophysiol. 2015 Feb;8(1):152-8. doi: 10.1161/circep.114.001997. PMID: 25417892.

91. Su H, Bao P, Chen KY, et al. Influence of the Right Ventricular Lead Location on Ventricular Arrhythmias in Cardiac Resynchronization Therapy. Chin Med J (Engl). 2018;131(20):2402-9. doi: 10.4103/0366-6999.243560.

92. Sherrid MV. Pathophysiology and Treatment of Hypertrophic Cardiomyopathy. Prog. Cardiovasc. Dis. 2006 2006;49(2):123-51.

93. Milano G, Raucci A, Scopece A, et al. Doxorubicin and Trastuzumab Regimen Induces Biventricular Failure in Mice. J. Am. Soc. Echocardiogr. 2014 2014.

94. Maron BJ, Weiner HL, Maron MS, et al. Surviving malignant hypertrophic cardiomyopathy with all major complications in a single patient. Am J Cardiol. 2015 Feb 1;115(3):402-4. doi: 10.1016/j.amjcard.2014.11.004. PMID: 25499402.

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

96. Krahn AD, Snell L, Yee R, et al. Biventricular pacing improves quality of life

and exercise tolerance in patients with heart failure and intraventricular conduction delay. Can J Cardiol. 2002 2002 Apr;18(4):380-7.

97. Mortensen PT, Sogaard P, Mansour H, et al. Sequential biventricular pacing: evaluation of safety and efficacy. Pacing Clin Electrophysiol. 2004 2004 Mar;27(3):339-45.

98. Stahlberg M, Braunschweig F, Gadler F, et al. Three year outcome of cardiac resynchronization therapy: a single center evaluation. Pacing Clin Electrophysiol. 2005 2005 Oct;28(10):1013-7.

99. Niu HX, Hua W, Wang FZ, et al. Complications of cardiac resynchronization therapy in patients with congestive heart failure. Chin Med J (Engl). 2006 2006 Mar 20;119(6):449-53.

100. de Cock CC, van Campen CM, Visser CA. Major dissection of the coronary sinus and its tributaries during lead implantation for biventricular stimulation: angiographic follow-up. Europace. 2004 2004 Jan;6(1):43-7.

101. Shamoun F, De Marco T, DeMets D, et al. Impact of Degree of Left Ventricular Remodeling on Clinical Outcomes From Cardiac Resynchronization Therapy. JACC: Heart Failure. 2019;7(4):281-90. doi: 10.1016/j.jchf.2018.11.004.

102. Azizi M, Castel MA, Behrens S, et al. Experience with coronary sinus lead implantations for cardiac resynchronization therapy in 244 patients. Herzschrittmacherther Elektrophysiol. 2006 2006 Mar;17(1):13-8.

103. Takaya Y, Noda T, Nakajima I, et al. Electrocardiographic predictors of response to cardiac resynchronization therapy in patients with intraventricular conduction delay. Circ. J. 2014 2014;78(1):71-7.

104. Verbrugge FH, De Vusser P, Rivero-Ayerza M, et al. Cardiac resynchronization therapy with or without defibrillator: experience from a high-volume Belgian implantation centre. Acta Cardiol. 2013 2013 Feb;68(1):37-45.

105. Killu AM, Wu JH, Friedman PA, et al. Outcomes of cardiac resynchronization therapy in the elderly. Pacing Clin Electrophysiol. 2013 2013 Jun;36(6):664-72.

106. Verbrugge FH, Dupont M, De Vusser P, et al. Response to cardiac resynchronization therapy in elderly patients ((greater-than or equal to)70 years) and octogenarians. Eur. J. Heart Fail. 2013 2013;15(2):203-10.

107. Swindle JP, Rich MW, McCann P, et al. Implantable cardiac device procedures in older patients: use and in-hospital outcomes. Arch Intern Med. 2010 2010 Apr 12;170(7):631-7.

108. Romeyer-Bouchard C, Da Costa A, Dauphinot V, et al. Prevalence and risk factors related to infections of cardiac resynchronization therapy devices. Eur Heart J. 2010 2010 Jan;31(2):203-10.

109. Barra S, Providencia R, Boveda S, et al. Device complications with addition of defibrillation to cardiac resynchronisation therapy for primary prevention. Heart. 2018 Sep;104(18):1529-35. doi: 10.1136/heartjnl-2017-312546. PMID: 29540431.

110. Doring M, Ebert M, Dagres N, et al. Cardiac resynchronization therapy in the ageing population - With or without an implantable defibrillator? Int J Cardiol. 2018 Jul 15;263:48-53. doi: 10.1016/j.ijcard.2018.03.087. PMID: 29754922.

111. Nakajima I, Noda T, Kanzaski H, et al. Development of Heart Failure From Transient Atrial Fibrillation Attacks in Responders to Cardiac Resynchronization Therapy. JACC Clin Electrophysiol. 2018 Sep;4(9):1227-34. doi: 10.1016/j.jacep.2018.06.010. PMID: 30236398.

112. Nevzorov R, Porter A, Mostov S, et al. Gender-Related Differences in Outcomes of Patients with Cardiac Resynchronization

Therapy. Isr Med Assoc J. 2018 May;5(20):311-5. PMID: 29761679.

113. Looi KL, Gavin A, Sidhu K, et al. Utilization of cardiac resynchronization therapy in patients with heart failure in the Northern Region of New Zealand. J Arrhythm. 2018((Looi K.-L., khanglil@adhb.govt.nz; Sidhu K.; Cooper L.; Lever N.) Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand)doi: 10.1002/joa3.12134.

114. Pappalardo F, Nisi T, Melisurgo G, et al. Aortic cannula disruption following long-term LVAD support. J Card Surg. 2013 2013 Jul;28(4):472-4.

115. Selthofer-Relatic K. Time of Anderson-Fabry Disease Detection and Cardiovascular Presentation. Case Rep Cardiol. 2018;2018:6131083. doi: 10.1155/2018/6131083. PMID: 29755794.

116. You C-C, Tseng Y-T, Hsieh M-H. An epsilon wave in arrhythmogenic right ventricular cardiomyopathy/dysplasia. Int. J. Cardiol. 2007 2007;119(2):e63-e4.

117. Leclercq C, Burri H, Curnis A, et al. Cardiac resynchronization therapy non-responder to responder conversion rate in the more response to cardiac resynchronization therapy with MultiPoint Pacing (MORE-CRT MPP) study: results from Phase I. Eur Heart J. 2019 Mar 11doi: 10.1093/eurheartj/ehz109. PMID: 30859220.

118. Ziacchi M, Zucchelli G, Ricciardi D, et al. Performance and clinical comparison between left ventricular quadripolar and bipolar leads in CRT: Observational research. Indian Heart J. 2018((Ziacchi M., matteo.ziacchi@gmail.com; Boriani G.; Biffi M.) Istituto di Cardiologia, Policlinico S. Orsola-Malpighi, Università di Bologna, Bologna, Italy)doi: 10.1016/j.ihj.2018.05.007.

119. Forleo GB, Di Biase L, Panattoni G, et al. Improved implant and postoperative lead performance in CRT-D patients implanted with a quadripolar left ventricular lead. A 6-month follow-up analysis from a multicenter prospective comparative study. J Interv Card Electrophysiol. 2015 Jan;42(1):59-66. doi: 10.1007/s10840-014-9956-1. PMID: 25504267.

120. Laish-Farkash A, Bruoha S, Khalameizer V, et al. Multisite cardiac resynchronization therapy for traditional and non-traditional indications. J Interv Card Electrophysiol. 2018 Mar;51(2):143-52. doi: 10.1007/s10840-018-0316-4. PMID: 29442199.

121. Albertsen AE, Mortensen PT, Jensen HK, et al. Adverse effect of right ventricular pacing prevented by biventricular pacing during long-term follow-up: a randomized comparison. Eur J Echocardiogr. 2011 2011 Oct;12(10):767-72.

122. Doshi RN, Daoud EG, Fellows C, et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). J Cardiovasc Electrophysiol. 2005 2005 Nov;16(11):1160-5.

123. Yu CM, Fang F, Luo XX, et al. Long-term follow-up results of the pacing to avoid cardiac enlargement (PACE) trial. Eur J Heart Fail. 2014 Sep;16(9):1016-25. doi: 10.1002/ejhf.157. PMID: 25179592.

124. Stockburger M, Gomez-Doblas JJ, Lamas G, et al. Preventing ventricular dysfunction in pacemaker patients without advanced heart failure: results from a multicentre international randomized trial (PREVENT-HF). Eur J Heart Fail. 2011 2011 Jun;13(6):633-41.

125. Kronborg MB, Mortensen PT, Poulsen SH, et al. His or para-His pacing preserves left ventricular function in atrioventricular block: a double-blind, randomized, crossover study. Europace. 2014 Aug;16(8):1189-96. doi: 10.1093/europace/euu011. PMID: 24509688.

126. Occhetta E, Bortnik M, Magnani A, et al. Prevention of ventricular desynchronization by permanent para-Hisian pacing after atrioventricular node ablation in chronic atrial fibrillation: a crossover, blinded, randomized study versus apical right

ventricular pacing. J Am Coll Cardiol. 2006 May 16;47(10):1938-45. doi: 10.1016/j.jacc.2006.01.056. PMID: 16697308.

127. Zanon F, Bacchiega E, Rampin L, et al. Direct His bundle pacing preserves coronary perfusion compared with right ventricular apical pacing: a prospective, cross-over mid-term study. Europace. 2008 May;10(5):580-7. doi: 10.1093/europace/eun089. PMID: 18407969.

128. Sharma PS, Dandamudi G, Naperkowski A, et al. Permanent His-bundle pacing is feasible, safe, and superior to right ventricular pacing in routine clinical practice. Heart Rhythm. 2015 Feb;12(2):305-12. doi: 10.1016/j.hrthm.2014.10.021. PMID: 25446158.

129. Bhatt AG, Musat DL, Milstein N, et al. The Efficacy of His Bundle Pacing: Lessons Learned From Implementation for the First Time at an Experienced Electrophysiology Center. JACC Clin Electrophysiol. 2018 Nov;4(11):1397-406. doi: 10.1016/j.jacep.2018.07.013. PMID: 30466843.

130. Shan P, Su L, Zhou X, et al. Beneficial effects of upgrading to His bundle pacing in chronically paced patients with left ventricular ejection fraction <50. Heart Rhythm. 2018 Mar;15(3):405-12. doi: 10.1016/j.hrthm.2017.10.031. PMID: 29081396.

131. . Heart Failure Society of America (HFSA) practice guidelines. HFSA guidelines for management of patients with heart failure caused by left ventricular systolic dysfunction--pharmacological approaches. J Card Fail. 1999 1999 Dec;5(4):357-82.

132. Daubert C, Gold MR, Abraham WT, et al. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. J Am Coll Cardiol. 2009 2009 Nov 10;54(20):1837-46.

133. Kindermann M, Hennen B, Jung J, et al. Biventricular versus conventional right ventricular stimulation for patients with standard pacing indication and left ventricular dysfunction: the Homburg Biventricular Pacing Evaluation (HOBIPACE). J Am Coll Cardiol. 2006 2006 May 16;47(10):1927-37.

134. Curtis AB, Worley SJ, Adamson PB, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med. 2013 2013 Apr 25;368(17):1585-93.

135. McAlister FA, Ezekowitz J, Hooton N, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. JAMA. 2007 Jun 13;297(22):2502-14. doi: 10.1001/jama.297.22.2502. PMID: 17565085.

136. Jiang M, He B, Zhang Q. Comparison of CRT and CRT-D in heart failure: systematic review of controlled trials. Int J Cardiol. 2012 Jun 28;158(1):39-45. doi: 10.1016/j.ijcard.2010.12.091. PMID: 21262545.

137. Cleland JG, Abraham WT, Linde C, et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. Eur Heart J. 2013;34(46):3547-56. doi: 10.1093/eurheartj/eht290.

138. Zusterzeel R, Selzman KA, Sanders WE, et al. Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. JAMA Intern Med. 2014 Aug;174(8):1340-8. doi: 10.1001/jamainternmed.2014.2717. PMID: 25090172.

139. Adabag S, Roukoz H, Anand IS, et al. Cardiac resynchronization therapy in patients with minimal heart failure: A systematic review and meta-analysis. Journal of the American College of Cardiology. 2011 2011;58(9):935-41.

140. Bryant AR, Wilton SB, Lai MP, et al. Association between QRS duration and outcome with cardiac resynchronization therapy: a systematic review and meta-analysis. J Electrocardiol. 2013 Mar-Apr;46(2):147-55. doi: 10.1016/j.jelectrocard.2012.12.003. PMID: 23394690.

141. Ganesan AN, Brooks AG, Roberts-Thomson KC, et al. Role of AV nodal ablation in cardiac resynchronization in patients with coexistent atrial fibrillation and heart failure: A systematic review. J. Am. Coll. Cardiol. 2012 2012;59(8):719-26.

142. Garg N, Thomas G, Jackson G, et al. Cardiac resynchronization therapy in CKD: A systematic review. Clin. J. Am. Soc. Nephrol. 2013 2013;8(8):1293-303.

143. Hess PL, Jackson KP, Hasselblad V, et al. Is cardiac resynchronization therapy an antiarrhythmic therapy for atrial fibrillation? A systematic review and meta-analysis. Curr Cardiol Rep. 2013 Feb;15(2):330. doi: 10.1007/s11886-012-0330-6. PMID: 23299710.

144. Lubitz SA, Leong-Sit P, Fine N, et al. Effectiveness of cardiac resynchronization therapy in mild congestive heart failure: Systematic review and meta-analysis of randomized trials. Eur. J. Heart Fail. 2010 2010;12(4):360-6.

145. McAlister FA, Ezekowitz JA, Wiebe N, et al. Systematic review: cardiac resynchronization in patients with symptomatic heart failure. Ann Intern Med. 2004 Sep 7;141(5):381-90. PMID: 15353430.

146. Nery PB, Ha AC, Keren A, et al. Cardiac resynchronization therapy in patients with left ventricular systolic dysfunction and right bundle branch block: A systematic review. Heart Rhythm. 2011 2011;8(7):1083-7.

147. Proietti R, Manzoni GM, Cravello L, et al. Can Cardiac Resynchronization Therapy Improve Cognitive Function? A Systematic Review. Pacing Clin Electrophysiol. 2013 2013 Dec 20.

148. Santangeli P, Di Biase L, Pelargonio G, et al. Cardiac resynchronization therapy in patients with mild heart failure: a systematic review and meta-analysis. J Interv Card Electrophysiol. 2011 Nov;32(2):125-35. doi: 10.1007/s10840-011-9584-y. PMID: 21594629.

149. Tu R, Zhong G, Zeng Z, et al. Cardiac resynchronization therapy in patients with mild heart failure: a systematic review and meta-analysis of randomized controlled trials. Cardiovasc Drugs Ther. 2011 Aug;25(4):331-40. doi: 10.1007/s10557-011-6313-9. PMID: 21750900.

150. van Rees JB, de Bie MK, Thijssen J, et al. Implantation-related complications of implantable cardioverter-defibrillators and cardiac resynchronization therapy devices: a systematic review of randomized clinical trials. J Am Coll Cardiol. 2011 Aug 30;58(10):995-1000. doi: 10.1016/j.jacc.2011.06.007. PMID: 21867832.

151. Wilton SB, Leung AA, Ghali WA, et al. Outcomes of cardiac resynchronization therapy in patients with versus those without atrial fibrillation: a systematic review and meta-analysis. Heart Rhythm. 2011 Jul;8(7):1088-94. doi: 10.1016/j.hrthm.2011.02.014. PMID: 21338711.

List of Abbreviations

Abbreviations	Definitions
6MHWD	6-minute Hall Walk Distance
AF	Atrial fibrillation
AHRQ	Agency for Healthcare Research and Quality
AVB	Atrioventricular block
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 therapy
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
SD	Standard deviation
SMART AV	Smart Delay Determined AV Optimization
U.S.	United States
VA	Ventricular Arrhythmia