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Cardiac Resynchronization Therapy and Implantable Cardiac Defibrillators in Left Ventricular Systolic Dysfunction

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Preface

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

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

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

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

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Structured Abstract

Objectives: To determine the efficacy, effectiveness, and safety of cardiac resynchronization therapy (CRT) and/or implantable cardioverter defibrillators (ICD) in patients with left ventricular systolic dysfunction (LVSD).

Data Sources: A systematic and comprehensive literature search was conducted to identify randomized controlled trials (RCTs) evaluating efficacy and observational studies evaluating effectiveness or safety of CRT and/or ICD in patients with LVSD.

Review Methods: Study selection, quality assessment, and data extraction were completed by several investigators in duplicate and independently. Random-effects models were used for analyses.

Results: From 11,340 citations, we identified 14 RCTs (4,420 patients) for the CRT efficacy review, 106 studies (9,209 patients) for the CRT effectiveness review, 89 studies (9,677 patients) for the CRT safety review, 12 RCTs (8,516 patients) for the ICD efficacy review, 48 studies (15,097 patients) for the ICD effectiveness review, and 49 studies (12,592 patients) for the ICD safety review—all studies enrolled only patients with LVSD. An additional 12 studies (68,848 patients) were included for an analysis of peri-implant outcomes for all patients with ICD (i.e., not only LVSD patients).

All patients in the CRT studies had LVSD (mean LVEF from 21 to 30 percent) and prolonged QRS duration (mean from 155 to 209 msec), and 91 percent had New York Heart Association (NYHA) class III or IV symptoms. In patients with LVSD and heart failure symptoms, CRT improved ejection fraction (weighted mean difference 3.0 percent [95% CI, 0.9 to 5.1]), quality of life (weighted mean reduction in Minnesota Living with Heart Failure Questionnaire 8.0 points [95% CI, 5.6 to 10.4 points]), and function (59 percent of CRT recipients vs. 37 percent of controls improved by at least one NYHA class in the RCTs and between 63 percent and 82 percent of CRT recipients improved by at least one NYHA class in observational studies). The proportion of patients hospitalized for HF was reduced by 37 percent (95% CI, 7 to 57 percent) and all-cause mortality was reduced by 22 percent (95% CI, 9 to 33 percent; NNT=29 over 6 months). Implant success rate was 93 percent, 0.3 percent of patients with LVSD died during implantation. Over a median 11-month followup, 6.6 percent of CRT devices exhibited lead problems and 5 percent malfunctioned.

In patients with LVSD, ICD reduced all-cause mortality by 20 percent (95% CI, 10 to 29 percent; NNT=20 over 35 months). ICD implant success rate was 99 percent and peri-implant deaths occurred in 1.2 percent of LVSD patients and 1.3 percent of all implantees. The frequency of post-implantation complications in LVSD patients per 100 patient years included 1.4 (95% CI, 1.2 to 1.6) device malfunctions, 1.5 (95% CI, 1.3 to 1.8) lead problems, 0.6 (95% CI, 0.5 to 0.8) implant site infections, and 19.1 (95% CI, 16.5 to 22.0) inappropriate discharges in RCT participants and 4.7 (95% CI, 4.3 to 5.1) inappropriate discharges in patients enrolled in observational studies.

Conclusions: ICD and CRT reduce all-cause mortality in patients with LVSD meeting RCT entry criteria. The incremental benefit of CRT plus ICD over CRT alone in patients with LVSD

remains uncertain. None of the trials reported differences in the efficacy of CRT or ICD across patient subgroups, nor did our meta-regression detect any subgroup effects; however, subgroup analyses and meta-regression using aggregate trial data are post-hoc analyses and were underpowered to detect such effects. Examination of individual patient trial data is urgently needed to define which clinical subgroups are most likely to benefit from these devices.

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Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/defib/defib.pdf

Executive Summary

Introduction

Cardiac resynchronization therapy (CRT) refers to atrial-synchronized biventricular pacing (i.e., pacing the right atrium, right ventricle, and left ventricle). CRT improves the electrical dyssynchrony found in many patients with heart failure (HF) and thereby can improve mechanical dyssynchrony leading to increased left ventricular filling time, reduced mitral regurgitation, and reduced septal dyskinesis.[1,2] Implantable cardioverter defibrillators (ICD) have at least one lead which resides in the right ventricle dedicated to pacing and/or defibrillating lethal cardiac arrhythmias. More advanced ICD (dual-chamber devices) have leads in the right atrium and right ventricle to help discriminate arrhythmic events and have the potential to be programmed to provide dual chamber pacing (e.g., DDD pacing mode).

Although earlier systematic reviews of CRT and ICD did report benefits from both therapies when evaluated individually in patients with HF, questions remained. For one, as these earlier systematic reviews focused on randomized efficacy trials, the generalizability of their results to clinical practice were uncertain (particularly with respect to potential adverse effects). Second, neither of the earlier reviews (which focused on individual devices) was able to clarify the incremental benefits conferred by combined CRT-ICD devices over CRT alone or ICD alone devices, nor were these earlier reviews able to define which patient groups would benefit most from which devices. Finally, a number of large trials have been published since the earlier systematic reviews were performed and their impact on the pooled evidence base required assessment.

Study Questions

1. In adult patients with symptomatic or asymptomatic LV systolic dysfunction, what is the efficacy and effectiveness of CRT alone, ICD alone, or combined CRT-ICD devices compared to usual medical therapy?
2. In adult patients with symptomatic or asymptomatic LV systolic dysfunction, what is the efficacy and effectiveness of single-chamber ICD compared to that of dual-chamber ICD?
3. In adult patients with symptomatic or asymptomatic LV systolic dysfunction, how safe is CRT alone, ICD alone, or combined CRT-ICD devices?
4. Which patients would benefit from ICD alone, CRT alone, or combined CRT-ICD devices?

Methods

Literature Search

We systematically searched various electronic databases (including trial registries and the website of the U.S. Food and Drug Administration), the reference lists of relevant reviews and identified studies, and contacted authors of included studies as well as device manufacturers: Medtronic Inc. (Minneapolis, MN), Boston Scientific (formerly Guidant Corp., Indianapolis,

IN), and St. Jude Medical Inc. (St. Paul, MN). The search was not limited by language or publication status and is considered current to November 14, 2006. A full list of search strategies and search terms (adapted for each database) and search results are included in Appendix A* of the main report.

Selection and Inclusion

To address efficacy, we analyzed randomized controlled trials (RCTs) that compared active CRT, active ICD, or combined CRT-ICD devices with either placebo pacing, univentricular (right-sided) pacing, or drug therapy alone. To address effectiveness, we evaluated studies with contemporaneous comparison arms (e.g., cohort studies, RCTs, or controlled non-randomized trials). To address safety, we included evidence from both RCTs and observational studies (including those without contemporaneous control arms, such as case series and registry data).

For assessing efficacy or effectiveness, we selected those studies that enrolled greater than 25 participants with LV systolic dysfunction (LVEF $\leq$ 35 percent), whether they had HF symptoms or not, followed participants for at least 2 weeks, and reported at least one of the following outcomes of interest: mortality (all-cause, cardiac, HF, sudden cardiac death), quality of life, functional class (NYHA), 6-minute walk test, hospitalization (all-cause or HF), or LVEF. For assessing safety, we selected studies that enrolled greater than 25 participants with LV systolic dysfunction (LVEF $\leq$ 35 percent), whether they had HF symptoms or not, followed participants for at least 2 weeks, and reported at least one of the following outcomes of interest: implant success rates, peri-, or post-implantation risks with either device. On the advice of our expert panel, we also examined safety outcomes in all patients receiving ICDs (i.e., not just those with definite LV systolic dysfunction).

Data Extraction and Analysis

Study selection, quality assessment, and data extraction were completed by several investigators in duplicate, independently, and blinded; random-effects models were used for analyses in Review Manager 4.2.5 (The Cochrane Collaboration, Copenhagen, DK). Only period one data were extracted from crossover studies. For dichotomous results (e.g., HF hospitalizations), we calculated relative risks (RR) and for continuous variables (e.g., 6-minute walk test) we calculated weighted mean difference (WMD) for the pooled estimates. All results were reported with 95 percent confidence intervals (CI). Statistical heterogeneity was quantified using the I-squared (I^2) statistic.[3] Relevant direct subgroup comparisons were summarized, including effects of CRT in patients with more severe HF symptoms (New York Heart Association [NYHA] Class III or IV). Meta-regression was used to examine the relation between a variety of covariates classified at the study level (e.g., percent of enrolled subjects with atrial fibrillation) and the efficacy of CRT, ICD, and combined CRT- ICD devices.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/defibtp.htm

Results

Literature Search (Figures 2 and 3 in Evidence Report)

From 11,340 citations, we identified 14 RCTs[4-17] (4,420 patients) for the CRT efficacy review, 106 studies for the CRT effectiveness review[17-122] (9,209 patients from 2 controlled but non-randomized trials and 104 observational studies—13 retrospective and 91 prospective), and 89 studies for the CRT safety review,[4-17] 2 clinical trials, and 73 observational studies[17,20,22,26,27,29-33,35,36,39,41,42,44-46,49,50,52,53,55-58,60,63-70,73,76,78,80,82,83,85-87,89,91-94,97,98,100,102-106,108,109,111-113,117,118,123-132] (9,677 patients, 14 randomized trials, 2 controlled trials, and 73 observational studies—10 retrospective and 63 prospective). We identified 12 RCTs[11,133-143] (8,516 patients) for the ICD efficacy review, 48 studies for the ICD effectiveness review[144-191] (15,097 patients from 3 RCTs and 45 observational studies—25 retrospective and 20 prospective), and 49 studies for the ICD safety review,[11,133-136,138-145,147,148,152,155-159,161,162,164,165,169,171,176,178-181,184,186-189,191-202] (12,592 patients from 11 RCTs, 6 RCTs without efficacy outcomes, and 32 observational studies—17 retrospective and 15 prospective). An additional 12 studies (68,848 patients) were included in our secondary analysis of peri-implant safety with ICD for all patients (i.e., not restricted to patients with LV systolic dysfunction).[203-214]

Description of Included Patients (Tables 5, 7, 9, and 11 in Evidence Report)

CRT. All patients in the CRT studies had LV systolic dysfunction (mean LVEF ranged from 21 to 30 percent), prolonged QRS duration (mean QRS ranged between 155 msec and 209 msec, with 64 percent of trial participants exhibiting a left bundle branch block), and HF symptoms (79 percent were NYHA class III functional status at baseline, 12 percent were NYHA class IV, and 9 percent were NYHA class II). The mean age of patients was 65.4 ± 10.8 years, 72 percent were male, and patients with atrial fibrillation constituted 5 percent of all trial participants. Of the patients in the intervention arms, 1,310 (47%) received CRT alone and 1,474 (53%) received a combined CRT-ICD device. Eleven of the trials (n = 2,166 patients) randomized patients after successful CRT implantation; 3 trials (n = 2,439 patients) randomized patients before attempted CRT implantation. Median follow-up in these trials was 6 months, with the longest follow-up duration being 29 months.

ICD. All patients in the ICD studies had LV systolic dysfunction (mean LVEF ranged from 21 to 28 percent in the primary prevention trials and from 32 to 46 percent in the secondary prevention trials) and the majority had HF symptoms (50 percent had NYHA class II symptoms at baseline, 36 percent NYHA class III symptoms, and 3 percent NYHA Class IV)—11 percent of trial participants were defined as NYHA class I at baseline. The mean age of enrolled patients was 60.8 ± 4.2 years and 74 percent were male. All but three of the primary prevention trials specified other electrocardiographic entry criteria to identify high-risk patients, such as a history of nonsustained ventricular tachycardia,[137,138] elevated heart rate or reduced heart rate variability, or abnormal signal-averaged ECG. Although devices were specified to be single-chamber ICD in

all but two trials, protocol adherence to single-chamber vs. dual-chamber ICD was not reported in any trial.

Efficacy, Effectiveness, and Safety of CRT

Efficacy of CRT (Figures 4 to 14 and Table 19 in Evidence Report). CRT improved ejection fraction (WMD = 3.0 percent; 95% CI, 0.9 to 5.1 percent), quality of life (weighted mean reduction in Minnesota Living with Heart Failure Questionnaire 8.0 points [95% CI, 5.6 to 10.4 points]), and function (59 percent of CRT recipients vs. 37 percent of controls improved by at least one NYHA class) in trial participants. The proportion of patients hospitalized for HF was reduced by 37 percent (95% CI, 7 to 57 percent) and all-cause mortality was reduced by 22 percent (95% CI, 9 to 33 percent; Number Needed to Treat to prevent one death over 6 months = 29), driven largely by reductions in progressive HF deaths (RR = 0.64; 95% CI, 0.49 to 0.84).

Within the CRT trials, there was no consistent pattern of definitive differences in effects for different subgroups. Isolated trials reported greater effects in patients with longer QRS duration,[12] patients with septal coronary sinus leads implanted outside of the anterolateral region,[215] and patients with nonischemic disease,[216] but these findings were either based on small numbers of patients or not confirmed in other studies.[9,11,15] None of the CRT trials, however, were powered to detect subgroup effects of small to moderate magnitude. In univariate meta-regressions using trial-level data, no single factor was associated with the magnitude of CRT mortality benefit. Three factors suggestive of less severe HF—presence of an ICD in both controls and CRT patients, NYHA class II at baseline, and higher LVEF—were significantly associated with smaller CRT effects on HF hospitalizations (see Table 19 in main report). These analyses, however, are also underpowered to detect subgroup differences in the efficacy of CRT.

The efficacy of combination CRT-ICD devices and CRT-only devices appeared similar, based on meta-regression of aggregate trial data and indirect comparisons (i.e., comparisons between trials with different comparators but similar control groups). However, in the absence of head-to-head trials comparing the two devices, this conclusion should not be considered definitive. Two of the treatment arms of the COMPANION trial[11] provide the only opportunity to compare combined CRT-ICD devices vs. CRT alone devices within the same trial, but this was not a primary pre-specified aim of this trial. Although the mortality benefits were slightly greater with the CRT-ICD device (hazard ratio [HR] = 0.64; 95% CI, 0.48 to 0.86) than with CRT alone (HR = 0.76; 95% CI, 0.58 to 1.01), this difference was not statistically significant (p=0.13) and HF hospitalizations did not differ between patients receiving the combined CRT-ICD device compared to those receiving the CRT alone device. [11] In the highest risk subgroup of COMPANION (NYHA class IV patients), the time to death analysis did not demonstrate any benefit of the CRT-ICD device over the CRT alone device (HR = 1.27; 95% CI 0.68 to 2.37).[6]

Effectiveness of CRT (Figures 4 to 14, Figures 22 and 24, and Table 21 in Evidence Report). Survival during follow-up was similar in the randomized trials and the observational studies for patients who received CRT devices. The pooled effectiveness estimates from the observational studies were consistent with our findings from the efficacy trials. For example, in the RCTs, 59 percent of patients implanted with a CRT device improved by at least one NYHA class and in the observational studies between 63 and 82 percent of CRT recipients improved by at least one NYHA class. No covariates were consistently shown across studies to predict CRT response. Only one observational study compared outcomes in patients with CRT to outcomes in

contemporaneous controls without CRT – their findings of improved LVEF (WMD = 4.6 percent; 95% CI, 2.9 to 6.3 percent) and lower mortality rates (RR = 0.64; 95% CI, 0.26 to 1.56) in the CRT arm were consistent in magnitude to the findings from our meta-analysis of the CRT trials.

Safety of CRT (Tables 22 and 23 in Evidence Report). Implant success rate was 93 percent (95% CI, 92.2 to 93.7 percent) and peri-implant deaths occurred in 0.3 percent (95% CI, 0.1 to 0.6 percent) of individuals, with no appreciable differences either between those receiving CRT alone or combined CRT-ICD devices, or between participants in RCTs and observational studies. Over a median 11-month follow-up, lead problems occurred in 6.6 percent (95% CI, 5.6 to 7.4 percent) of CRT devices and 5 percent (95% CI, 4 to 7 percent) of these devices malfunctioned. Frequencies were similar in the RCTs and observational studies, and combined CRT-ICD devices demonstrated similar frequencies of device malfunction (5 percent; 95% CI, 4 to 6 percent) and lead problems (5.9 percent; 95% CI, 5 to 6.9 percent).

Efficacy, Effectiveness, and Safety of ICD

Efficacy of ICD (Figures 15 to 21 and Table 20 in Evidence Report). ICDs reduced all-cause mortality in patients with LV systolic dysfunction by 20 percent (95% CI, 10 to 29 percent; NNT = 20 over a median follow-up of 35 months but with significant heterogeneity between trials), due largely to a 54 percent reduction in sudden cardiac deaths (95% CI, 37 to 63 percent, with no appreciable heterogeneity between trials). In the two trials which reported such outcomes, ICDs did not demonstrate an appreciable impact on functional status or morbidity; however, insufficient studies have reported functional or quality of life outcomes with ICD to draw definitive conclusions. ICDs were equally beneficial in reducing all-cause mortality in both primary prevention trials (RR = 0.81; 95% CI, 0.69 to 0.95) and secondary prevention trials (RR = 0.77; 95% CI, 0.65 to 0.91) (see Figure 20 [p-value for comparison = 0.56]), although the absolute benefits were greater in the secondary prevention trials due to the higher baseline risk in those patients.

Only the SCD-HeFT trial reported a significant subgroup effect (greater benefits in patients with NYHA class II symptoms vs. NYHA class III symptoms at baseline – $p<0.001$); however, these trials were not powered to detect such subgroup effects. In a series of univariate meta-regression analyses using trial-level data, none of the covariates we examined explained the heterogeneity of treatment effect on all-cause mortality. Of note, none of these RCTs compared single chamber with dual chamber ICDs directly. Although the Dual Chamber and Atrial Tachyarrhythmias Adverse Events Study[140] reported fewer inappropriate shocks with dual-chamber ICD than with standard single right ventricular lead ICD, a secondary post-hoc analysis of the MADIT-II Trial comparing the 404 patients who received a single-chamber ICD with the 313 patients who received a dual-chamber ICD (the choice of which was left to the discretion of attending physicians and not randomized) revealed that dual-chamber ICD were associated with non-significant trends to higher rates of death (HR = 1.27; 95% CI, 0.76-2.12) or HF hospitalization (HR = 1.27; 95% CI, 0.87-1.86).

Effectiveness of ICD (Figures 15 to 21 and Figure 23 in Evidence Report). Survival during follow-up was similar in the randomized trials and the observational studies for patients who received ICD devices. The pooled effectiveness estimate from controlled observational studies,

however, suggested a greater benefit from ICD on all-cause mortality (RR = 0.54; 95% CI 0.43 to 0.68) than that reported in the RCTs. The fact that the controlled observational studies also demonstrated a benefit of ICDs on non-cardiac death (RR = 0.74; 95% CI, 0.65 to 0.85; Figure 18) suggests that selection bias (clinicians preferentially selecting healthier patients for ICD insertion) may explain the exaggerated mortality benefit seen in observational studies.

Between three-quarters and two-thirds of ICD recipients never received any therapeutic ICD discharges in the observational studies – this is consistent with the RCTs demonstrating that between 5 and 12 percent of trial participants receive a therapeutic ICD discharge per year.[217]

Safety of ICD (Table 24 in Evidence Report). ICD implant success rate was 99 percent (95% CI, 98.8 to 99.3 percent) and peri-implant deaths occurred in 1.2 percent (95% CI, 09 to 1.5 percent) of individuals (1.7 percent [1.2 to 2.4 percent] of RCT participants vs. 0.8 percent [0.5 to 1.2 percent] of subjects in observational studies). We also examined peri-implant deaths and success rates for 12 studies (68,848 patients) that enrolled all patients undergoing ICD implant (i.e., not just those patients with LV systolic dysfunction). The frequencies were similar to those reported in the studies restricted to patients with LV systolic dysfunction: implant success rate of 98.6 percent (95% CI, 98.3 to 98.9 percent) and peri-implant death rate of 1.3 percent (95% CI, 1.2 to 1.4 percent). The frequency of post-implantation complications per 100 patient-years of follow-up included 1.4 (95% CI, 1.2 to 1.6) device malfunctions, 1.5 (95% CI, 1.3 to 1.8) lead problems, 0.6 (95% CI, 0.5 to 0.8) implant site infections, and 19.1 (95% CI, 16.5 to 22.0) inappropriate discharges in RCT participants and 4.7 (95% CI, 4.3 to 5.1) inappropriate discharges in patients enrolled in observational studies.

Implications of Findings

Table 1 summarizes the conclusions which are possible given the currently available evidence for therapeutic devices in patients with LV systolic dysfunction.

CRT. There is high quality evidence that CRT improves ventricular function and remodelling, symptoms, and exercise capacity, while also reducing HF hospitalizations and death in patients comparable to those enrolled in the trials: (1) NYHA class III or IV HF despite optimal medical management, (2) LVEF ≤ 35 percent, (3) sinus rhythm, and (4) ventricular dyssynchrony (i.e., prolonged QRS duration). Although the mortality reduction with CRT was evident by six months in these trials, a long-term extension of the CARE-HF Trial confirmed that over 3 years of follow-up the relative benefits of CRT were stable (i.e., constant HR) and as such the absolute magnitude of benefit increased over time (thus, although our meta-analysis demonstrates that one death will be prevented within 6 months for every 23 trial patients receiving CRT, the CARE-HF follow-up data suggest that one death would be prevented over 2 years for every 13 CRT recipients, and one death prevented over 3 years for every 9 CRT recipients.[218]

The magnitude of these benefits are similar to those reported for angiotensin converting enzyme inhibitors, beta-blockers, and aldosterone antagonists in recent trials.[219-223] Balanced against these benefits, the peri-procedural risks of CRT appear modest: peri-implantation mortality was less than 1 percent (similar to the frequency reported for patients undergoing implantation of conventional dual-chamber pacemakers).[224] In contrast to isolated reports raising concerns about a potential excess risk of ventricular arrhythmias or sudden deaths in patients receiving CRT,[225] pooled results from multiple RCTs revealed no significant risk of sudden

death (RR = 1.07; 95% CI, 0.79 to 1.46) or noncardiac death (RR = 0.81; 95% CI, 0.43 to 1.52) in recipients of a CRT device.

Implantation of a biventricular CRT pacemaker (in particular the LV lead) can be technically challenging, even in experienced hands. Our review identified an implantation failure rate of 7 percent; given that these results came from RCTs and early cohort studies that tend to be reported by acknowledged experts in the field, this estimate may be conservative. Further, as the estimates of safety outcomes with CRT are derived from only a few thousand patients, they should not be considered definitive. Given the recent experiences with ICD recalls and FDA advisories, it seems prudent to recommend that all patients with LV systolic dysfunction who have either a CRT or an ICD device implanted be entered into a registry and followed for long-term risks and benefits (and this would also permit evaluations to define patient, device, or operator characteristics which impact on the benefit:safety ratio of CRT devices).

CRT does not always restore mechanical synchrony, even when lead placement is felt to be successful—while 59 percent of CRT recipients in these RCTs improved by at least one NYHA class, 41 percent did not.[226] In patients outside of RCTs, the rates of nonresponse to CRT have varied widely: from 20 to 28 percent in those studies using a functional status definition for response (an improvement of at least one in NYHA Class) and between 32 to 45 percent in studies employing an echocardiographic definition (most commonly a decrease of at least 15 percent in left ventricular end-systolic volume).[227] Studies to define which patients are most likely to benefit from CRT (such as the ongoing Predictors of Response to Cardiac Resynchronization Therapy Study)[228] and which positions in the ventricular wall are most appropriate for implantation of the pacing leads are clear research priorities. [226,229]

ICD. There is also high quality evidence that ICD reduces all-cause mortality in patients with LVEF ≤ 35 percent and NYHA class II and III symptoms. The relative reduction in all-cause mortality—20 percent—equates to preventing one death over 35 months for every 20 patients receiving an ICD. Neither functional status nor morbidity outcomes are improved by ICDs in the existing RCTs. Our analyses of observational studies with contemporaneous control groups confirmed that the benefits of ICD extend beyond the trial setting.

Trial eligibility criteria are commonly cited as a means by which to identify patients who will benefit from an ICD; however, identifying particular patient groups who are at increased risk for sudden cardiac death and thus most likely to benefit from an ICD is vitally important.[230,231] Two-quarters to two-thirds of ICD recipients in the reviewed trials never received any therapeutic ICD discharges;[217] even in those who received an appropriate discharge, the benefits were offset over time by deaths due to progressive HF;[232] and less than a quarter of cardiac arrest victims have a LVEF < 30 percent prior to their event.[233] Although our meta-regression analyses did not reveal any statistically significant differences in the subgroups we examined, these analyses were post hoc and underpowered due to the small number of trials. A meta-analysis of individual patient data would be necessary to appropriately examine this issue. The establishment of the ICD Registry by the American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR) in conjunction with the Heart Rhythm Society is also an important initiative which will permit the collection of comprehensive data on ICD implants and long-term outcomes. This data should help to identify whether particular patient subgroups derive more or less benefit than the average results reported in this report and whether specific devices or programming parameters are associated with better or worse outcomes.[234]

Combined CRT-ICD Devices. Our analyses indicate that the mortality benefits from CRT and ICD appeared to be independent (i.e. CRT provided mortality benefits whether or not an ICD was present, and ICD provided mortality benefits whether or not CRT was present) – this is consistent with our understanding of their distinct physiological mechanisms and their effects on different cardiac endpoints. This should not be taken to mean that the benefits of each device were additive, however. Indeed, the COMPANION Trial suggests that any incremental benefits with the combined device may be smaller than expected given the apparently independent mortality benefits with each component of the device; however, this comparison was not pre-specified or adequately powered in the COMPANION Trial and further studies are required to define the incremental benefits of the combined device.

Recommendations for Future Research:

A number of areas of uncertainty remain with respect to CRT and ICD therapy in patients with left ventricular systolic dysfunction, some of which are the subject of ongoing trials (for details, see "Implications of our Findings" on page 176 of the full Evidence Report):

1. Further information is still needed on the real world safety and effectiveness of CRT and/or ICD, since much of the data presented here comes from trials or selected cohorts, including trials which enrolled patients only after successful implantation of the device. These studies may overestimate the potential benefit:safety ratio from CRT and/or ICD. Although our review improves on previous reviews by including observational study data, expanding the prospective ACC-NCDR Registry to include CRT as well as ICD would add important "real world" estimates of benefits and risks with both of these devices.

2. Better information is needed on the effects of CRT, ICD, and combined CRT-ICD devices over longer time frames and in patient subgroups largely excluded from the trials conducted to date (such as those with atrial fibrillation, chronic kidney disease, or less symptomatic degrees of HF). In addition, registry data may help compare effectiveness and safety of single-vs. dual-chamber ICD-devices and track changes in complication rates as device implanters, the tools for implantation, and the sophistication of the devices change over time.

3. Collation of individual patient data from the available trials should be a priority to allow exploration for differential subgroup effects. In the words of one editorialist, "it is the entry criterion and not the group actually studied that has driven practice guidelines."[235]

4. The incremental benefit of combined CRT- ICD devices over ICD alone is uncertain and is the subject of ongoing trials. The incremental benefit of combined CRT-ICD devices over CRT alone is also uncertain yet is not to our knowledge currently being tested in any randomized trials. Given the changing epidemiology of HF mortality (i.e., due to disease modifying agents such as ACE inhibitors and beta-blockers, patients are now more likely to die of progressive HF than sudden death),[236] the incremental benefits of ICD therapy in a patient who has a CRT device may be smaller than suggested from the ICD trial data in this report. A trial targeting those patients who currently do not qualify for ICD therapy—for example, patients with LVEF in the range of 30 to 40 percent or patients with NYHA class IV symptoms—might require over 1,300 patients per arm followed for 3 years to establish

(or refute) a clear marginal benefit of combined devices over CRT alone. Given the markedly higher costs for combined CRT-ICD devices and the rapidly expanding population of HF patients eligible for such devices, such a trial is nonetheless justified.

Table 1. Summary of evidence for devices in patients with left ventricular systolic dysfunction*

Device	Other characteristics		Quantity of evidence for that patient subgroup	Quality of evidence	Magnitude of effect (95% CI)	Conclusion
	Symptom status	ECG criteria				
CRT alone	NYHA class III or IV	QRS > 120 msec and sinus rhythm	13 RCTs, 3,481 patients	High (multiple RCTs with homogeneous results)	Reduced mortality: RR = 0.78 (0.67 to 0.91) Reduced HF hospitalizations: RR = 0.51 (0.41 to 0.64)	Definite benefit
	NYHA class II	QRS > 120 msec and sinus rhythm	5 RCTs, 344 patients	Moderate (one small RCT PLUS post-hoc meta-regression of aggregate trial data from 14 RCTs, but few patients in these RCTs had NYHA Class II) Ongoing RCTs: REVERSE, RAFT	No significant effect on mortality (RR = 1.19, 95% CI 0.17 to 8.26 in the one RCT); In meta-regression, proportion of patients with Class II symptoms was not significantly associated with reduction in mortality (p = 0.76) Effect on hospitalization may be smaller in Class II HF than Class III/IV (in meta-regression, proportion of patients with Class II symptoms significantly associated with reduction in hospitalization (p = 0.003)	Inconclusive
	NYHA class III or IV	QRS > 120 msec and brady-arrhythmia or atrial fibrillation	3 RCTs, 191 patients	Low (post-hoc meta-regression of aggregate trial data from 14 RCTs) Ongoing RCTs: Trip HF, RAFT, APAF, BLOCK HF	No significant association in meta-regression between proportion of patients with atrial fibrillation and reduction in mortality or hospitalizations (p = 0.73 and 0.58, respectively)	Inconclusive
	NYHA class III or IV	QRS duration < 120 msec; any rhythm	5 studies, 120 patients	Low (secondary analyses of small observational studies)	Improvements in symptoms and LV remodelling not significantly different between patients with narrow QRS and patients with wide QRS in any of the studies	Inconclusive
	NYHA class I	Any QRS duration; any rhythm	None	No published evidence Ongoing RCT: REVERSE	Not applicable	Inconclusive

CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardiac defibrillator; LV = left ventricular; msec = microsecond; NYHA = New York Heart Association; RCT = randomized control trial

*****Note that other considerations may outweigh the trial evidence in some situations (e.g., the patient who wishes to be "do not resuscitate") and there is no data on the effects of either CRT or ICD in patients with advanced age or severe comorbidities (such as end-stage renal disease).

Table 1. Summary of evidence for devices in patients with left ventricular systolic dysfunction (continued)

Device	Other characteristics		Quantity of evidence for that patient subgroup	Quality of evidence	Magnitude of effect (95% CI)	Conclusion
Combined CRT-ICD device (vs. no device)	NYHA class III or IV	QRS > 120 msec and sinus rhythm	1 RCT, 903 patients in relevant comparison arms	Moderate (one large RCT) Ongoing RCTs: DECREASE, RAFT	Reduced mortality: hazard ratio = 0.64 (0.48 to 0.86) Reduced mortality or all-cause hospitalization: hazard ratio = 0.80 (0.68 to 0.95)	Definite benefit
	All other patient subgroups		None	No published evidence Ongoing RCTs: MADIT-CRT, RAFT	Not applicable	Inconclusive
Combined CRT-ICD device (vs. CRT alone)	NYHA class III or IV	QRS > 120 msec and sinus rhythm	1 RCT, 1,212 patients in relevant comparison arms	Moderate (one large RCT, but this comparison was not a priori specified or adequately powered)	No significant effect on mortality (RR = 0.83; 95% CI, 0.66 to 1.05) and no significant effect on time to death in NYHA class IV subgroup (hazard ratio = 1.27; 95% CI 0.68 to 2.37)	Inconclusive
	All other patient subgroups		None	No published evidence	Not applicable	Inconclusive
ICD alone	Secondary prevention in patients with history of ventricular fibrillation or tachycardia		3 RCTs, 1,963 patients	High (multiple RCTs with homogeneous results)	Reduced mortality: RR = 0.77 (0.65 to 0.91)	Definite benefit
	Primary prevention in NYHA class II or III patients		9 RCTs, 5,636 patients	High (multiple RCTs with homogeneous results)	Reduced mortality: RR = 0.81 (0.69 to 0.95) No significant effect on HF hospitalizations: 1.10 (0.76 to 1.59)	Definite benefit
	Primary prevention in NYHA class I patients		6 RCTs, 721 patients	Low (post-hoc meta-regression using aggregate trial data from 12 RCTs)	No significant association in meta-regression between proportion of patients with Class I symptoms and reduction in mortality (p = 0.13)	Inconclusive
	Primary prevention in NYHA class IV patients		1 RCT, 217 patients	Moderate (within-RCT comparison, but not primary aim of RCT, PLUS post-hoc meta-regression using aggregate trial data from 12 RCTs)	Mortality hazard ratio = 1.27 (0.68 to 2.37) in CRT-ICD vs. CRT alone arms in the class IV patients in the COMPANION Trial, PLUS p = 0.62 for mortality meta-regression comparing impact of ICD in NYHA class IV patients vs. impact in class II or III patients	Inconclusive

Evidence Report

Chapter 1. Introduction

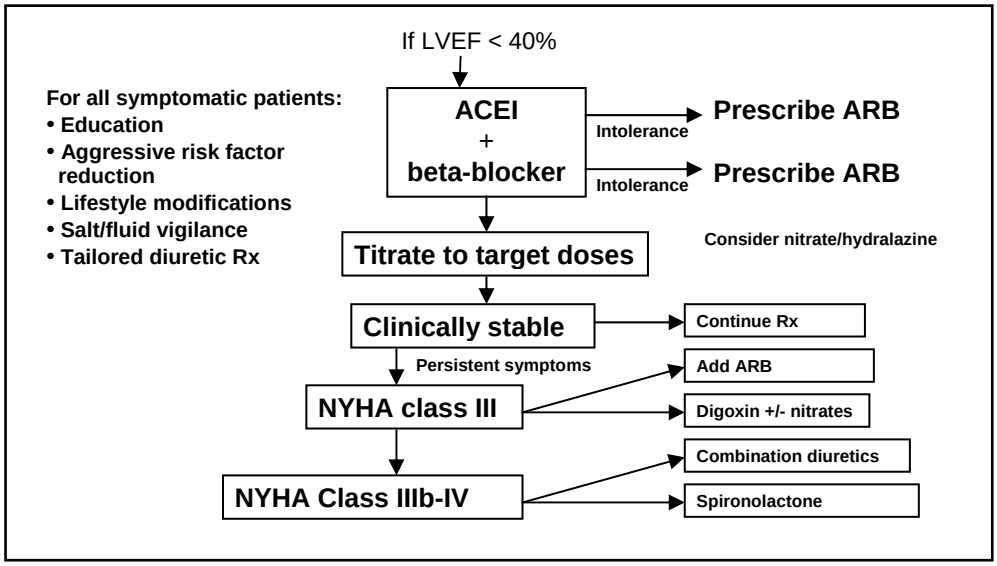
The American College of Cardiology (ACC), the American Heart Association (AHA), and the Heart Rhythm Society (HRS) commissioned this report to review the current evidence about the efficacy, safety, and effectiveness of implantable cardioverter defibrillators (ICD), cardiac resynchronization therapy (CRT), and combined CRT-ICD devices in patients with heart failure (HF) or asymptomatic left ventricular (LV) systolic dysfunction.

Background

Heart failure (HF) leads to significant morbidity and mortality; in 2001 it accounted for almost one million hospitalizations in the United States (as the most responsible diagnosis) and $29.6 billion in direct and indirect costs.[237] HF is the fastest growing cardiovascular diagnosis in North America: the community prevalence is estimated at 0.4 percent to 2.4 percent in adults,[237-240] with the annual incidence approaching 10 cases/1,000 in people over 65 years of age.[237] Indeed, the lifetime risk of developing HF is estimated at 20 percent in North America.[241] Despite many advances in diagnosis and therapy over the past two decades, HF still carries a poor prognosis.[237,242] The functional status of patients with HF is described using the New York Heart Association (NYHA) Classification system: NYHA Class I patients are those who are asymptomatic; NYHA Class II patients are those who develop symptoms (dyspnea or fatigue) with moderate exertion (climbing two flights of stairs or walking two blocks); NYHA Class II patients are symptomatic with mild exertion (climbing one flight of stairs or walking one block); and NYHA Class IV patients are symptomatic at rest.

HF is a clinical syndrome characterized by specific symptoms and is accompanied in most cases by a decreased ejection fraction ("left ventricular systolic dysfunction").[243] A plethora of randomized trials over the past 2 decades have established a variety of treatment options for systolic heart failure, as outlined in schematic form below.[243,244]

Figure 1. Treatment of systolic heart failure (Adapted from Canadian Cardiovascular Society Guidelines[244])



In general, management of HF involves a combination of nonpharmacological (e.g., lifestyle modification, education, smoking cessation) and pharmacological approaches. Pharmacological treatment of HF involves a combination of the use of vasodilators (e.g., nitrates), neuro-hormonal agents (e.g., angiotensin-receptor blocker [ARB] and angiotensin-converting enzyme [ACE] inhibitors), beta-blockers, diuretics (e.g., furosemide, spironolactone) and inotropes (e.g., digoxin). In special cases, such as atrial fibrillation, cardiac rate control and/or antiarrhythmic therapy may also be warranted. Prevention of complications such as cardiac embolism (using ASA, warfarin, or both) and infectious diseases (through immunization) are also warranted in this patient group. Finally, due to the complexity of the disease, multidisciplinary approaches to management, including specialized heart function clinics, are strongly encouraged.

Despite evidence-based care using optimal combinations of the nonpharmacologic and pharmacologic approaches summarized above, rates of morbidity and mortality remain high and quality of life is poor for many patients with systolic HF. Attempts to reduce mortality in HF are directed at the two main causes of cardiac death in these patients: sudden cardiac death (electrical failure) and progressive heart failure (mechanical failure).[245] Sudden cardiac death accounts for more deaths than progressive heart failure in patients with NYHA Class I or II symptom status. On the other hand, progressive heart failure is the predominant cause of death in those with NYHA Class III or IV symptoms.[246] It is important to emphasize that not all therapies that improve functional outcomes (such as symptoms, quality of life, ejection fraction, and other hemodynamic measurements) in HF patients confer survival benefits.[247] Thus, it is essential that any novel therapies for patients with HF be evaluated for their impact on hospitalization and/or death.

Clearly, there is a need for additional treatment strategies in HF that can improve function, diminish symptoms, reduce hospitalizations, and increase survival. Recently, attention has focused on the potential for cardiac resynchronization therapy (CRT)—atrial-synchronized biventricular pacing (i.e., pacing the right atrium, right ventricle, and left ventricle)—to reduce the mechanical dyssynchrony common in patients with left ventricular systolic dysfunction, and thereby improve left ventricular filling time, reduce mitral regurgitation, and reduce septal-posterior wall dyskinesis.[1,2] An earlier systematic review of the clinical trials of CRT established that, in selected patients with advanced HF and mechanical LV dyssynchrony, CRT improves quality of life, NYHA class, 6-minute walk test results, and reduces both hospitalizations and all-cause mortality (produced primarily by a 40 percent reduction in progressive HF deaths).[248] However, the previous systematic review had two important weaknesses: (1) it was unable to clarify the relative survival benefits conferred by CRT alone vs. combined CRT-ICD devices given the relative paucity of data at that time, and (2) it was based on efficacy data derived from randomized controlled trials conducted on highly select patients (NYHA III/IV symptoms, sinus rhythm, LVEF < 35 percent, QRS ≥ 120 msec, and on optimal medical therapy) seen at large-volume hospitals by clinicians experienced in CRT device implantation and monitoring.[249] Thus, this earlier systematic review needed to be updated to (1) incorporate randomized efficacy trials published in the subsequent 3 years, (2) expand the analyses beyond randomized trial evidence to examine the safety and effectiveness of CRT devices when they are used in clinical practice (which may possibly differ from the effect estimates reported in trial participants and settings), and (3) clarify the incremental benefits conferred by combined CRT-ICD devices over CRT alone or ICD alone (which could not be properly evaluated before due to a paucity of evidence at that time) and to define the patient groups most appropriate to receive a CRT device.

ICDs are devices consisting of at least one lead which resides in the right ventricle dedicated to pacing and/or defibrillating lethal cardiac arrhythmias. More advanced ICDs (dual-chamber devices) consist of leads in the right atrium and right ventricle and have the potential to be programmed as a dual-chamber pacemaker (e.g., DDD pacing mode) and for the atrial lead to help discriminate arrhythmic events. ICDs do not improve functional outcomes in patients with HF; however, they do confer a substantial mortality benefit (through the prevention of sudden cardiac death) in patients who have a history of ventricular arrhythmias or who are at high risk for ventricular ectopy due to the severity of their left ventricular dysfunction.[250] Since an earlier systematic review of ICDs proving the benefits of these devices in the secondary prevention of ventricular arrhythmia deaths in high risk patients, a number of large trials have evaluated the effects of ICDs for primary prevention in patients with symptomatic or asymptomatic left ventricular systolic dysfunction but without known ventricular arrhythmias. As with the CRT review, there are issues concerning the impact of ICDs when used in clinical practice compared with their impact in the optimal settings and highly select participants involved in efficacy trials. Thus, there is a need to (1) update the earlier meta-analysis to incorporate randomized efficacy trials published in the subsequent 4 years, and (2) expand our analyses to examine the safety and effectiveness of ICDs when they are used in clinical practice.

The issue of device effectiveness and safety in clinical practice is particularly important as the rates of implantation for CRTs and ICDs are increasing exponentially. In 2001, 48,127 ICDs were implanted in the United States, of which only two percent were combined CRT-ICD devices.[251] However, in 2005 over 156,000 ICDs were implanted in the United States, with 42 percent being combined CRT-ICD (Merril Lynch Industry Model Book, May 2006).

This review will examine the evidence for the efficacy, effectiveness, and safety of CRT alone, ICD alone, or combined CRT-ICD in patients with LV systolic dysfunction and will attempt to define the potential role of CRT and/or ICD in managing these patients.

Study Questions

1. In adult patients with symptomatic or asymptomatic LV systolic dysfunction, what is the efficacy and effectiveness of CRT alone, ICD alone, or combined CRT-ICD devices compared to usual medical therapy?

2. In adult patients with symptomatic or asymptomatic LV systolic dysfunction, what is the efficacy and effectiveness of single-chamber ICD compared to that of dual-chamber ICD?

3. In adult patients with symptomatic or asymptomatic LV systolic dysfunction, how safe is CRT alone, ICD alone, or combined CRT-ICD devices?

4. Which patients would benefit from ICD alone, CRT alone, or combined CRT-ICD devices?

Chapter 2. Methods

Literature Search

We systematically searched the following 17 electronic resources: MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials (which contains the Cochrane Heart Group's Trial Registry; this group hand searches journals pertinent to its content area and adds relevant trials to the registry), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), EMBASE, Science Citation Index Expanded (via Web of Science®), International Pharmaceutical Abstracts, PubMed®, National Library of Medicine (NLM) Gateway, OCLC Proceedings First and Papers First, CRISP (Computer Retrieval of Information on Scientific Projects), The National Research Register (UK), Australian Clinical Trials Registry, ClinicalTrials.gov, and Current Controlled Trials. We also searched for relevant reports from the U.S. Food and Drug Administration and for abstracts from the annual Heart Rhythm Society meetings. The reference lists of relevant reviews and included studies were reviewed, and authors of included studies were contacted for additional citations and information. Finally, additional unpublished data (including individual patient data) were sought from the following CRT and ICD manufacturers: Medtronic Inc. (Minneapolis, MN), Guidant Corporation (Indianapolis, IN), and St. Jude Medical Inc. (St. Paul, MN). The search was not limited by language of publication or publication status and is considered current up to November 14, 2006.

The search terms were adapted from the search strategies used in two previous reviews[248,250] and included "biventricular pacing," "biventricular pacer," "biventricular stimulation," "BiV," "artificial cardiac pacing," "chronic cardiac failure resynchronization therapy," "single chamber pacing," "dual chamber pacing," "cardiac resynchronization," "Medtronic," "InSync," "ELA medical," "Guidant," "St. Jude," "implantable defibrillators," "AICD," "ICD," "single chamber ICD," "dual chamber ICD," "congestive heart failure," "CHF," "chronic heart failure," and "heart diseases." Along with the terms for randomized controlled trials (RCTs), the following terms were used to refine the search for evidence: "controlled clinical trial," "meta-analysis," "multi-center trial," "safety," "risk," "adverse effects," or "adverse symptoms," "side effects," "harm," "contraindications," "causation," "causality," "predict," "complications," "inappropriate shocks" or "inappropriate pacing," "bleeding," "hemorrhage," and "infection."

The complete search strategies (adapted for each database) and search results are included in Appendix A*.

Selection and Inclusion

To address efficacy questions, we limited our analyses to randomized controlled trials (RCTs). To address effectiveness questions, our inclusion criteria were expanded to include non-RCTs that used contemporaneous comparison arms (e.g., cohort studies). To address safety questions, we included evidence from both RCTs and non-RCTs (including study designs

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/defibtp.htm

without contemporaneous control arms, such as case series, registry data, etc.) since adverse events are uncommon and uncommonly reported in RCTs (which generally have short followup durations).

To assess efficacy and effectiveness of CRT, ICD, and combined CRT-ICD devices, we selected studies that enrolled greater than 25 participants with a left ventricular ejection fraction (LVEF) ≤ 35 percent, followed patients for at least 2 weeks, and reported at least one outcome of interest: mortality (all-cause, cardiac, HF, sudden cardiac death), quality of life, NYHA functional class, 6-minute walk test, hospitalization (all-cause or HF), or LVEF. To assess the safety of CRT alone or with ICD, we selected studies that enrolled greater than 25 participants with LVEF ≤ 35 percent, followed patients for at least 2 weeks, and reported at least one outcome of interest: implant success rates, or peri-, and post-implantation risks. To assess the safety of ICD, we selected studies that enrolled greater than 25 participants with LVEF ≤ 35 percent, followed patients for at least 2 weeks, and reported at least one outcome of interest: implant success rates, or peri-, and post-implantation risks. After reviewing our draft report, the Technical Expert Panel suggested that we also examine the implant success rates and peri-implant safety of ICD in all patients (not just those patients with LV systolic dysfunction). Although we recognize that many of these patients would have symptomatic HF or asymptomatic LV systolic dysfunction, we decided to analyze peri-implant safety of ICD for all patients, but to report the results for patients known to have LV systolic dysfunction as a subgroup analysis.

Table 2. Inclusion and exclusion criteria for efficacy review

Study design	*Include:* RCT (parallel or crossover) > 2 weeks duration. *Exclude:* non-RCTs, acute physiological studies and studies that do not involve human subjects.
Participants	*ICD alone:* Include patients with asymptomatic LV systolic dysfunction or symptomatic HF and LVEF ≤ 35%. *CRT alone or combined CRT-ICD devices:* Include patients with symptomatic HF (NYHA Class II-IV) while receiving stable optimal drug therapy, LVEF ≤ 35%, and prolonged QRS. Studies with < 25 participants were excluded.
Interventions	Treatment with active CRT, active ICD, or combined CRT-ICD compared to either placebo pacing, or uni-ventricular (right-sided) pacing, or drug therapy alone. Studies comparing combined CRT-ICD to ICD alone were also included.
Outcomes	Mortality (all-cause, cardiac, HF, sudden cardiac death), quality of life, NYHA functional class, 6-minute walk test, morbidity (including all-cause or HF hospitalization, ED visit), and LVEF.

ED = emergency department; HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; = RCT = randomized controlled trial

Table 3. Inclusion and exclusion criteria for effectiveness and safety review

Study design	*Include:* RCT (parallel or crossover) or non-RCT (e.g., registry data, prospective cohort, case series, FDA document, etc.) > 2 weeks duration. *Exclude:* acute physiological studies and studies not involving human subjects.
Participants	*ICD alone:* Include patients with asymptomatic LV systolic dysfunction or symptomatic HF and LVEF ≤ 35% (but for peri-implant success rates and complications, include all ICD patients). *CRT alone or combined CRT-ICD devices*: Include patients with symptomatic HF (NYHA Class II-IV) while receiving stable optimal drug therapy, LVEF ≤ 35%, and prolonged QRS. Studies with < 25 participants were excluded.
Interventions	Treatment with active CRT, active ICD, or combined CRT-ICD. Comparison group not necessary.
Outcomes	*Effectiveness*: Mortality (all-cause, cardiac, HF, sudden cardiac death), quality of life, NYHA functional class, 6-minute walk test, morbidity (including all-cause or HF hospitalization, ED visit), LVEF. *Safety*: Successful implant rate, risks during implantation (death, lead misplacement, device-related malfunctions, procedural complications, implant tools, heart function, and patient complaints), risks following implantation (mechanical malfunction, lead dislodgment, infection, pain), and battery longevity. For ICD devices, data on inappropriate delivery of therapy, need for additional medication, and need for hospitalization for HF.

ED = emergency department; HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RCT = randomized controlled trial

Quality Assessments

Efficacy Review

The methodological quality of RCTs was assessed independently by two reviewers using two quality assessment methods without being blinded to authors, setting, or results. First, allocation concealment was assessed as adequate, inadequate, or unclear using the Cochrane approach.[252] Second, a five-point scoring system validated by Jadad[253] was used to assess randomization, double blinding, and reporting of withdrawals and dropouts. In addition, the funding source and whether authors reported the use of intention-to-treat analysis were noted. Decision rules regarding the application of the tool were developed a priori and discrepancies were resolved through discussion between the two reviewers.

Effectiveness and Safety Review

The methodological quality of RCTs was assessed as outlined above. The quality of observational studies included in the effectiveness and safety review were assessed independently by two reviewers using a validated checklist developed by Downs and Black.[254] The checklist includes 28 questions evaluating five criteria: reporting (10 questions, total score 11), external validity (three questions, total score 3), internal validity—bias (seven questions, total score 7), internal validity—confounding (six questions, total score 6) and power (two questions, total score 2). Decision rules regarding the application of the tool were developed a priori and discrepancies in quality assessment were resolved through discussion between the two reviewers.

Data Extraction

Data were extracted using standardized forms and entered into an Excel (Microsoft Corp., Redmond, WA) spreadsheet. Data were extracted by one reviewer (DD, NH, or CS) and checked for accuracy and completeness by a second (BV). Extracted data included the outcomes described in Tables 2 and 3, study characteristics, inclusion/exclusion criteria, baseline drug use, characteristics of participants, and procedural data.

Data Analysis

Efficacy Review

The following data assumptions were made and imputations performed to transform reported data into the form required for this review. Standard errors (SE) were converted into standard deviations (SD). Graph extraction was performed using CorelDRAW® 9.0 (Corel Corp., Ottawa, Canada). Means were approximated by medians, and 95 percent empirical intervals were used to calculate approximate SDs. Change from baseline data were used wherever possible for continuous data; however, since correlations between baseline and endpoint data were never reported, a correlation of 0.5 was assumed[255] to calculate the appropriate standard deviation for change from baseline data. Change from baseline and endpoint data were combined; both entities estimate differences between treatment groups. When provided, efficacy results were extracted rather than intention-to-treat results.

Numerical results were meta-analyzed primarily in Review Manager version 4.2.5 (The Cochrane Collaboration, Copenhagen, Denmark). For dichotomous results (e.g., CHF hospitalizations), the review reported relative risks (RR) for each individual study as well as a pooled result among those studies that could be combined. For continuous variables (e.g., 6-minute walk test) mean differences were calculated for separate studies and the weighted mean difference (WMD) was calculated for the pooled estimate. All results were reported with 95 percent confidence intervals (CIs) where possible.

Due to the differences expected between studies (particularly in control group therapies), we decided a priori to combine results primarily using random effects models.[256] Statistical heterogeneity was quantified and appropriated using the I-squared (I^2) statistic.[3] This statistic can be roughly interpreted as the percentage of total variance in the meta-analysis that is due to between-study variation. Inclusion of studies with active control arms was assessed in sensitivity analyses. Relevant direct subgroup comparisons were summarized, including effects of CRT in patients with more severe heart failure symptoms (NYHA Class III or IV). ICDs were considered in an indirect subgroup comparison using meta-regression. Any other reasons for heterogeneity were also explored using meta-regression.

Estimates of carryover effect were extracted from crossover designs. Only period one data were used for irreversible outcomes (i.e., death and CHF hospitalizations). Standard errors for crossover WMD were calculated according to Curtin.[257]

For our primary outcome, all-cause mortality, we tested for publication bias visually using the funnel plot and quantitatively using the rank correlation test,[258] the graphical test,[259] and the trim and fill method.[260] Meta-regression and publication bias calculations were performed using STATA 7.0 (StataCorp., College Station, TX).

Effectiveness Review

The procedures used for the analysis of efficacy were also used to test for effectiveness, although we did not test for publication bias in observational studies. In addition, mortality rates for both RCTs and observational studies were plotted against followup time and a regression coefficient was computed for each of the three groups (CRT alone, ICD Alone, and CRT+ICD).

Safety Review

Quantitative results were meta-analyzed primarily in S-PLUS® 6.0 (Insightful Corp., Seattle, WA). Risks were simply pooled and all results were reported with 95% CIs. Statistical heterogeneity was assessed using the Chi-square test; $p<0.10$ was considered heterogeneous.[261] Also, heterogeneity was quantified and appropriated using the I^2 statistic.[3] The exclusion of NYHA class II data and studies with active control arms was assessed in sensitivity analyses; however, these are not reported here. The possibility that reports may have been less judicious in reporting adverse events was considered. Sensitivity analyses were performed where studies (RCT or cohort) did not report a particular risk (e.g., death); zero adverse events were assumed for these studies. In addition, some implantation risks were reported by event and not by patient. This nonindependence was small and was not expected to affect the results importantly.

Which HF Patients Would Benefit From CRT, ICD, or Combined CRT-ICD Devices?
Within-trial subgroup reports and meta-regression across trials were used to examine the relation between a variety of covariates and the efficacy of CRT, ICD, and combined CRT-ICD devices. Individual patient data was requested from each device manufacturer; however, insufficient data were available to perform an individual patient data meta-analysis by January 9, 2007.

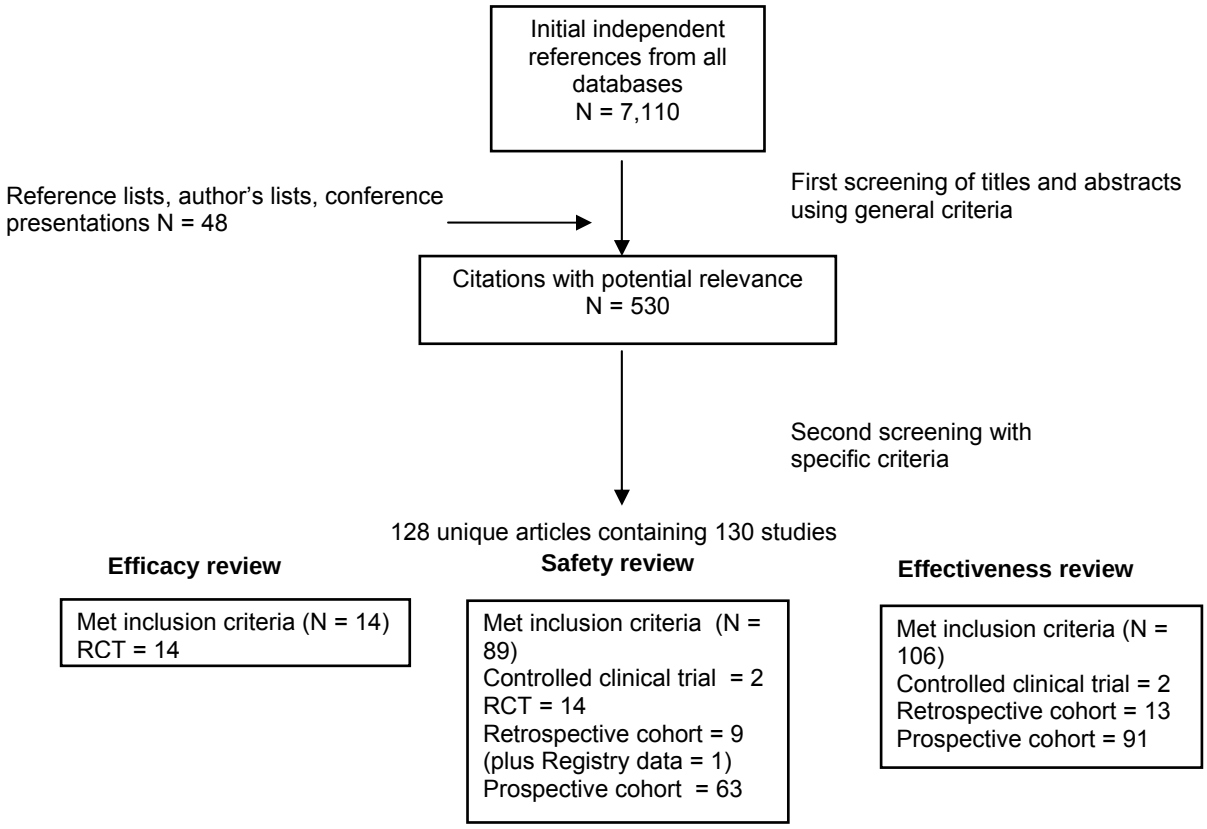
Chapter 3. Results

Literature Search

CRT Alone or Combined CRT-ICD Devices

Of 7,110 initial references retrieved from electronic databases and 48 references identified by hand searching reference lists in published studies or by contacting content experts (including primary study authors), we included 128 unique articles (reporting data from 130 studies). Fourteen RCTs[4-17] were included for the efficacy review, 106 studies[17-122] (2 clinical trials, 104 observational studies) for the effectiveness review, and 89 studies (14 RCTs,[4-17] 2 clinical trials,[39,73] and 73 observational studies[17,20,22,26,27,29-33,35,36,41,42,44-46,49,50,52,53,55-58,60,63-70,76,78,80,82,83,85-87,89,91-94,97,98,100,102-106,108,109,111-113,117,118,123-132]) for the safety review (Figure 2). Many of the studies were included in more than one of the efficacy, safety, and effectiveness reviews. Additional data to those reported in the journal publications or conference presentations were provided by the investigators from four trials[4-6,10] and are included in these analyses.

Figure 2. Flow diagram of study retrieval and selection for CRT alone or combined CRT-ICD devices



Many of the included trials were associated with multiple publications that either expanded on the main results or reported secondary outcomes not included in the primary report. In such cases, only the primary report for each trial was included; however, data on secondary outcomes were extracted if they were only reported in these secondary publications. Appendix C* identifies the associated multiple publications for each included study (there were 49 in total).

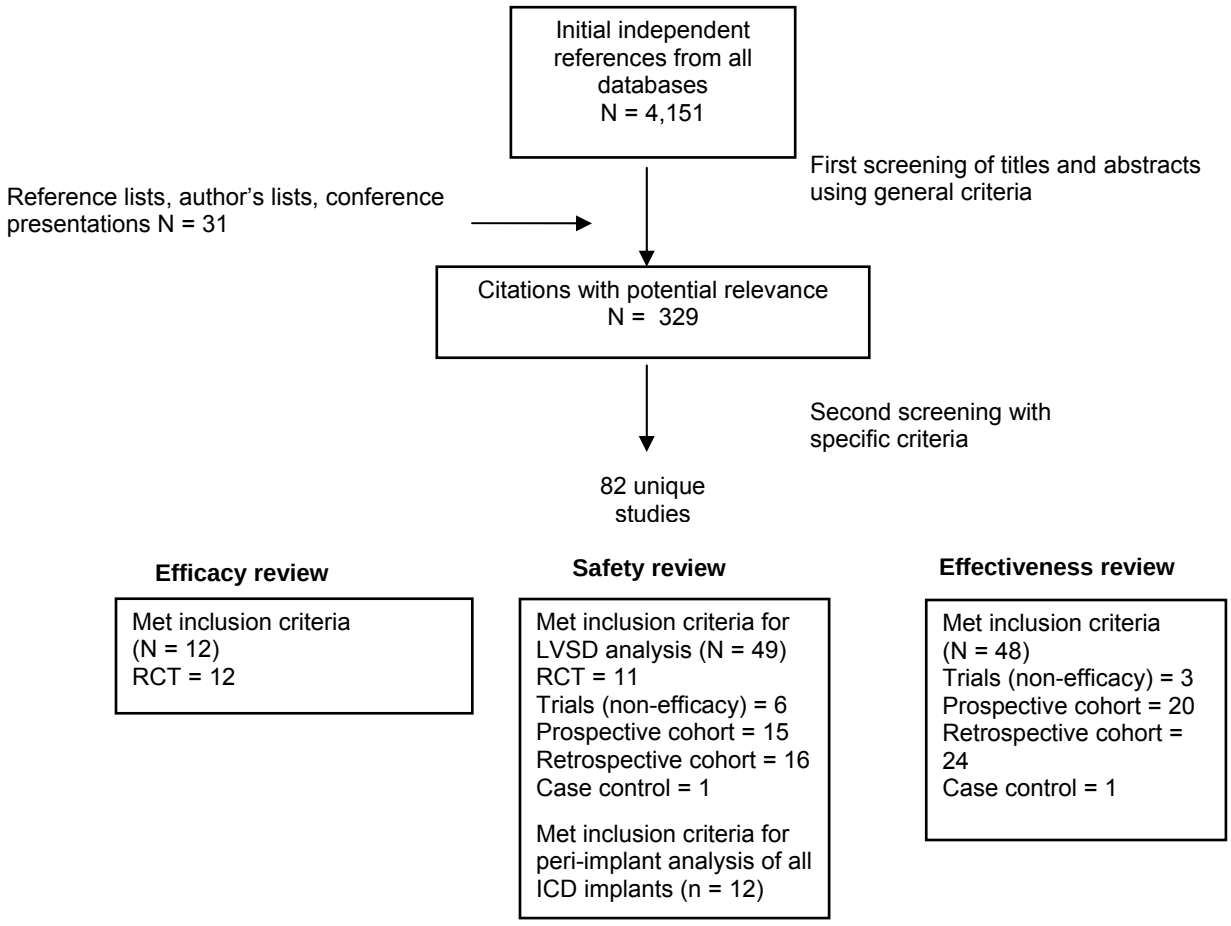
There were three main reasons for excluding studies from the CRT review on the second detailed screening: (1) the intervention studied was not CRT (48 studies); (2) the article was a review, protocol, editorial, or did not present primary data (139 studies); or (3) the study did not report required outcomes (134 studies), leaving 32 studies which were excluded for other reasons (including small sample size). The list of excluded studies and reasons for exclusion are identified in Appendix D*.

ICD Alone

Of 4,151 initial references retrieved from electronic databases and 31 references identified by hand searching reference lists in published studies or by contacting content experts (including primary study authors), we included 82 unique studies. Twelve RCTs[11,133-143] were accepted for the efficacy review, 48 studies[144-191] (3 trials, 45 observational studies) were accepted for the effectiveness review, and 49 studies (11 efficacy studies,[11,133-136,138-143] 38 observational studies[144,145,147,148,152,155-159,161,162,164,165,169,171,176,178-181,184,186-189,191-202]) for the safety review (Figure 3). An additional 12 studies (68,848 patients) were included in our secondary analysis of peri-implant safety with ICD for all patients (i.e., not restricted to only those patients with LV systolic dysfunction).[203-214]

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/defibtp.htm

Figure 3. Flow diagram of study retrieval and selection for ICD alone



Many of the included trials were associated with multiple publications that either expanded on the main results or reported secondary outcomes not included in the primary report. In such cases, only the primary report for each trial was included; however, data on secondary outcomes were extracted if they were only reported in these secondary publications. Appendix C* identifies the associated multiple publications for each included study (there were three in total).

There were three main reasons for exclusion of studies from the ICD review on the second detailed screening: (1) the population did not have LVSD (61 studies); (2) the article was a review, protocol, editorial, or did not present primary data (105 studies); or (3) the study did not report required outcomes (64 studies), leaving 14 studies which were excluded for other reasons (including small sample size). The list of excluded studies and reasons for exclusion are identified in Appendix D*.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/defibtp.htm

Description of Included Studies: Efficacy Review

CRT Alone or Combined CRT-ICD Devices

Fourteen randomized trials met the inclusion criteria for the efficacy review and are listed below:

1. The MIRACLE (Multicenter InSync Randomized Clinical Evaluation) Trial[4]
2. The MUSTIC-SR (Multisite Stimulation in Cardiomyopathies Sinus Rhythm) Trial[5]
3. The MIRACLE ICD (Multicenter InSync Randomized Clinical Evaluation ICD) Trial[6]
4. The MUSTIC-AF (Multisite Stimulation in Cardiomyopathies Atrial Fibrillation) Trial[7]
5. The PATH-CHF (Pacing Therapies for Congestive Heart Failure) Trial[8]
6. The CONTAK-CD Trial[9]
7. The RD-CHF Trial[10]
8. The COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure) Trial[11]
9. The PATH-CHF II (Pacing Therapies for Congestive Heart Failure II) Trial[12]
10. The HOBIPACE (Homburg Biventricular Pacing Evaluation) Trial[13]
11. The MIRACLE ICD II (Multicenter InSync Randomized Clinical Evaluation ICD II) Trial[14]
12. The CARE-HF (Cardiac Resynchronization-Heart Failure) Trial[15]
13. The VecTOR (Ventricular Resynchronization Therapy Randomized) Trial[16]
14. The RHYTHM ICD (Resynchronization for Hemodynamic Treatment for Heart Failure Management) Trial[17]

Publication Status. Eleven of these trials have been published, and 3 three were located from other sources as mentioned in Figure 2. Seven of the trials were conducted in North America, and the other seven were conducted in Europe. Characteristics of the trials are summarized in Table 4.

Trial Participants (Table 5). In total, 4,892 patients were enrolled in these trials and 4,420 (90.3 percent) were randomized to receive CRT (n = 2,703) or control (n = 1,717). Of the patients in the intervention arms, 1,310 (48 percent) received CRT alone and 1,393 (52 percent) received a CRT-ICD device. The majority of those who were enrolled but not randomized had failed implant attempts. The mean age of enrolled patients (in the 11 studies[4-9,13,14,16] that reported patient age) was 65.4±10.8 years and 72 percent were male (in the 12 studies that reported patient gender[4-9,11-16]). Approximately 79 percent of trial participants were considered NYHA class III at baseline (range 0 to 100 percent), and 12 percent were classified as NYHA class IV at baseline (range 0 to 67 percent). Five trials included patients with NYHA class II symptoms (range 6 to 33 percent in four trials[9,16,17] and 100 percent in the fourth trial[14])—approximately 9 percent of all trial participants were judged to be NYHA Class II at baseline. Five trials specified a 6-minute walk test result of less than 450 meters as an inclusion criterion.[4,5,7,16,17] The physical exam findings at baseline were similar among trials with systolic blood pressure (range 110 to 118 mm Hg), diastolic blood pressure (range 67 to 70 mm Hg), and heart rate (range 69 to 80 bpm) all similar to other trials in heart failure. No trial specifically

recruited patients based on the etiology of their heart failure, although patients with uncorrectable valvular disorders and hypertrophic or restrictive cardiomyopathy were excluded from all trials. In the six trials that evaluated CRT-ICDs, the majority of patients had ischemic etiology (~59 percent);[6,9,11,12,14,17] in the other trials, ischemic etiology ranged from 37 percent[5] to 55 percent.[4]

Left Ventricular Ejection Fraction. Although PATH-CHF[8] did not specify LVEF in entry criteria, 11 trials enrolled patients with LVEF < 35 percent, 1 trial[12] enrolled those patients with LVEF < 30 percent, and 1 trial[13] specified LVEF < 40 percent as an entry criterion. The mean ejection fractions were similar in all trials, and ranged from 21 to 30 percent. Nine trials also specified a left ventricular end diastolic diameter: ≥ 55 mm in four trials[4,6,14,16] and ≥ 60 mm in the other four trials.[5,7,11,13] The reported mean left ventricular end diastolic diameters for the trials were similar (66 to 75 mm).

QRS Width. QRS width was a criterion for all but one of the trials, with five trials specifying ≥ 120 msec, [8,9,11,12,15] three trials ≥ 130 msec,[4,6,14] one trial > 140 msec,[16] two trials > 150 msec,[5,17] one trial > 180 msec,[10] and one trial > 200 msec.[7] Twelve of the 14 trials had a mean QRS between 155 msec and 175 msec, with the MUSTIC-AF trial having a mean QRS of 209 msec and RD-CHF having a mean QRS of 206 msec. Left bundle branch block was present in most patients (mean 64 percent; range 0 to 100 percent).

Rhythm. Nine trials[4,5,8,9,11,12,15-17] were restricted to patients in normal sinus rhythm, one was restricted to patients with atrial fibrillation,[7] and patients with atrial fibrillation constituted between 14 and 52 percent of trial participants in the three trials[6,10,13] that enrolled patients with or without atrial fibrillation (5 percent of all trial participants had atrial fibrillation). One trial[14] made no mention of whether or not patients with atrial fibrillation were included. Only one trial[13] recruited patients with symptomatic bradycardia and an indication for traditional RV pacing, and two trials[8,11] required a prolonged PR interval > 150 msec for inclusion (four trials reported PR intervals that ranged from 195 to 215 msec).

In the four trials testing combined CRT-ICD against ICD alone,[6,9,14,17] there was a general requirement that study patients meet indications for ICD placement. (Note that although 34 of the 86 patients in PATH-CHF II had a combined CRT-ICD device, results for this subgroup were not reported separately.) Although it was not specified by which ICD criteria patients were evaluated, the indications in MIRACLE ICD[6] and CONTAK-CD[9] were consistent with the AHA/ACC guidelines for secondary prevention at the time of enrollment.[262]

Medications. Medication use was specified in all but three trials.[8,10,16] ACE inhibitors were required or were taken by the vast majority of participants in all trials, beta-blockers were required in three trials,[4,11,13] and spironolactone was required in one trial.[11] Baseline medication use in the efficacy review trials is detailed in Table 5. Three trials reported that approximately one-third of trial participants used amiodarone,[5,8,13] and between 24 and 38 percent of patients in three other trials[6,14,17] were on non-beta-blocker anti-arrhythmic agents. Digoxin was used in 43 to 76 percent of patients, with four of the five largest trials having at least 75 percent of their patients on digoxin.[4,6,9,11,15]

Design. Nine of the trials employed a parallel study design.[4,6,9,11,14-17] One of these had planned a crossover period but was required to change its protocol mid-study and excluded crossover data from its analysis;[9] five others completed a crossover design.[5,7,8,12,13] The duration of treatment was 4 weeks in PATH-CHF;[8] 3 months per phase in MUSTIC AF,[7] MUSTIC SR,[5] PATH-CHF II,[12] and HOBIPACE;[13] 6 months in MIRACLE,[4] MIRACLE ICD,[6] MIRACLE ICD II,[14] VecTOR,[16] and RHYTHM ICD;[17] 12 months in the COMPANION[11] trial; and a mean of 29 months in the CARE-HF trial.[15] Thirteen of the 14 trials used a transvenous approach for placement of the epicardial leads (54 patients in CONTAK-CD[9] required a transthoracic approach), while PATH-CHF[8] used a transthoracic approach (in PATH-CHF II[12] 61 of 86 patients implanted with devices had this done transthoracically and 25 had transvenous implants performed).

Timing of Randomization. Eleven of the trials (n = 2,166 patients) randomized patients after successful CRT implantation; 3 trials (n = 2,439 patients) randomized patients before attempted CRT implantation.[11,15,16] We explored the influence of randomization timing on efficacy results in meta-regression analysis as discussed later in this document.

Description of Each Trial.

Parallel-Arm trials. The MIRACLE trial[4] enrolled 453 patients (NYHA Class III or IV); 228 were randomized to CRT "on," 225 to CRT "off" after device implantation and the primary outcomes were quality of life, 6-minute walk test, and NYHA class.

The MIRACLE-ICD trial[6] randomized 369 patients with NYHA Class III/IV symptoms at baseline: 187 to CRT "on" and 182 to CRT "off" after device implantation. All patients in MIRACLE-ICD[6] received an ICD and the primary outcomes were quality of life, 6-minute walk test, and NYHA class.

CONTAK-CD[9] was a two-part trial with an initial pilot crossover involving two 3-month phases and a parallel design study with 6-month followup in the second part. The primary outcome was progression of heart failure (all-cause mortality, HF hospitalization, and ventricular tachycardia/fibrillation requiring ICD intervention). As with MIRACLE-ICD, all patients in CONTAK-CD were implanted with a device with ICD capabilities and were randomized to CRT "on" or "off" after device implantation. The primary outcome was a composite of all-cause mortality, HF hospitalizations, and ventricular arrhythmias requiring device intervention.

COMPANION[11] was a three-arm, parallel-group trial that compared optimal pharmacological therapy (n = 308), CRT alone (n = 617), and combined CRT-ICD (n = 595) randomized in a 1:2:2 manner before device implantation. The primary outcome was a composite of all-cause mortality and all-cause hospitalization (including emergency department [ED] presentations or unscheduled office visits requiring >4 hours of intravenous vasoactive or inotropic drugs).

The MIRACLE ICD II trial[14] randomized 186 patients with an indication for an ICD and NYHA class II symptoms to CRT "on" or "off" after device implantation (all patients in both groups had the ICD function turned on). The primary outcome was change in peak VO_2 from baseline and a variety of functional assessments were collected.

The CARE-HF trial[15] randomized 813 patients (NYHA Class III or IV) to either medical therapy plus CRT (n = 409) or medical therapy alone (n = 404); randomization was before

device implantation. The primary outcome was a composite of all-cause death or unplanned hospitalization for major cardiovascular event.

The VecTOR trial[16] randomized 106 patients to either CRT "on" or "off" for 6 months, then all patients received CRT "on"—the outcomes were presented at 6 months (before all patients were crossed into the "on" arm). Randomization in VecTOR was conducted before device implantation.

The RHYTHM ICD Trial[17] randomized 183 patients after device implantation to having the CRT function on their device on or off (all patients in both groups had the ICD function turned on).

Crossover Trials. In MUSTIC SR,[5] 67 patients were enrolled and implantation attempted, followed by 8 to 12 weeks of observation; 58 patients were then randomized into a 3-month crossover of either CRT "on" or "off" phases *after* device implantation (Phase 1: n = 29, Phase 2: n = 29).

In MUSTIC AF,[7] 64 patients were enrolled and implantation attempted, followed by 8 to 12 weeks of observation; 43 were then randomized into a 3-month crossover of CRT "on" or "off" phases *after* device implantation (Phase 1: n = 25, Phase 2: n = 18). Both trials used the 6-minute walk test as the primary outcome. Neither trial used a washout period between phases and neither detected a carryover effect.

PATH-CHF[8] was a 4-week crossover study in which 42 patients were enrolled and implantation attempted; 41 patients were then randomized to CRT "on" or "off" in two phases *after* device implantation with a 4-week washout period between the two phases (Phase 1: n = 24, Phase 2: n = 17). The primary endpoint was peak oxygen uptake on a maximal exercise test. This trial did detect a carryover effect.

PATH-CHF II[12] was a 6-month crossover study in which 86 patients had a CRT device implanted (34 of whom had a device with ICD capabilities) and were randomized to LV pacing lead "on" or "off" in two phases *after* device implantation without a washout phase. The primary endpoint was change in exercise capacity.

HOBIPACE[13] was a 3-month crossover study in which 33 patients with indications for a conventional pacemaker had a CRT device implanted and were randomized to biventricular pacing or RV pacing in two phases *after* device implantation and medication optimization, without a washout phase.

Subgroup Analyses. Subgroup analyses were reported in seven of these trials,[4,6,9,11-13,15] although three trials[11,12,15] reported that their subgroups were specified a priori and only two[12,15] stratified their randomization by subgroups. The subgroups reported in each trial were:

- MIRACLE: beta-blockers, ischemic etiology, LVEF, left or right bundle branch block, QRS duration, sex, age;
- MUSTIC-SR: none reported;
- MIRACLE ICD: beta-blocker, underlying heart disease (ischemic vs nonischemic), morphology of the QRS complex (left vs right bundle branch block), QRS duration;
- MUSTIC AF: none reported;
- PATH-CHF: none reported;
- CONTAK-CD: beta-blockers, ischemic etiology, LVEF, left or right bundle branch block, QRS duration, sex, age;
- RD-CHF: none reported;

- COMPANION: age, sex, ischemic etiology, NYHA, LVEF, LVEDD, QRS, LBBB, heart rate, systolic BP, diastolic BP, ACE inhibitor, beta-blocker, loop diuretic, spironolactone
- PATH-CHF II: QRS duration;
- HOBIPACE: atrial fibrillation, bundle branch block pattern, site of LV lead placement
- MIRACLE ICD II: none reported;
- CARE-HF: Age, sex, NYHA, dilated cardiomyopathy, systolic blood pressure, brain natriuretic peptide, LVEF, end-systolic volume index, QRS, IMD, glomerular filtration rate, medication;
- VecTOR: none reported; and
- RHYTHM ICD: none reported

Subgroup effects were tested using appropriate statistical methods (i.e., treatment*subgroup interaction (or heterogeneity) test) in 3 of these trials.[9,11,15] The MIRACLE trial presented subgroup-stratified analyses but didn't report an interaction test. The 3 most frequently examined subgroups (and number of trials doing so) were QRS duration (6 trials), bundle branch block pattern (5 trials), and ischemic etiology (5 trials).

ICD Alone

Twelve randomized trials[11,133-143] met the inclusion criteria for the efficacy review and are listed below:

Primary Prevention Trials (i.e., trial participants did not have history of ventricular fibrillation or ventricular tachycardia requiring resuscitation):

1. MADIT (Multicenter Automatic Defibrillator Implantation Trial)[133]
2. The CABG Patch (Coronary Artery Bypass Graft Patch) Trial[134]
3. MADIT II (Multicenter Automatic Defibrillator Implantation Trial II)[135]
4. The CAT (Cardiomyopathy) Trial[136]
5. AMIOVIRT (Amiodarone vs. Implantable Defibrillator Randomized Trial)[137]
6. The DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) Trial[138]
7. DINAMIT (Defibrillator in Acute Myocardial Infarction Trial)[139]
8. SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) [140]
9. The COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure) Trial[11]

Secondary Prevention Trials (i.e., in patients with history of ventricular fibrillation or ventricular tachycardia requiring resuscitation):

1. The AVID (Antiarrhythmics Vs. Defibrillators) Trial[141]
2. The CIDS (Canadian Implantable Defibrillator Study) Trial[142]
3. The CASH (Cardiac Arrest Study Hamburg) Trial[143]

Publication Status. All of these trials have been published, and supplemental data were located from other sources as mentioned in Figure 2. Characteristics of the trials are summarized in Table 6.

Trial Participants (Table 7). In total, 8,516 patients were randomized in these trials to receive ICD (n = 4,301) or control (n = 4,215). The mean age of enrolled patients was 60.8 ± 4.2 years and 74 percent were male. The majority of trial participants had HF symptoms (in the trials that reported baseline functional class, 50 percent had NYHA class II symptoms at baseline, 36 percent NYHA class III symptoms, and 3 percent Class IV functional status). Seven trials enrolled asymptomatic patients (i.e., those with NYHA class I HF), and this percent ranged from 13 to 37 percent in these trials such that 11 percent of all ICD trial participants with left ventricular systolic dysfunction did not have HF symptoms at baseline.[142] Most trials excluded Class IV patients. Four trials enrolled patients that had an ischemic etiology for their left ventricular dysfunction,[133-135,139] 3 trials enrolled patients with a non-ischemic dilated cardiomyopathy[136-138] and 5 trials included either etiology.[11,140-143] Of note, patients with other indications for defibrillators were not enrolled in these trials, nor were patients with acute myocarditis, hypertrophic/ restrictive/or constrictive cardiomyopathy, or arrhythmogenic right ventricular dysplasia.

Left Ventricular Ejection Fraction. Although all trials enrolled patients with left ventricular systolic dysfunction (mean LVEF ranged from 21 percent to 28 percent in the primary prevention trials and from 32% to 46% in the secondary prevention trials), they used different entry criteria for ejection fraction: ≤30 percent;[135,136] ≤35 percent,[11,133,134,137-140]; and ≤40 percent.[141] Two trials did not specify an ejection fraction in their eligibility criteria but their mean ejection fractions were 34 percent[142] and 46 percent.[143]

ECG Criteria. Of the primary prevention trials, all but 3 trials specified other electrocardiographic entry criteria to identify high risk patients.[135,136,140] The other "primary prevention" trials identified higher risk patients for study using non-sustained ventricular tachycardia,[133,137,138] elevated heart rate or reduced heart rate variability,[139] or abnormal signal-averaged ECG[134] as markers of increased risk.

Medications. Baseline medication use varied substantially, in part due to the range of years in which the trials were initiated and completed (Table 7). One trial enrolled the first patient before 1990,[143] 5 trials between 1990 and 1995, [133,134,136,141,142] 5 trials between 1996 and 2000,[135,137-140] and in one trial it was unclear.[11] Baseline beta-blocker use varied between trials (4 to 87 percent), as did digoxin use (20 to 86 percent) and angiotensin-converting enzyme inhibitor use (42 to 96 percent).

Design. All trials employed a parallel study design and all randomized patients prior to implantation of the ICD. ICDs were compared to usual care,[133-136,138,139] amiodarone alone,[137,141,142] amiodarone or placebo, [140] and amiodarone or metoprolol.[143] In the COMPANION trial, 2 of the 3 study arms (CRT vs. optimal medical therapy) were used in the CRT review while data from the combined CRT-ICD and CRT alone arms were used in the ICD analyses.[11] In the trials in which amiodarone was not a comparator, amiodarone use ranged from

4 to 13 percent, with 84 percent of patients in the MADIT trial being placed on non-trial anti-arrhythmic agents.

Type of ICD. The type of devices used for the trials were unspecified[137], epicardial or endocardial,[133,141-143] epicardial only[134] or endocardial only.[11,135,136,138-140] Devices were specified to be single-chamber ICD in all but the COMPANION and MADIT-II trials, but protocol adherence to a single-chamber device was not reported in any trial.[11,135] The MADIT-II Trial subsequently reported that 44% of intervention arm devices were in fact dual-chamber ICD in a second publication.[263]

Description of Each Trial:

Primary Prevention Trials. MADIT randomized 196 patients with a prior myocardial infarction and NYHA I-III to either an ICD (n = 95) or usual care (n = 101).[133]

CABG Patch enrolled 900 patients with ischemic cardiomyopathy undergoing CABG and abnormal signal-averaged ECG to either an ICD (n = 446) or usual care (n = 454).[134]

MADIT II enrolled 1,232 patients with a prior myocardial infarction >1 month prior and NYHA I-III to an ICD (n = 742) or usual care (n = 490) in a 3:2 manner.[135]

The Cardiomyopathy Trial (CAT) enrolled 104 patients with a dilated cardiomyopathy ≤9 months in duration to an ICD (n = 50) or usual care (n = 54).[136]

AMIOVIRT randomized 103 patients with non-ischemic cardiomyopathy with non-sustained VT, to either amiodarone (n = 52) or an ICD (n = 51).[137]

DEFINITE enrolled 458 patients with a non-ischemic dilated cardiomyopathy and NSVT to an ICD (n = 229) or usual care (n = 229).[138]

DINAMIT randomized 674 patients between 6 and 40 days post-MI with impaired autonomic function to an ICD (n = 332) or usual care (n = 342).[139]

SCD-HeFT enrolled 2,521 patients with either ischemic or non-ischemic NYHA II-III heart failure to an ICD (n = 829), amiodarone (n = 845) or placebo (n = 847). [140]

COMPANION (described in full in the CRT trial section above) enrolled 1,520 patients randomized to optimal medical therapy (n = 308), CRT alone (n = 617) or CRT-ICD (n = 595).[11]

Secondary Prevention Trials. The AVID trial enrolled 1,016 patients (resuscitated after near-fatal VF, sustained VT with syncope or sustained VT with LVEF < 40 percent) randomized to an ICD (n = 507) or drug therapy (n = 509), mainly amiodarone.[141]

CIDS randomized 659 patients resuscitated from a cardiac arrest, or with ventricular tachycardia or fibrillation to either an ICD (n = 328) or amiodarone (n = 331).[142]

CASH randomized patients resuscitated from a cardiac arrest to one of four arms (ICD, amiodarone, metoprolol, or propafenone) in a 1:1:1:1 manner.[143] The propafenone arm was stopped early due to increased harm, and the remaining 288 patients were randomized to an ICD (n = 99), amiodarone (n = 92), or metoprolol (n = 97).

Subgroup Analyses. Subgroup analyses were reported in 11 of these trials - 9 trials reported that their subgroups were specified a priori and 6 stratified their randomization by subgroups. The subgroups reported in each trial were:

Primary Prevention Trials:

- MADIT: age, sex, cardiac history (including NYHA class, treatment for VT, CHF, hypertension, IDDM, smoking, CABG, angioplasty, pacemaker), interval since MI, pulmonary edema, urea, cholesterol, LBBB, LVEF, NSVT, EP study results;
- CABG Patch: ischemic etiology, heart failure, diabetes, NYHA class, sex, age, LVEF, QRS, angiotensin-converting enzyme inhibitors, beta-blocker, class I or III antiarrhythmics;
- MADIT II: ischemic etiology, NYHA class, sex, age, LVEF, QRS, LBBB, time from MI, diabetes, hypertension, atrial fibrillation, type of ICD, urea;
- CAT: ischemic etiology, NYHA, sex, age, LVEF, LVEDD, LVESD, QRS, rhythm, Q-T interval, Holter findings, EP study findings, medications;
- AMIOVIRT: none reported;
- DEFINITE: amiodarone, age, sex, LVEF, QRS, NYHA, atrial fibrillation;
- COMPANION: age, sex, ischemic etiology, NYHA class, LVEF, LVEDD, QRS, LBBB, heart rate, systolic BP, diastolic BP, ACE inhibitor, beta-blocker, loop diuretic, spironolactone;
- DINAMIT: ischemic etiology, diabetes, NYHA class, sex, age, LVEF, QRS, atrial fibrillation, NSVT, heart rate, SDRR, reperfusion method; and
- SCD-HeFT: ischemic etiology, NYHA class, sex, age, race, LVEF, QRS, 6-minute walk test, beta-blocker, diabetes.

Secondary Prevention Trials:

- AVID: age, LVEF, etiology, qualifying arrhythmia, beta-blockers, heart failure, revascularization, atrial fibrillation;
- CIDS: age, sex, index arrhythmia, LVEF, NYHA class, etiology; and
- CASH: LVEF, NYHA class, ischemic etiology

Subgroup effects were tested using appropriate statistical methods (i.e., treatment x subgroup interaction or heterogeneity tests) in all but two of these trials.[137,139] Six trials presented the results of their subgroup analysis in the primary manuscript.[11] The three most frequently examined subgroups were LVEF (tested in 11 trials), NYHA class (examined in 10 trials, and age (examined in 10 trials).[138,140,141,143]

Description of Included Studies: Effectiveness Review

CRT Alone or Combined CRT-ICD Devices

In addition to the 14 RCTs, an additional 106 studies met the inclusion criteria for the review of effectiveness of CRT alone or combined CRT-ICD devices (Table 8). Forty-two of these studies met the inclusion criteria for the review of effectiveness but not safety. The 106 studies included two controlled clinical trials (CCTs), 91 prospective cohort studies, and 13 retrospective cohort studies. Sixty of these studies looked at CRT alone; the other 46 looked at a mix of patients receiving CRT alone and a combined CRT-ICD device. Sixty-eight studies reported that devices were implanted transvenously, two transthoracically,[56,97] and five used a mixture of

approaches.[12,63,73,84,86] Medtronic Inc., Guidant Corp., ELA Medical, St. Jude Medical Inc., or Biotronik manufactured all implanted devices; the models and leads varied among and within trials.

Study Participants (Table 9). In total, 9,846 patients were enrolled; of these, 9,209 patients received CRT alone or combined CRT-ICD devices. The mean age was 66 ± 11 years, and 78 percent were male. The majority of participants had NYHA class III (range 0 to100 percent within studies), or NYHA class IV (range 0 to 87 percent within studies) symptoms at baseline (Table 9). Nineteen studies included patients with NYHA class II symptoms (range 0 to 100 percent).[8,12,20,26,32,36,40,48,69,74,83,84,98-100,109,114,121,130] One study included patients with NYHA class I.[20] No studies specifically based inclusion on the etiology of HF of the patients. Patients with correctable valvular disorders, hypertrophic or restrictive cardiomyopathy, unstable angina, or acute myocarditis were excluded from these studies.

Left Ventricular Ejection Fraction. Sixty-three studies limited inclusion to patients with an ejection fraction ≤ 35 percent, 3 of which enrolled patients with LVEF < 30 percent,[47,50,71] 17 enrolled patients with LVEF < 40 percent, and 26 did not specify this criterion. The mean ejection fraction ranged from 17 percent to 35.6 percent in these studies. Thirteen studies specified a left ventricular end diastolic dimension inclusion criterion of ≥55 mm,[19,34,40,48,51,60,65,69,70,83,104,112,114] and eleven studies specified a left ventricular diastolic dimension ≥60 mm in their eligibility criteria.[21,43,45,46,58,67,68,73,87,113,115]

QRS Duration. QRS width was a criterion for 81 studies, with 1 specifying ≥ 110 msec, 33 specifying ≥ 120 msec, 22 studies ≥ 130 msec, 11 studies ≥ 140 msec, and 13 studies > 150 msec. One study compared a 120-to-150 msec group to a ≥ 150 group.[120] Fifty studies reported a mean QRS between 140 msec and 180 msec, and 15 ranged from 181 msec to 206 msec.

Medications. Concomitant medication use was not specified in 22 of the 106 studies included in our effectiveness review. ACE inhibitors and/or an angiotensin-receptor blocker use ranged from 12 percent to 100 percent and beta-blockers use ranged from 35 percent to 100 percent. Diuretic use ranged from 76 percent to 100 percent, and spironolactone use ranged from 25 percent to 100 percent in the studies that reported the use of these medications (55 studies and 32 studies, respectively). Importantly, use of amiodarone ranged from 14 percent to 79 percent (although amiodarone usage rates were only reported in 20 studies). In 34 studies reporting digoxin use, between 0 percent and 95 percent of participants were on digoxin.

ICD Alone

In addition to the 12 RCTs, there were 48 additional studies that met the inclusion criteria for the review of effectiveness of ICD (Table 10). Twenty-one of these studies met the inclusion criteria for the review of effectiveness but not safety. The 48 additional studies included five parallel RCTs that did not report efficacy endpoints of interest, 20 prospective cohort studies, 22 retrospective cohort studies, and one case control study.[180] Thirteen studies reported that devices were implanted transvenously,[145,147,162,163,165,169,173,174,181,184,187,189,193] and five used a combination of transvenous, endocardial or epicardial approaches.[144,155,171,185,188]

Study Participants (Table 11). In total, 25,111 patients were enrolled in these studies of ICD effectiveness; of these, 15,097 patients received ICD. Some patients were excluded or withdrew due to unsuccessful implants, death, heart transplantation, or miscellaneous reasons. The mean age was 62.6 ± 13.2 years, 79 percent were male. Most studies included patients with NYHA class II symptoms (range 0 to 95 percent within studies) and NYHA class III symptoms (range 9 to 100 percent within studies). Fifteen studies reported including patients in NYHA class IV, with a range between 2 percent and 33 percent (Table 11).[144,148,155,157,158,161,165,170,172,173,175,179,185,187,190] Two studies required patients to be survivors of sudden cardiac death,[146,157] and eight studies required patients to have other high risk features.[147,148,176,183,186,191,193] Eighteen studies did not state exclusion criteria. Ischemic etiology was present in approximately 70 percent of patients (range 0 to 100 percent).

Left Ventricular Ejection Fraction. Ejection fraction was a criterion for 10 studies, with 5 studies specifying LVEF < 35 percent,[146,148,154,176,191] 3 specifying LVEF < 40 percent,[151,162,189] and 2 specifying LVEF < 45 percent.[145,149] The remaining studies did not specify an entry criterion. The mean ejection fraction ranged from 19 to 46 percent.

Medications. Concomitant medication use was not reported in 16 studies. ACE inhibitors were reported in 23 studies (range 55 to 95 percent), beta-blockers were reported in 33 studies (range 10 to 89 percent), and spironolactone was reported in three studies (5 to 36 percent). Thirty-two studies reported the use of antiarrhythmic drugs, including amiodarone (range 10 to 61 percent).

Description of Included Studies: Safety Review

CRT Alone or Combined CRT-ICD Devices

Fourteen randomized trials and 75 additional studies met the inclusion criteria for the review of safety of CRT (Table 8). The 75 additional studies included 2 controlled but not randomized trials,[39,73] one registry study, 9 retrospective cohort studies,[26,44,63,68,102,109,123,128,129] and 63 prospective cohort studies. Sixty-five studies reported that devices were implanted transvenously, two transthoracically,[85,97] and six using both approaches.[9,12,56,63,66,73] Medtronic Inc., Guidant Corp., ELA Medical Inc, St. Jude Medical Inc., or Biotronik manufactured all implanted devices; the models and leads varied among and within trials.

Study Participants (Table 9). In total, 12,471 patients were enrolled; of these, 9,677 patients received CRT alone or combined CRT-ICD device. The mean age was 66 ± 10 years, and 77 percent were male. Approximately 80 percent of these study participants had NYHA class III symptoms at baseline (range 13 to100 percent), and 11 percent were NYHA class IV (range 0 to 100 percent) (Table 9). Twenty-two studies included patients with NYHA class II symptoms (range 4 to 50 percent).[9,12,16,17,20,26,32,33,36,48,49,57,69,83,86,98,100,104,109,130,264] Five studies included patients with NYHA class I.[16,17,32,86] No studies specifically based inclusion on the etiology of HF, although patients with correctable valvular disorders, hypertrophic or restrictive cardiomyopathy, unstable angina, or acute myocarditis were excluded from these studies.

Left Ventricular Ejection Fraction. Fifty-five studies limited inclusion to patients with an ejection fraction < 35 percent. Three of these enrolled patients with LVEF < 30 percent,[12,50,128] nine enrolled patients with LVEF < 40 percent,[13,31,35,57,98,104,111,113,119] and 24 did not specify this criterion.[8,10,20,26,27,44,49,52,53,56,63,64,76,85-87,91,100,108,123,125,126,130,264] The mean ejection fraction ranged from 19 percent to 36 percent in these studies. Twenty-five studies specified a left ventricular end diastolic dimension inclusion criterion of ≥55 mm,[4,6,14,16,60,65,69,70,83,104,112] or ≥60 mm.[5,7,13,45,46,58,66-68,73,87,113,129,131] One study specified ≥33 indexed to height.[15]

QRS Duration. QRS width was a criterion for 72 studies, with 1 study specifying ≥ 110 msec,[57] 28 ≥ 120 msec,[7-9,11,12,15,22,29-32,35,42,67,69,73,78,80,82,87,103,106,109,112,117,125,126,129] 18 ≥ 130 msec,[4,6,14,17,49,50,60,64,65,70,83,92-94,102,104,111,132] 9 ≥ 140 msec,[16,33,55,56,85,89,98,119,124] 15 > 150 msec,[5,17,36,39,45,46,58,68,91,105,108,113,128,130,131] and 1 > 200 msec.[66] Forty-seven studies reported a mean QRS between 142 msec and 187 msec, and 15 ranged from 181 msec to 206 msec.[27,41,45,46,56,66-68,73,85,86,93,98,99,131]

Rhythm. Ten studies were restricted to patients in normal sinus rhythm,[5,8,11,12,89,104,113,128,130,131] but one was restricted to patients with atrial fibrillation.[7] In the others, 6 percent to 90 percent of patients had atrial fibrillation.

Medications. Concomitant medication use was not specified in 30 of the 89 studies included in our safety review. ACE inhibitors and/or an angiotensin-receptor blocker use ranged from 62 percent to 100 percent, beta-blockers use ranged from 35 percent to 88 percent, loop diuretic use from 43 percent to 100 percent, and spironolactone use ranged from 32 percent to 59 percent. Importantly, use of amiodarone ranged from 14 percent to 79 percent (in the 13 studies reporting amiodarone usage rates). In 17 studies reporting digoxin use, between 0 percent to 95 percent of participants were on digoxin.

ICD Alone

Forty-nine studies met the inclusion criteria for the review of safety of ICD (Table 10). Eleven of the 12 trials included in the efficacy review were eligible: Strickberger et al. did not include any safety outcomes.[137] The 38 additional studies included 6 trials that did not report efficacy endpoints of interest and were treated as cohort studies,[156,176,192-194,200] 15 prospective cohort studies,[144,145,147,148,152,155,160,165,178,187,188,196,198,199,201] 16 retrospective cohort studies,[157,158,161,162,164,169,171,179,181,184,186,189,191,195,197,202] and 1 case control study.[180] Ten studies reported that devices were implanted transvenously,[135,136,145,156,162,165,184,189,192,197] two used both transvenous and transthoracic approaches,[133,142] and six used a combination of transvenous, endocardial or epicardial approaches.[134,143,144,147,171,188]

Study Participants (Table 11). In total, 22,044 patients were enrolled in the studies of ICD safety; of these, 12,592 patients received ICD. Some patients were excluded or withdrew due to unsuccessful implants, death, heart transplantation, or miscellaneous reasons. The mean patient age was 61.4 ± 11.9 years and 80 percent were male. Approximately 50 percent of each study population was NYHA class II (range 16 to 70 percent) and 38 percent were NYHA class III (range 9 to 100 percent). Ten studies reported including patients in NYHA class IV, with a range between 2 and 18 percent (Table 11).[11,133,135,142,144,148,155,157,179,202] Six studies required patients to

be survivors of sudden cardiac death,[141-144,156,157] and 13 studies required patients to have other high-risk features.[135,139,148,155,156,161,176,183,186,191-193,201] Twenty-one studies did not state exclusion criteria.[144,146-148,150,152,155,157,158,160,163-166,169,178,179,187,189,195,196] Ischemic etiology was present in approximately 55 percent of patients (range 0 to 100 percent).

Left Ventricular Ejection Fraction. Ejection fraction was a criterion for 19 studies, with 3 studies specifying an ejection fraction of < 30 percent,[135,136,191] 11 specifying LVEF < 35 percent,[11,133,134,138-140,146,148,176,189,195] three specifying LVEF < 40 percent,[141,162,193] and one specifying LVEF < 45 percent.[145] The mean ejection fraction ranged from 19 to 46 percent.

Medications. Concomitant medication use was not reported in 14 studies. ACE inhibitors were reported in 25 studies (range 42 to 98 percent), beta-blockers were reported in 31 studies (range 4 to 89 percent), and spironolactone was reported in two studies (5 and 14 percent). Thirty studies reported the use of antiarrhythmic drugs, including amiodarone (range 2 to 96 percent).

Additional Studies of all ICD Implants (i.e., studies not restricted to patients with left ventricular systolic dysfunction). Twelve additional ICD studies that did not meet the inclusion criterion of a mean baseline LVEF ≤ 35 percent were examined for implantation success rates and peri-implant safety data after input from the Technical Expert Panel who reviewed our initial draft report (Table 12).[203-214] Five were randomized (two parallel, three crossover), two each were retrospective or prospective cohorts, and three involved registry data. Implant techniques varied and included transvenous, thoracotomy, pectoral, subpectoral, abdominal, epicordial and nonthoracic approaches. In total, 68,930 patients were enrolled in these 12 studies of ICD safety; of these, 68,848 received ICD (Table 13). The mean age across studies was 61 years, and approximately 80 percent were male. Half of the studies reported baseline NYHA class: approximately 35 percent of each study population was in NYHA class I (range 19 to 100 percent): 54 percent were NYHA class II (range 39 to 62 percent) and 19 percent were NYHA class III (range 13 to 24 percent). Two studies reported patients in NYHA class IV (0.09 and 1 percent).[208,211] One author reported 23 percent of the population was greater than NYHA class II.[212] None of these studies required patients to be survivors of sudden cardiac death, but one only included patients who had suffered Sudden Unexplained Death Syndrome[210] though otherwise apparently healthy. Ischemic etiology was present in approximately 66 percent of patients (median 71; range 0 to 100 percent). Ejection fraction was not a criterion for enrolment into these studies; however, 66 percent of studies reported a baseline LVEF that ranged from an average of 36 ± 12.4 to 66 ± 10.3 percent. Concomitant medication use was not reported in two studies. ACE inhibitors were reported in one study (88 percent), beta-blockers were reported in five (range 24 to 44.3 percent), Sotalol in four (range 5-8 percent), amiodarone in six (0 to 39 percent) and other antiarrhythmic therapy in four studies (range 3.1 to 79 percent).

Methodological Quality of Included Studies: Efficacy Review

CRT Alone or Combined CRT-ICD Devices

As a measure of methodological quality for the included trials, the Jadad[253] score (maximum 5 points) was 5 for one trial,[4] 4 for three trials,[6,8,14] 3 for four trials,[5,7,16,17] 2 for five trials,[9,11-13,15] and 1 for the remaining study[10] (Table 14).

All trials were described as randomized; however, the description of randomization detail varied. Three were adequately randomized[4,5,7] and the rest were unclear. Two reported clear concealment of allocation[4,14] and the remaining trials were unclear. Six trials were double-blind (patient and the outcome assessor blinded), [4,6,8,14,16,17] four were single-blind,[5,7,12,13] and four were not blinded.[9-11,15] In CONTAK CD,[9] MIRACLE,[4] MIRACLE ICD,[6] and CARE-HF,[15] the independent events committee was blinded to the trial arm the patient was in; no information was available for COMPANION.[11] Three trials randomized patients before device implantation,[11,15,16] while all other trials randomized patients after their device was successfully implanted. An intention-to-treat statistical analysis was specified in all trials, and MIRACLE[4] and PATH-CHF[8] performed an intention-to-treat analysis. Withdrawals and dropouts were clearly described in all trials. Unscheduled crossovers occurred in 0 to 9 percent of the patients in these trials and the number of patients were generally balanced between study arms. Withdrawals ranged from 0 to 3 percent for the cardiac resynchronization group and from 0 to 2.5 percent for the control groups.

Industry sponsored 12 of the 14 trials; 2 also received funding from government sources.[5,7] Guidant Corp. sponsored four,[8,9,11,12] Medtronic Inc. sponsored six,[4-7,14,15] ELA Medical Inc. funded two,[5,7] and St. Jude Medical Inc. funded two.[16,17] Kindermann did not receive industry funding.[13] Funding for RD-CHF[10] is not known**.**

ICD Alone

As a measure of methodological quality for the included trials, the Jadad[253] score was 3 for three trials,[134,139,140] 2 for six trials,[11,133,135,137,138,142] and 1 for the remaining three (Table 15).[136,141,143] All trials were described as randomized; however, the description of randomization detail varied. Four described their randomization methods adequately,[133,134,139,142] and the rest were unclear. Three reported clear concealment of allocation,[134,136,139] and the rest were unclear. One ICD trial was double-blind; [140] however, in five trials the independent events committee was blinded to the trial arm the patient was in,[136-139,142] and in seven trials blinding was unclear.[11,133-135,140-142] An intention-to-treat statistical analysis was specified and performed in all trials. Withdrawals and dropouts were clearly described in all but five trials.[133,136,141-143] Unscheduled crossovers occurred in 0 to 22 percent of the patients in these trials and were generally balanced between study arms. Withdrawals ranged from 0 to 6 percent for the ICD group and from 0 to 32 percent for the control groups. Allocation concealment was unclear for all but three trials.[134,136,139]

Industry sponsored 10 of the 12 trials; 4 also received funding from institute or foundation sources[134,140-142] and 3 from pharmaceutical companies. [140,142,143] Guidant Corp. sponsored seven,[11,133-137,143] Medtronic Inc. sponsored one[140] and St. Jude Medical Inc. funded two.[138,139]

Methodological Quality of Included Studies: Effectiveness and Safety Reviews

CRT Alone or Combined CRT-ICD Devices

Overall, the studies were rated as having "good" quality on the Downs and Black[254] scoring system. Fourteen studies were described as randomized (described in Table 14) and the remaining 113 were observational studies.(Table 16). Reporting ranged from fair to good with 51 percent rating 10 or 11 out of 11, the rest ranging from scores of 3 to 9. External validity assessment posed some problems because authors did not report the source population for patients or the proportion of eligible patients selected for inclusion, nor compare the distribution of main confounding factors with the source population. For this review we defined the source population as those with symptomatic HF. Since this procedure can only be performed in specialized centers, we determined that all facilities were representative of patients in usual practice. Internal validity concerning assessment of bias ranged from scores of 0 to 7 out of 7 (median = 5); the lack of blinding was the main shortfall. Internal validity assessments concerning confounding ranged from scores of 0 to 5 out of 6 (median = 4), with 17 studies scoring 2 or less. This is in part due to the studies having no randomization component. Many authors did not state the period of time over which patients were recruited or the source of patients. Three studies included a power calculation,[36,83,125] and 102 out of 113 had sufficient sample sizes to determine a clinically important effect.

Most studies did not report funding, but the majority of those that did received funding from industry.[17,25,27,36,40,42,49,52,59,61,65,70,77,83,106,116,118] Sixteen received funding from either government or foundations.[20,28,30-32,36,44,51,62,64,93,108,114,115,122,128]

ICD Alone

Overall, the studies were rated as having "good" quality on the Downs and Black scoring system. Twelve studies were described as randomized (Table 15) and the remaining 57 were observational studies (Table 17). Reporting was generally good with 37 of 57 scoring 10 or 11 out of 11, the rest scoring from 4 to 9. External validity assessment posed some problems because authors did not report the source population for patients or the proportion of eligible patients selected for inclusion, nor did they compare the distribution of main confounding factors with the source population. For this review we defined the source population as those with left ventricular dysfunction. Since this procedure is mainly performed in specialized centers, we determined that the facilities were representative. Internal validity concerning assessment of bias ranged from scores of 0 to 7 out of 7 (median = 5); the lack of blinding was the main shortfall. Internal validity assessments concerning confounding ranged between scores of 0 to 6 out of 6 (median = 4), with four studies receiving scores of 2 or less.[146,173,186,199] Seven studies included a power calculation.[151,156,175,192-194,200]

Most studies did not report on funding. Thirteen reported sponsorship funding from industry,[151,154,156,160,175-177,185,187,190,193,194,198] and three reported government funding in addition to industry.[154,175,177] Two received funds from foundations.[147,161]

Safety Review for Peri-Implant Complications of ICD Alone

These 12 observational studies were rated as having "good" quality on the Downs and Black scoring system. Reporting was generally good with eight studies scoring 10 or 11 out of 11, the rest ranging from 5 to 9 (Table 18). External validity assessment posed some problems because authors did not report the source population for patients or the proportion of eligible patients selected for inclusion, nor did they compare the distribution of main confounding factors with the source population. For this review, we defined the source population as those having an ICD implanted for any reason, such that not all had left ventricular systolic dysfunction. Since this procedure is mainly performed in specialized centers, we determined that the facilities were representative. Internal validity concerning assessment of bias ranged from 3 to 6 out of 7 (median = 5); the lack of blinding was the main shortfall. Internal validity assessments concerning confounding ranged between scores of 1 to 4 out of 6 (median = 4), with two receiving scores of 2 or less.[208,209] Two studies included a power calculation,[205,210] and six (50%) had sufficient sample sizes to determine a clinically important effect.[156,175,192,193,200]

Half of the studies did not report on funding. Three reported sponsorship funding from industry,[204,205,213] one reported government funding,[209] two received funds from foundations.[210,212]

Table 4. Description of studies in the efficacy review: CRT alone or combined CRT-ICD devices

Author Year Trial Name	Country	Design Duration	Control	Participants: Number enrolled	Number excluded	Number randomized	Number in treatment*	Number in Control*	Number of withdrawals	Device Method of implant	Authors' primary outcomes	Other outcomes
CRT alone												
Abraham[4] 2002 MIRACLE	United States, Canada (45 sites)	RCT parallel 6 mo.	Pacer inactive	571	NR	453	228	225	Treatment 1 Control 8	Medtronic InSync® 8040 Transvenous	NYHA, QOL, 6MWT	Peak O_2 consumption, time on treadmill, LVEF, severity of mitral regurgitation, QRS, clinical response, mortality, days in hospital
Cazeau[5] 2001 MUSTIC-SR	Europe (15 sites)	RCT cross-over 3 mo.	Pacer inactive	67	3	58	29	29	Treatment 4 Control 3	ELA Chorum™ 7336, Medtronic InSync® 8040 Transvenous	6MWT	QOL, NYHA, peak O_2 uptake, hospitalization due to CHF, patient preference, mortality
Leclercq[7] 2002a MUSTIC-AF	Europe (15 sites)	RCT cross-over 3 mo.	RV pacing	64	10	43	25	18	Treatment 1 Control 2	NR Transvenous	6MWT	Peak O_2 consumption, QOL, hospitalization for CHF, mortality, patient preference
Auricchio[8] 2002a PATH-CHF	Germany, Nether-lands (5 sites)	RCT cross-over 1 mo.	Univentric-ular pacing (4 RV, 36 LV)	42	1	41	24	17	Treatment 2 Control 5	Guidant Vigor®, Discovery® Transthoracic	O_2 uptake at peak exercise, O_2 uptake at anaerobic threshold, 6MWT	NYHA, QOL

CHF = congestive heart failure; CRT = cardiac resynchronization therapy; CRT+ICD = CRT with implanted cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; NA = not applicable; NR = not reported; NYHA = New York Heart Association class; O_2 = oxygen; OPT = optimal pharmacological therapy; QOL = quality of life; RCT = randomized controlled trial; RV = right ventricular; 6MWT = 6-minute walk test; VO_2 max = maximal oxygen consumption; VA = ventricular arrhythmia; VT = ventricular tachycardia

*The intervention that patients in crossover studies received in the first period

Table 4. Description of studies in the efficacy review: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial Name	Country	Design Duration	Control	Participants: Number enrolled	Number excluded	Number randomized	Number in treatment*	Number in Control*	Number of withdrawals	Device Method of implant	Authors' primary outcomes	Other outcomes
Leclercq[10] 2003 RD-CHF	France (NR)	RCT cross-over 3 mo.	RV pacing	56	NR	44	22	22	Treatment NR Control NR	NR Transvenous	CHF hospitalization	NYHA, 6MWT, QOL
Kindermann[13] 2006 HOBIPACE	Germany (1 site)	RCT cross-over 3 mo.	RV pacing	33	1	32	15	15	Treatment 0 Control 1	NR Transvenous	LV end-systolic volume, LVEF, peak O_2 consumption	NYHA, QOL, serum concentration, exercise testing, echocardiography
Cleland[15] 2005 CARE-HF	Europe (82 sites)	RCT parallel 1, 3, 6, 9, 12,18 mo., then every 6 mo.	OPT	NR	NR	813	409	404	Treatment 14 Control 14	Medtronic InSync®, InSync® III Transvenous	Composite all-cause mortality or unplanned hospitalization for major CV event	NYHA, QOL
St. Jude[16] 2005 VecTOR	United States, Canada (41 sites)	RCT parallel 6 mo.	Pacer inactive	144	0	106	59	47	Treatment 1 Control 2	St. Jude Medical Frontier® 5508 NR	Peak VO_2	NYHA, QOL, 6MWT, echocardiographic parameters, mortality
Combined CRT-ICD												
Young[6] 2003 MIRACLE-ICD	United States, Canada (53 sites)	RCT (post implant) parallel 6 mo.	CRT off + ICD on	639	270	369	187	182	Treatment 6 Control 5	Medtronic InSync® ICD Transvenous	NYHA, QOL, 6MWT	Complications, QRS, peak O_2 uptake, echocardiographic indices, VT response, hospitalization, mortality

Table 4. Description of studies in the efficacy review: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial Name	Country	Design Duration	Control	Participants						Device Method of implant	Authors' primary outcomes	Other outcomes
				Number enrolled	Number excluded	Number randomized	Number in treatment*	Number in Control*	Number of withdrawals			
Higgins[9] 2003 CONTAK-CD	United States (47 sites)	RCT Phase I period 1 cross-over 3 mo.; Phase II parallel 6 mo.	CRT off + ICD on	581	15	490	245	245	Treatment 3 Control 1	Guidant Contak® CD 1823 Transvenous, transthoracic	Mortality, CHF hospitaliza-tion, VT requiring device therapy	Peak O_2 consumption, 6MWT, QOL, complications
Abraham[14] 2004 MIRACLE-ICD II	United States (53 sites)	RCT parallel 6 mo.	CRT off + ICD on	222	36	186	85	101	Treatment 3 Control 3	Medtronic InSync® ICD 7272 NR	Peak VO_2	VO_2max, NYHA, QOL, 6MWT, LV volumes, LVEF, change in clinical status
St. Jude[17] 2004a RHYTHM ICD	United States (49 sites)	RCT parallel 12 mo.	CRT off + ICD on	205	1	179	119	59	Treatment 3 Control 0	St. Jude Medical Epic™ HF ICD NR	Complications	VF detection times, peak VO_2, NYHA, 6MWT, mortality
CRT alone and combined CRT-ICD												
Bristow[11] 2004 COMPANION	United States (128 sites)	RCT parallel 3 arms 15 mo.	OPT	NR	NR	1,520	CRT = 617; CRT+ ICD = 595	308	Treatment 37 Control 42	Guidant Contak® TR models 1241, 4510-4513, Contak® CD 1823 Transvenous	All-cause mortality, hospitaliza-tion	Cardiac morbidity, peak O_2 uptake at exercise, complications, implant success
Auricchio[12] 2003 PATH-CHF II	Germany, Nether-lands (9 sites)	RCT cross-over 3 mo.	Pacer inactive	101	NR	86	43	43	Treatment 5 Control 9	Guidant (various models) Transvenous, thoracotomy	Exercise capacity, peak VO_2, VO_2 max, 6MWT	NYHA, QOL

Table 5. Baseline characteristics of patients in trials included in the efficacy review: CRT alone or combined CRT-ICD devices

Author Year Trial name	Study group	Males, n (%)	Mean age, yr. mean ± SD	Ischemic %	NYHA class			Other measures			Baseline measures taken pre/post-implantation
					II, %	III, %	IV, %	Atrial fibrill-ation, n (%)	QRS interval, msec mean ± SD	LVEF, % mean ± SD	
CRT alone											
Abraham[4] 2002 MIRACLE	CRT	155 (68)	64 ± 11	50	0	90	10	0	167 ± 21	22 ± 6	Pre
	Control	153 (68)	65 ± 11	58	0	91	9	0	165 ± 20	22 ± 6	Pre
Cazeau[5] 2001 MUSTIC-SR	CRT first	19 (66)	64 ± 11	NR	0	100	0	NR	172 ± 22	NR	Post
	Control first	24 (83)	64 ± 8	NR	0	100	0	NR	175 ± 19	NR	Post
	All	43 (74)	64 ± 9	37	0	100	0	NR	174 ± 20	23 ± 7	Post
Leclercq[7] 2002a MUSTIC-AF	CRT first	21 (84)	65 ± 9	NR	0	100	0	25 (100)	209 ± 21	23 ± 7	Post
	Control first	14 (78)	66 ± 9	NR	0	100	0	18 (100)	208 ± 12	30 ± 12	Post
	All	35 (81)	65 ± 8	43	0	100	0	43 (100)	209 ± 18	26 ± 10	Post
Auricchio[8] 2002a PATH-CHF	CRT first	11 (46)	59 ± 7	42	0	88	13	NR	174 ± 30	21 ± 6	Pre
	Control first	10 (59)	60 ± 5	6	0	82	18	NR	178 ± 34	20 ± 7	Pre
	All	21 (50)	60 ± 7	29	0	86	14	NR	175 ± 32	21 ± 7	Pre
Leclercq[10] 2003 RD-CHF	CRT	NR	73 ± 8	NR	0	III or IV = 100		23 (52)	206 ± 26	25 ± 9	NR
Kindermann[13] 2006 HOBIPACE	All	23 (77)	69.6 ± 8.1	17	0	III or IV = 100		12 (37)	174 ± 42	26.1 ± 7.8	Post
Cleland[15] 2005 CARE-HF	OPT	293 (73)	66 median IQR 59-72	144	0	377	27	0	160 median IQR 152-180	25 median IQR 22-29	Pre
	CRT+OPT	304 (74)	67 median IQR 60-73	165	0	386	23	0	160 median IQR 152-180	25 median IQR 21-29	Pre

CRT = cardiac resynchronization therapy; ICD = implanted cardioverter defibrillator; IQR = interquartile range; OPT = optimal pharmacological therapy; NR = not reported

Table 5. Baseline characteristics of patients in trials included in the efficacy review: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study group	Males, n (%)	Mean age, yr. mean ± SD	Ischemic %	NYHA class			Other measures			Baseline measures taken pre/post-implantation
					II, %	III, %	IV, %	Atrial fibrill-ation, n (%)	QRS interval, msec mean ± SD	LVEF, % mean ± SD	
St. Jude[16] 2005 VecTOR	All	66 (62.5)	67.1 ± 9.7	NR	29	65	6	NR	≥ 140	≤ 35	Pre
Combined CRT-ICD											
Young[6] 2001 MIRACLE-ICD	CRT III/IV	142 (76)	67 ± 11	64	0	88	12	NR	165 ± 22	24 ± 7	Pre
	Control III/IV	141 (78)	68 ± 9	76	0	89	11	NR	162 ± 22	24 ± 6	Pre
Higgins[9] 2003 CONTAK-CD	CRT II-IV	210 (85)	66 ± 11	67	32	60	8	NR	160 ± 27	21 ± 7	Post
	Control II-IV	211 (83)	66 ± 11	70	33	57	10	NR	156 ± 26	22 ± 7	Post
Abraham[14] 2004 MIRACLE ICD II	CRT/ICD on	75 (88)	63 ± 12.8	55	100	0	0	NR	166 ± 25	24.4 ± 6.6	Post
	Control CRT off	91 (90)	63.1 ± 12.1	58	100	0	0	NR	165 ± 23	24.6 ± 6.7	Post
St. Jude[17] 2004a RHYTHM ICD	CRT on	NR	NR	NR	5	87	7	0	169 ± 16	25.6 ± 8.3	Post
	Control CRT off	NR	NR	NR	7	85	5	0	167 ± 15	23.3 ± 6.4	Post
CRT alone and combined CRT-ICD											
Bristow[11] 2004 COMPANION	CRT+OPT	415 (67)	67	54	0	87	13	NR	160	20	Post
	CRT+ICD+OPT	401 (67)	66	55	0	86	14	NR	160	22	Post
	OPT	213 (69)	68	59	0	82	18	NR	158	22	Post
Auricchio[12] 2003 PATH-CHF II	All	57 (66)	60 ± 9	38	II or III = 33		67	16	155 ± 20	23 ± 7	Post
	Inactive first	27 (63)	58 ± 8	33	II or III = 28		72	7	157 ± 23	23 ± 8	Post
	Active first	30 (70)	61 ± 9	44	II or III = 37		63	26	154 ± 18	23 ± 7	Post

Table 6. Description of studies included in the efficacy review: ICD alone

Author Year Study name	Country	Design Duration Type of outcomes	Treatment	Control	Partcipants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals		
Primary prevention											
Moss[133] 1996 MADIT	United States, Germany, Italy	RCT parallel 27mo. Efficacy, safety	ICD	OPT	253	196	95	101	18	Guidant Transthoracic, transvenous	All-cause mortality, arrhythmic death
Bigger[134] 1997 CABG-Patch	United States, Germany	RCT parallel 32 mo. Efficacy, safety	CABG+ ICD	CABG + usual care	1,055	900	446	454	70	Guidant Epicardial	All-cause mortality, time to shock, adverse events
Moss[135] 2002 MADIT II	United States, Europe	RCT parallel 20 mo. Efficacy, safety	ICD	OPT	NR	1,232	742	490	3	NR Transvenous	All-cause mortality, adverse events
Bänsch[136] 2002 CAT	Germany	RCT parallel 66 mo. Efficacy, safety	ICD	Usual care	104	104	50	54	0	Guidant Ventak® P2, P3, PrX II, CPI Transvenous	All-cause mortality, sustained VT, VT requiring treatment, adverse events, inappropriate shocks

DER = defibrillation energy requirement; EPS = electrophysiological study; ICD = implanted cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; NA = not applicable; NR = not reported; OPT = optimal pharmacological therapy; QOL = quality of life; RCT = randomized controlled trial; RV = right ventricular; VO_2 max = maximal oxygen consumption; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia

Table 6. Description of studies included in the efficacy review: ICD alone (continued)

Author Year Study name	Country	Design Duration Type of outcomes	Treatment	Control	Partcipants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals		
Strickberger[137] 2003 AMIOVIRT	United States	RCT parallel 2 yr. Efficacy	ICD	Amiodarone	NR	103	51	52	NR	NR Transvenous	All-cause mortality, sudden cardiac death, QOL, cost, appropriate therapy
Bristow[11] 2004 COMPANION	United States	RCT parallel 3 arms 15 mo. Efficacy, safety	ICD+CRT CRT	OPT	NR	1,520	CRT = 617; CRT+ ICD = 595	308	Treat-ment = 37 Control = 42	Guidant Contak® TR models 1241, 4510-4513, Contak® CD 1823 Transvenous	All-cause mortality, hospitali-zation, cardiac morbidity, peak O_2 uptake at exercise, complica-tions, implant success
Kadish[138] 2004 DEFINITE	United States, Israel	RCT parallel 29 mo. Efficacy, safety	ICD Single chamber	OPT	NR	458	229	229	6	St Jude NR	All-cause mortality, adverse events
Hohnloser[139] 2004 DINAMIT	Europe, Canada, United States	RCT parallel 30 mo. Efficacy, safety	ICD Single chamber	OPT	NR	674	332	342	24	St Jude NR	All-cause mortality, adverse events
Bardy[140] 2005 SCD-HeFT	United States, Canada	RCT parallel 3 arms 46 mo. (median) Efficacy, safety	ICD single chamber	Amiodarone, placebo	NR	2,521	829	Amiodarone = 845, Placebo = 847	50	Medtronic 7223 NR	All-cause mortality, inappropriate shocks

Table 6. Description of studies included in the efficacy review: ICD alone (continued)

Author Year Study name	Country	Design Duration Type of outcomes	Treatment	Control	Partcipants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals		
Secondary prevention											
Antiarrhythmics vs. Implantable Defibrillators (AVID) Investigators[141] 1997 AVID	United States	RCT parallel 18 mo. Efficacy, safety	ICD	Amiodarone or Sotalol	1,885	1,016	505	509	2	Guidant, Medtronic, Ventritex, Sulzer Intermedics Transvenous, epicardial	All-cause mortality, QOL, cost, adverse events, time to rehospital-ization
Connolly[142] 2000 CIDS	Canada	RCT parallel 35 mo. Efficacy, safety	ICD	Amiodarone	NR	659	328	331	NR	NR Transvenous, thoracotomy	All-cause mortality, arrhythmic death, adverse events
Kuck[143] 2000 CASH	Germany	RCT parallel 3 arms 57 mo. Efficacy, safety	ICD	Metoprolol Amiodarone	293	288	99	Metoprol = 97, Amiodarone = 92	NR	Guidant Ventak® AID, Ventak® AICD, Ventak® P, Ventak® PRx, Ventak® Mini™ Epicardial, endocard-ial	All-cause mortality, sudden cardiac death

Table 7. Baseline characteristics of patients in trials included in the efficacy review: ICD alone

Author Year Trial name	Study group	Males n (%)	Age, yr. mean ± SD	Ischemic, %	NYHA class			Other measures			Baseline measures taken pre/post implantation
					II, %	III, %	IV, %	Atrial fibril-lation, %	QRS interval, msec mean ± SD	, %	
Primary prevention											
Moss[133] 1996 MADIT	ICD	87 (92)	62 ± 9	34	II or III = 63		0	NR	NR	27 ± 7	Pre
	CMT	93 (92)	64 ± 9	29	II or III = 67		0	NR	NR	25 ± 7	Pre
Bigger[134] 1997 CABG PATCH	CABG+ICD	386 (86.5)	64 ± 9	100	II or III = 71		NR	NR	71% ≥ 100 msec	27 ± 6	Pre
	CABG	373 (82.2)	63 ± 9	100	II or III = 74		NR	NR	74% ≥100 msec	27 ± 6	Pre
Moss[135] 2002 MADIT II	ICD	623 (84)	64 ± 10	100	35	25	5	9	50% ≥120 msec	23 ± 5	Pre
	CMT	417 (85)	65 ± 10	100	34	23	4	8	51% ≥120 msec	23 ± 6	Pre
Bänsch[136] 2002 CAT	All	83 (79.8)	52 ± 11	0	65.3	34.6	0	15.76	108 ± 29	24 ± 7	Pre
	ICD	43 (86)	52 ± 12	0	66.7	33.3	0	20.4	102 ± 29	24 ± 6	Pre
	Control	40 (74)	52 ± 10	0	64.1	35.8	0	11.3	114 ± 29	25 ± 8	Pre
Strickberger[137] 2003 AMIOVIRT	All	72 (69.9)	59 ± 11	0	64	19.4	0	NR	NR	22 ± 9	Pre
	ICD	34 (67)	58 ± 11	0	64	16	0	NR	NR	22 ± 10	Pre
	Amiodarone	38 (74)	60 ± 12	0	63	24	0	NR	NR	23 ± 8	Pre
Bristow[11] 2004 COMPANION	CRT + OPT	413 (67)	Median 67	54	Exc	87	13	NR	≥120 msec	Median 20	Pre
	CRT+ICD +OPT	399 (67)	Median 66	55	Exc	86	14	NR	≥120 msec	Median 22	Pre
	OPT only	213 (69)	Median 68	59	Exc	82	18	NR	≥120 msec	Median 22	Pre

CRT = cardiac resyncrhonization therapy; ICD = implanted cardioverter defibrillator; NR = not reported; OPT optimal pharmacological therapy

Table 7. Baseline characteristics of patients in trials included in the efficacy review: ICD alone (continued)

Author Year Trial name	Study group	Males n (%)	Age, yr. Mean ± SD	Ischemic, %	NYHA class			Other measures			Baseline measures taken pre/post implantation
					II, %	III, %	IV, %	Atrial fibril-lation, %	QRS interval, msec mean ± SD	LVEF, %	
Kadish[138] 2004 DEFINITE	All	326 (71.2)	58 range 20-84	0	57.4	21	0	24.5	115.1 range 78-196	21.4 range 7-35	Pre
	ICD	166 (72.5)	58 range 20-84	0	54.2	20.5	0	22.7	114.7 range 78-196	20.9 range 7-35	Pre
	Control	160 (69.9)	58 range 22-79	0	60.7	21.4	0	26.2	115.5 range 79-192	21.8 range 10-35	Pre
Hohnloser[139] 2004 DINAMIT	ICD	252 (75.9)	61.5 ± 10.9	100	NR	NR	0	NR	107 ± 24	28 ± 5	Pre
	Control	262 (76.6)	62.1 ± 10.6	100	NR	NR	0	NR	105 ± 23	28 ± 5	Pre
Bardy[140] 2005 SCD-HeFT	ICD	639 (76)	60 Median IQR 52-69	52	71	29	0	16	NR	25 median	Pre
	Amiodarone	639 (77)	60 Median IQR 52-68	50	70	30	0	17	NR	25 median	Pre
	Placebo	655 (77)	59.7 Median IQR 51-68	53	68	32	0	14	NR	25 median	Pre

Table 7. Baseline characteristics of patients in trials included in the efficacy review: ICD alone (continued)

Author Year Trial name	Study group	Males n (%)	Age, yr. Mean ± SD	Ischemic, %	NYHA class			Other measures			Baseline measures taken pre/post implantation
					II, %	III, %	IV, %	Atrial fibril-lation, %	QRS interval, msec mean ± SD	LVEF, %	
Secondary prevention											
AVID Investigators[141] 1997 AVID	ICD	395 (78)	65 ± 11	81	I or II = 48	7	0	21	116 ± 26	32 ± 13	Pre
	Antiarrhythm-ics	412 (81)	65 ± 10	81	I or II = 48	12	0	26	117 ± 26	31 ± 13	Pre
Connolly[142] 2000 CIDS	ICD	280 (85.4)	63.3 ± 9.2	82.2	I or II = 37.8	III or IV = 11.0		NR	NR	34.3 ± 14.5	Pre
	Amiodarone	277 (83.7)	63.8 ± 9.9	82.9	I or II = 39.9	III or IV = 10.6		NR	NR	33.3 ± 14.1	Pre
Kuck[143] 2000 CASH	ICD	78 (79)	58 ± 11	73	59	18	0	NR	NR	46 ± 19	Pre
	Antiarrhythm-ics	152 (80)	57.5 ± 10	73.5	56	16	0	NR	NR	46 ± 17	Pre

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
CRT alone											
Abraham[4] 2002 MIRACLE	United States, Canada	RCT parallel 6 mo. Efficacy, safety	CRT	Pacer inactive	571	453	228	225	9	Medtronic InSync® 8040 Transvenous	NYHA, QOL, 6MWT, peak O_2 consumption, mortality, days in hospital
Achilli[18] 2003	Italy	Prospective cohort 6 mo. Effectiveness	CRT	NA	52	NA	52	NA	0	NR Transvenous	Interventricular asynchrony, 6MWT, mortality
Adamson[19] 2004 InSync III	United States	Prospective cohort 12 mo. Effectiveness	CRT	NA	397	NA	288	NA	0	Medtronic InSync® III 8042 NR	Heart rate variability, mortality, hospitalization
Albertsen[20] 2005	Denmark	Prospective cohort 16.7 mo. Effectiveness, safety	CRT	NA	120	NA	114	NA	0	Guidant 1241; Medtronic InSync® 8040, 8042 NR	Mortality, complications
Ansalone[23] 2002	Italy	Prospective cohort 1 mo. Effectiveness	CRT	NA	31	NA	31	NA	0	NR	LVEF, NYHA

CCT = controlled clinical trial; CHR = congestive heart failure; CRT = cardiac resynchronization therapy; CRT+ICD = CRT with implanted cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; NA = not applicable; NR = not reported; NYHA = New York Heart Association class; O_2 = Oxygen; OPT = optimal pharmacological therapy; QOL = quality of life; RCT = randomized control trial; RV = right ventricular; 6MWT = 6-minute walk test; VO_2 max = maximal oxygen consumption; VT = ventricular tachycardia

*The intervention that patients in crossover studies received in the first period

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Aranda[24] 2005	United States	Retrospective cohort 6 mo. Effectiveness	CRT	NA	60	NA	52	NA	0	NR	Change in beta-blocker treatment post CRT, NYHA, 6MWT, LVEF, VO_2 max
Auricchio[8] 2002a PATH-CHF	Germany, Netherlands	RCT crossover 1 mo. Efficacy, safety	CRT	Univentric-ular pacing (4 RV, 36 LV)	42	41	24	17	7	Guidant Vigor®, Discovery® Transthoracic	O_2 uptake at peak exercise, O_2 uptake at anaerobic threshold, 6MWT, NYHA, QOL
Auricchio[25] 2002b	Germany	Retrospective cohort 3 mo. Effectiveness	CRT	NA	135	NA	50	NA	0	NR Transvenous, thoracotomy	Changes in metabolic, ventilation and heart rate parameters, NYHA, LVEF
Baker[27] 2002	United States	Prospective cohort 18 mo. Effectiveness, safety	CRT	NA	60	NA	60	NA	6	NR Transvenous	Fesaibility of upgrade from RV to LV pacing, LVEF, NYHA, complications
Bax[28] 2003	Netherlands	Prospective cohort 6 mo. Effectiveness	CRT	NA	25	NA	25	NA	0	NR	NYHA, 6MWT, QOL, LVEF
Bleeker[30] 2005a	Netherlands	Prospective cohort 6 mo. Effectiveness, safety	CRT	NA	170	NA	170	NA	NR	Guidant Contak® TR, Contak® CD; Medtronic InSync® III, InSync® CD Transvenous	Mortality, NYHA, QOL, 6MWT, LVEF
Bleeker[31] 2005b	Netherlands	Prospective cohort 6 mo. Effectiveness, safety	CRT	NA	56	NA	56	NA	0	Contak® TR or CD Transvenous	Evaluate RV remodeling post CRT

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Bleeker[32] 2006	Netherlands	Prospective cohort 6 mo. Effectiveness, safety	CRT	NA	100	NA	100	NA	0	Guidant Contak® TR, Renewal™ TR2/1/2/4; Medtronic InSync® Marquis™ III, Sentry Transvenous	NYHA, 6MWT, QOL, QRS, LVEF
Bonanno[34] 2004	Italy	Prospective cohort 8.2 mo. Effectiveness	CRT	NA	37	NA	37	NA		Medtronic InSync® 8040, 8042, InSync® ICD® 7272; Transvenous	NYHA, LVEF
Bordachar[35] 2004	France	Prospective cohort 3 mo. Effectiveness, safety	CRT	NA	41	NA	41	NA	0	Medtronic InSync® III Transvenous	6MWT, QOL
Boriani[38] 2006c	Italy	Prospective cohort 3 mo. Effectiveness	CRT	NA	32	NA	32	NA	0	NR	Neurohormones, inflammatory mediators, NYHA,LVEF
Braunschweig[40] 2005	Europe	Prospective cohort 3 mo. Effectiveness	CRT	NA	56	NA	56	NA	0	Medtronic InSync® III 8042 Transvenous	6MWT, heart rate variability, NYHA
Cazeau[5] 2001 MUSTIC-SR	Europe	RCT crossover 3 mo. Efficacy, safety	CRT	Pacer inactive	67	58	29	29	7	ELA Chorum™ 7336; Medtronic InSync® 8040 Transvenous	6MWT, QOL, NYHA, peak O_2 uptake, hospitalization due to heart failure, mortality

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Cazeau[41] 2003	France	Prospective cohort NR Effectiveness, safety	CRT	NA	66	NA	66	NA	0	NR Transvenous	NYHA
Chalil[42] 2006	United Kingdom	Prospective cohort 2.2 yr Effectiveness, safety	CRT	NA	75	NA	75	NA	0	Medtronic InSync® III 8042, InSync® 8040, 8042, Sigma DR Transvenous	Mortality, SCD
Chan[43] 2003	Italy, Canada	Prospective cohort 3 mo. Effectiveness	CRT	NA	95	NA	95	NA	0	NR	6MWT, NYHA, QRS, LVEF
Cleland[15] 2005 CARE-HF	Europe	RCT parallel1, 3, 6, 9, 12, 18 mo., then every 6 mo. Efficacy, safety	CRT	OPT	NR	813	409	404	64	Medtronic InSync®, InSync® III Transvenous	Composite of all cause mortality or unplanned hospitalization for major CV event, NYHA, QOL
Daubert[46] 1998	France	Prospective cohort 10.2 mo. Effectiveness, safety	CRT	NA	47	NA	47	NA	10	ELA Chorus™ RM 7034, Chorus™ 7234 Transvenous	Complications, mortality
de Cock[124] 2004	Netherlands	Prospective cohort 3 mo. Safety	CRT	NA	103	NA	103	NA	0	NR	Complications
De Martino[125] 2004	Italy	Prospective cohort < 1 mo. Safety	CRT	NA	34	34	34	NA	0	NR Transvenous	Time to coronary sinus cannulation, complications

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
De Martino[126] 2005	Italy	Prospective cohort < 1 mo. Safety	CRT	NA	83	83	83	NA	NR	NR	Complications
Dixon[50] 2004	United Kingdom	Prospective cohort 12 mo. Effectiveness, safety	CRT	NA	27	NA	27	NA	0	NR	NYHA, hospitalization, 6MWT, mortality
Galvao[56] 2002	Brazil	Prospective cohort 5 mo. Effectiveness, safety	CRT	NA	28	NA	28	NA	0	NR Transvenous, mini-thoracotomy	Mortality, complications, NYHA
Gras[58] 2002 InSync	Europe, Canada	Prospective cohort up to 1 yr. Effectiveness, safety	CRT	NA	117	NA	103	NA	NR	Medtronic InSync® 8040 Transvenous	Feasibility, safety, long term effects, NYHA, QRS, 6MWT, QOL
Hua[60] 2006	China	Prospective cohort 7 days Effectiveness, safety	CRT	NA	142	NA	142	NA	0	Medtronic 2188 /2187 4189 /4191 4193 ELA UC28D Biotronic lead St Jude lead	Echocardiograph measures
Kautzner[128] 2004	Czechoslovakia	Retrospective cohort 24 mo. Safety	CRT	NA	138	NA	138	NA	0	NR Transvenous	Success rate of different LV lead insertions

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Kies[62] 2006	Netherlands	Retrospective cohort 6 mo. Effectiveness	CRT	NA	74	NA	74	NA	0	InSync® III/CD, Medtronic; Contak® TR/Renewal, Guidant Transvenous	Conversion from AF to SR; NYHA, QoL, 6MWT
Kindermann[13] 2006 HOBIPACE	Germany	RCT crossover 3 mo. Efficacy, safety	CRT	RV pacing	33	32	15	15	1	CRT (triple and dual chamber) Transvenous	LV end-systolic volume, LVEF, peak O_2 consumption, NYHA, QOL
Koos[63] 2004	Germany	Retrospective cohort 12 mo. Effectiveness, safety	CRT	NA	81	NA	52	NA	7	NR Transvenous, thoracotomy	Mortality, NYHA, LVEF, complications
Leclercq[66] 2000	Europe (15 sites)	Prospective cohort 1, 2, 6 mo., then every 6 mo. Effectiveness, safety	CRT	NA	37	NA	37	NA	0	Medtronic (various models) Transvenous, transthoracic	6MWT, peak O_2 consumption, QOL, hospitalization, mortality
Leclercq[7] 2002a MUSTIC-AF	France	RCT crossover 3 mo. Efficacy, safety	CRT	RV pacing	64	43	25	18	5	NR Transvenous	6MWT, peak O_2 consumption, QOL, hospitalization, mortality
Leclercq[67] 2002b	France	Prospective cohort 1, 3, 6, then every 6 mo. Effectiveness, safety	CRT	NA	NR	NA	125	NA	NR	NR Transvenous	Mortality, QRS, NYHA, LVEF, exercise tolerance
Leclercq[10] 2003 RD-CHF	France	RCT crossover 3 mo. Efficacy, safety	CRT	RV pacing	56	44	22	22	NR	NR Transvenous	CHF hospitalization, QRS, 6MWT, QOL, NYHA

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Lecoq[68] 2005	France	Retrospective cohort 6 mo. Effectiveness, safety	CRT	NA	158	NA	139	NA	0	ELA Chorum™ MSP; Guidant Contak®; Medtronic InSync® Transvenous	NYHA, 6MWT, VO_2 max, QRS, LVEF, hospitalizations, mortality
Leon[70] 2005	United States	Prospective cohort 6 mo. Effectiveness, safety	CRT	NA	422	NA	359	NA		InSync® III 8042 Medtronic Transvenous	6MWT, NYHA, QoL
Lindner[71] 2005	Germany	Prospective cohort 4 mo. Effectiveness	CRT	NA	NR	NA	42	NA	0	NR	Myocardial oxygen consumption and blood flow, LVEF, NYHA, 6MWT
Macioce[72] 2005	Italy	Prospective cohort 6 mo. Effectiveness	CRT	NA	30	NA	30	NA	0	Guidant Contak® TR CHFD; Medtronic InSync® Transvenous	Functional mitral regurgitation improvement, LVEF, NYHA
Mangiavacchi[74] 2006	Italy	Prospective cohort 1 yr. Effectiveness	CRT	NA	156	NA	156	NA		NR	Echocardiography, 6MWT
Marai[75] 2006	Isreal	Prospective cohort 3 mo. Effectiveness	CRT	NA	98	NA	98	NA	0	NR Transvenous	NYHA, 6MWT, QRS
Mascioli[76] 2002	Italy	Prospective cohort 36 mo. Effectiveness, safety	CRT	NA	96	NA	68	NA	0	NR Transvenous	All cause mortality, LVEF, NYHA, hospitalization

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Mele[77] 2006	Italy	Prospective cohort 6 mo. Effectiveness	CRT	NA	37	NA	37	NA	1	Easytrak, Guidant Transvenous	Association of baseline LV deformation dyssynchrony with CRT response.
Molhoek[78] 2002	Netherlands	Prospective cohort up to 2 yr. Effectiveness, safety	CRT	NA	40	NA	40	NA	0	Guidant Contak® TR, Contak® CD; Medtronic InSync® III Transvenous	Clinical benefit, long-term prognosis, NYHA, QOL, 6MWT, hospitalization, mortality
Mortensen[83] 2004 InSync III	Europe, Canada	Prospective cohort 3 mo. Effectiveness, safety	CRT	NA	198	NA	189	NA	15	Medtronic InSync® III 8042 Transvenous	6MWT, NYHA, complications, mortality
Nagele[85] 2001	Germany	Prospective cohort 8 mo. Effectiveness, safety	CRT	NA	32	NA	32	NA	0	Biotronik Triplos DR; ELA Chorus™ MST; Guidant Contak® TR Transvenous	Complications, NYHA, LVEF
Niu[87] 2006	China	Prospective cohort 1.7 yr Effectiveness, safety	CRT	NA	117	NA	111	NA	6	Medtronic InSync® 8040, 8042 Transvenous	Implant complications
O'Donnell[89] 2005	Australia	Prospective cohort 9 mo Effectiveness, safety	CRT	NA	63	NA	40	NA	0	Medtronic InSync® III,InSync® III Marquis CRT Transvenous	NYHA, 6MWT, symptom status, determine optimal programmed settings
Oliva[90] 2005	Italy	Prospective cohort 20 mo. Effectiveness	CRT	NA	258	NA	258	NA	0	NR	Clinical and hemodynamic benefits, mortality

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Ollitrault[91] 2003	France	Prospective cohort 15 mo. Effectiveness, safety	CRT	NA	62	NA	62	NA	0	NR	Complications
Penicka[93] 2004	Belgium	Prospective cohort 6 mo. Effectiveness, safety	CRT	NA	55	NA	49	NA	0	Guidant Contak® TR, Contak® CD Transvenous	LVEF, inter/intraventricular asynchrony, mortality
Porciani[95] 2006a	Italy	Prospective cohort 6 mo. Effectiveness	CRT	NA	30	NA	30	NA	0	Medtronic InSync®;Guidant Contak® TR CHFD Transvenous	LV function parameters, NYHA, QoL,
Porciani[96] 2006b	Italy	Prospective cohort 1 yr Effectiveness	CRT	NA	65	NA	65	NA	0	NR	All cause mortality or hospitalizaiton for worsening HF
Puglisi[97] 2004	Italy	Prospective cohort 12 mo. Effectiveness, safety	CRT	NA	315	NA	315	NA	0	NR Transvenous, Thoracotomy	NYHA, echocardiography, mortality
Reuter[99] 2000	France	Prospective cohort 8 mo. Effectiveness	CRT	NA	47	NA	47	NA	0	NR Transvenous	Echocardiography, LVEF, NYHA, VO_2 max, mortality
Ricci[101] 2002	Italy	Prospective cohort 8.8 mo. Effectiveness	CRT	NA	48	NA	48	NA	NR	Medtronic 8040 Transvenous	QRS, NYHA, 6MWT, LVEF

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Romeyer-Bouchard[131] 2005	France	Prospective cohort 8 mo. Safety	CRT	NA	103	NA	99 (CRT = 94, CRT+ICD = 5)	NA	0	Medtronic InSync®, InSync® III, InSync® Marquis™, InSync® ICD Transvenous	Feasibility of implantation technique, complications
Sawhney[105] 2004	United States	Prospective cohort 3 mo. Effectiveness, safety	CRT	NA	40	NA	40	NA	NR	NR Transvenous	NYHA, QOL, 6MWT, mortality
Schuchert[132] 2004	Germany, United Kingdom	Prospective cohort 24 mo. Safety	CRT	NA	102	NA	102	NA	0	St. Jude Medical Affinity™ DR, Frontier® 5510 Transvenous	Complications, NYHA
Sogaard[107] 2002	Denmark	Prospective cohort 12 mo. Effectiveness	CRT	NA	25	NA	25	NA	0	Medtronic InSync® Transvenous	LV performance, NYHA, LVEF, QRS, mortality
Stahlberg[108] 2005	Sweden	Prospective cohort 36 mo. Effectiveness, safety	CRT	NA	40	NA	40	NA	0	ELA Chorum™, Talent; Medtronic InSync®, Thera, Kappa; St. Jude Medical Frontier®, Affinity™ Transvenous	6MWT, NYHA, QOL, mortality
St. Jude[16] 2005 VecTOR	United States, Canada	RCT parallel 6 mo. Efficacy, safety	CRT	Pacer inactive	144	106	59	47	3	St. Jude Medical Frontier™ 508 NR	Peak VO_2, NYHA, QOL, 6MWT, echocardiographic parameters, mortality

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Taieb[109] 2002	France	Retrospective cohort 16.7 mo. Effectiveness, safety	CRT	NA	50	NA	50	NA	0	NR Transvenous	Mortality, NYHA, cardiac hospitalization
Tedrow[110] 2006	United States	Retrospective cohort 4 yr Effectiveness	CRT	NA	75	NA	75	NA	0	NR	Composite of death, cardiac transplant, or LVAD implantation
Toussaint[113] 2003	France	Prospective cohort 20 mo. Effectiveness, safety	CRT	NA	34	NA	34	NA	0	NR Transvenous	Ventricular function, LVEF, interventricular dyssynchrony, mortality
Witte[116] 2006	Canada	Prospective cohort 4 mo. Effectiveness	CRT	NA	71	NA	71	NA	o	NR Transvenous	Effect of CRTon LV dyssychrony, symptoms, renal function, echocardiographic indicies
Yu[118] 2002a	Hong Kong	Prospective cohort 4 mo. Effectiveness, safety	CRT	NA	25	NA	25	NA	0	Guidant Contak® TR, Contak® CD; Medtronic InSync® 8040 Transvenous	Echocardiography, 6MWT, QOL, mortality
Yu[119] 2002b	Hong Kong	Prospective cohort 3 mo. Effectiveness	CRT	NA	30	NA	30	NA	0	Guidant Contak® TR 1241; Medtronic InSync® 8040 Transvenous	QRS, 6MWT, NYHA, LVEF, QOL
Yu[121] 2005	Hong Kong	Prospective cohort 24 mo. Effectiveness	CRT	NA	141	NA	141	NA	2	NR Transvenous	NYHA, QOL, 6MWT, LV reverse modeling, mortality

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Zhang[122] 2006	Switzerland	Prospective cohort 3 mo. Effectiveness	CRT	NA	50	NA	50	NA	0	Medtronic InSync®, InSync® III, InSync® ICD; Guidant Contak® TR, Contak® CD NR	LV volumes and EF, NYHA, 6MWT, QoL
Combined CRT-ICD											
Abraham[14] 2004 MIRACLE-ICD II	United States	RCT parallel 6 mo. Efficacy, safety	CRT on + ICD on	CRT off + ICD on	222	186	85	101	6	Medtronic InSync® ICD 7272 NR	Peak VO_2, VO_2 max, NYHA, QOL, 6MWT, LV volumes, LVEF, change in clinical status
Boriani[36] 2006a	Europe	Prospective cohort 6 mo Effectiveness	CRT+ICD	NA	127	NA	121	NA	3	St..Jude Medical V-339 EPIC™ CRT-D NR	Complications, NYHA, 6MWT,QoL
Chugh[123] 2005	United States	Retrospective cohort ≤3 yr. Safety	CRT+ICD	NA	77	NA	77	NA	0	Guidant Contak® CD 1823; Medtronic Gem II, III DR, Marquis™ DR Transvenous	Inappropriate therapy
Gasparini[127] 2005	Italy	Prospective cohort 2 mo. Safety	CRT+ICD	NA	194	NA	194	NA		NR Transvenous	First shock effectiveness, device defibrillation failure, general outcome in the 2 month following implant, effectiveness of arrhythmia detection, ICD interventions

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Higgins[9] 2003 CONTAK-CD	United States	RCT Phase I period 1 of X-over 3 mo.; phase II parallel 6 mo. Efficacy, safety	CRT+ICD	CRT off + ICD on	581	490	245	245	4	Guidant Contak® CD 1823 Transvenous, transthoracic	Mortality, CHF hospitalization, VT requiring device therapy, peak O_2 consumption, 6MWT, QOL
Kuhlkamp[65] 2002	Germany	Prospective cohort 3 mo. Effectiveness, safety	CRT+ICD	NA	84	NA	81	NA	NR	Medtronic InSync® 7272 Transvenous	6MWT, QOL, NYHA, complictions, mortality
Murphy[84] 2006	United States	Prospective cohort 6 mo. Effectiveness	CRT+ICD	NA	54	NA	54	NA	0	NR Transvenous, epicardial	Placement of LV lead on LV reverse modelling and clinical outcomes
Ritter[102] 2006	Germany	Retrospective cohort 6 mo. Effectiveness, safety	CRT+ICD	NA	48	NA	48	NA	0	Guidant Contak® Renewal Transvenous	NYHA, echocardiographic parameters and hospitalization for heart failure
Saxon[106] 2006	United States	Prospective cohort 9 mo Effectiveness, safety	CRT+ICD	NA	170	NA	168	NA	0	Guidant Contak® Renewal Transvenous	Complication rate
St. Jude[17] 2004a RHYTHM ICD	United States	RCT parallel 12 mo. Efficacy, safety	CRT+ICD	CRT off + ICD on	205	179	119	59	3	St. Jude Medical Epic™ HF ICD NR	Complications, VF detection times, peak VO_2, NYHA, 6MWT, mortality

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
St. Jude[17] 2004b RHYTHM ICD QuickSite	United States	Prospective cohort NR Effectiveness, safety	CRT+ICD	NA	162	NA	162	NA	NR	St. Jude Medical Quicksite® Model 1056K LV lead with ICD/CRT system NR	Complications, adverse events
Theuns[112] 2005	Netherlands	Prospective cohort 21 mo. Effectiveness, safety	CRT+ICD	NA	86	NA	86	NA	NR	Guidant Contak® CD, Renewal™ I, Renewal™ II; Medtronic InSync® 7272, 7279; St. Jude Medical Epic™ HF NR	Mortality, incidence of VT, inappropriate therapy
Young[6] 2003 MIRACLE-ICD	United States, Canada (53 sites)	RCT (post implant) parallel 6 mo. Efficacy, safety	CRT+ICD	Pacer inactive	639	369	187	182	11	Medtronic InSync® ICD Transvenous	NYHA, QOL, 6MWT, complications, QRS, peak O_2 uptake, hospitalization, mortality
Ypenburg[117] 2006	Netherlands	Prospective cohort 2 yr Effectiveness, safety	CRT+ICD	NA	195	NA	191	NA	3	CONTAK® RENEWAL 3 AVT Guidant Transvenous	Number of ICD therapies in patients with and w/o prior VA who received a CRT+ICD; to determine predictors of VF/VT; response to CRT; mortality

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
CRT alone or combined CRT-ICD											
Alonso[21] 1999	France	Retrospective cohort 12 mo. Effectiveness	CRT, CRT+ICD	NA	26	NA	26 (CRT = 20, CRT+ICD = 6)	NA	0	NR Transvenous	Mortality, QRS, NYHA, VO_2 max, LVEF
Ammann[22] 2004	Switzerland	Prospective cohort 12 mo. Effectiveness, safety	CRT, CRT+ICD	NA	47	NA	43 (CRT = 19, CRT+ICD = 24)	NA	0	NR Transvenous	Mortality, NYHA, LVEF, hospitalization
Auricchio[12] 2003 PATH-CHF II	Germany, Netherlands	RCT crossover 3 mo. Efficacy, safety	CRT, CRT+ICD	Pacer inactive	101	86	43	43	14	NR Transvenous, thoracotomy	Exercise capacity peak VO_2, 6MWT, VO_2 max, NYHA, QOL
Azizi[26] 2006	Germany	Retrospective cohort 6 yr. Effectiveness, safety	CRT, CRT+ICD	NA	244	NA	244	NA	0	Biotronik, ELA Medical, Guidant, Medtronic, St. Jude Medical Vitatron Transvenous	Mortality, peri-operative complications
Bax[29] 2004	Netherlands	Prospective cohort 6 mo. Effectiveness, safety	CRT, CRT+ICD	NA	85	NA	85 (CRT = 37, CRT+ICD = 48)	NA	0	Guidant Contak® TR, Contak ® CD, Contak ® Renewal™; Medtronic InSync® III, InSync® III CD Transvenous	NYHA, QOL, 6MWT, QRS, LV volumes, LVEF, mortality
Bocchiardo[33] 2000	Italy	Prospective cohort 22 mo. Effectiveness, safety	CRT, CRT+ICD	NA	51	NA	48	NA	0	Guidant Contak® CD; Medtronic InSync® ICD Transvenous	Mortality, complications, inappropriate therapy, NYHA

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Boriani[37] 2006b	Italy (InSync ICD Registry)	Prospective cohort 4.yr. Effectiveness	CRT, CRT+ICD	NA	421	NA	CRT = 227CRT-ICD = 194	NA	0	Medtronic InSync® NR	Incidence of VT, LVEF, NYHA, mortality, hospitalization for heart failure
Braun[39] 2005	Germany	CCT 24 mo. Effectiveness, safety	CRT, CRT+ICD	ODT	124	NA	65 (CRT = 38, CRT+ICD = 27	57	0	Biotronik Logos, Deikos; Guidant Contak® TR, Contak® CD; Medtronic InSync® 8040, InSync® 7272 Transvenous	Mortality, hospitalization, NYHA, cardiac function, exercise performance, neurohormonal activation
Bristow[11] 2004 COMPANION	United States	RCT parallel, 3 arms 15 mo. Efficacy, safety	CRT + OPT, CRT+ICD + OPT	OPT	NR	1,520	CRT = 617CRT-ICD = 595	308	159	Guidant Contak® TR 1241, 4510-4513, Contak® CD 1823 Transvenous	All cause mortality, hospitalization, cardiac morbidity, peak O_2 uptake at exercise
Cowburn[44] 2005	Canada	Retrospective cohort 3 yr. Effectiveness, safety	CRT, CRT+ICD	NA	68	NA	68	NA	0	NR Transvenous	Contrast nephropathy, mortality
Da Costa[45] 2006	France	Prospective cohort 12 mo. Effectiveness, safety	CRT, CRT+ICD	NA	71	NA	67	NA	0	Medtronic InSync®, InSync® III, InSync® ICD, InSync® Marquis	Hospital readmission for class IV CHF, heart transplant, CHF mortality

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Davis[47] 2005	Canada	Retrospective cohort 36 mo. Effectiveness	CRT, CRT+ICD	NA	85	NA	85 (CRT = 67, CRT+ICD = 18)	NA	NR	Guidant Contak® TR 1241; Medtronic InSync® 8040, 8042 Transvenous	Mortality, QRS
De Sisti[48] 2005	France	Retrospective cohort 6 mo. Effectiveness	CRT, CRT+ICD	NA	102	NA	102	NA	0	Various Transvenous	Death from any cause and HF death
Diaz-Infante[49] 2005	Spain	Prospective cohort 6 mo. Effectiveness, safety	CRT, CRT+ICD	NA	197	NA	143 (CRT = 90, CRT+ICD = 53)	NA	0	NR Transvenous	Mortality, NYHA, 6MWT, QOL, QRS, LVEF
Duncan[51] 2006	United Kingdom	Retrospective cohort 6 mo. Effectiveness	CRT or CRT+ICD	NA	39	NA	39	NA	0	Guidant Contak® TR CHFD, Contak® CD CHFD, Renewal; Medtronic InSync® III 8040, InSync® ICD 7272, NR	Reduce ventricular dyssynchrony with CRT
Ellery[52] 2005	Austria, Brazil, France, Germany, Hungary, Italy, Netherlands, United Kingdom	Prospective cohort 12 mo. Effectiveness, safety	CRT, CRT+ICD	NA	96	NA	85 (CRT = 71, CRT+ICD = 14)	NA	NR	NR	Mortality, complications

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Ermis[53] 2004	United States	Prospective cohort 12 mo. Effectiveness, safety	CRT, CRT+ICD	CRT	158	NA	126 (CRT = 62, CRT+ICD = 64)	NA	0	NR	Mortality, hospitalization
Fung[54] 2005	Hong Kong	Prospective cohort 36 mo. Effectiveness	CRT, CRT+ICD	NA	53	NA	36	36	0	Guidant Contak® TR Medtronic; InSync®, InSync® III ICD Transvenous	Development of atrial fibrillation
Gaita[55] 2000	Italy	Prospective cohort 12 mo. Effectiveness, safety	CRT, CRT+ICD		96	NA	96 (CRT = 29, CRT+ICD = 67)	NA	0	NR	Mortality, NYHA
Gasparini[57] 2003a	Italy	Prospective cohort 11 mo. (median) Effectiveness, safety	CRT, CRT+ICD	NA	159	NA	158 (CRT = 102 CRT+ICD = 56)	NA	0	NR	QRS, NYHA, 6MWT, LVEF, QOL, hospitalization, mortality
Hernandez[59] 2004	Spain	Prospective cohort 10 mo. Effectiveness	CRT, CRT+ICD	NA	28	NA	28 (CRT = 16, CRT+ICD = 12)	NA	0	NR Transvenous	Mortality, NYHA, 6MWT, hospitalization, brain matriuretic peptide concentrations
Kies[61] 2005	Netherlands	Prospective cohort 18 mo. Effectiveness	CRT, CRT+ICD	NA	97	NA	97 (CRT = 45, CRT+ICD = 52)	NA	0	Guidant Contak® TR, Contak® Renewal™ CD; Medtronic InSync® III, InSync® CD Transvenous	Mortality, hospitalizations, NYHA, QOL, 6MWT, LVEF

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Krahn[64] 2002	Canada	Prospective cohort 1, 3, 6 mo., then every 6 mo. Effectiveness, safety	CRT, CRT+ICD	NA	45	NA	40	NA	NR	Guidant Contak® TM, Contak® CD; Medtronic, InSync® pacemaker, ICD Transvenous	QOL, NYHA, mortality, electrocardiographic measures
Lenom[69] 2005	France	Prospective cohort 6 mo. Effectiveness, safety	CRT, CRT+ICD	NA	36	NA	36 (CRT = 28, CRT+ICD = 7)	NA	2	Guidant Contak® TR 1241, Contak® CD; Medtronic InSync® 8040, Renewal™ II, InSync® ICD Transvenous	NYHA, 6MWT, QOL, LVEF
Lewicka-Nowak[129] 2005	Poland	Retrospective cohort 48 mo. Safety	CRT, CRT+ICD	NA	92	NA	92 (CRT = 70, CRT+ICD = 20)	NA	0	Biotronik Corox LV 415 NR	Complications
Mair[73] 2005	Germany, Belgium	CCT 16.4 mo. Effectiveness, safety	CRT, CRT+ICD	NA	86	NA	86 (CRT = 53, CRT+ICD = 33)	NA	0	Guidant Contak® TR Renewal™, Contak® TR; Medtronic InSync® 8040, 8042, InSync ICD, InSync® II Marquis™ 7289 Transvenous, epicardial	Compare LV lead placement strategies, mortality, complications

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Molhoek[79] 2004a	Netherlands	Prospective cohort 6 mo. Effectiveness	CRT, CRT+ICD	NA	NR	NA	60 (CRT = 32, CRT+ICD = 28)	NA	0	Guidant Contak® TR, Contak® Renewal™ CD; Medtronic InSync® III, InSync® CD Transvenous	NYHA, QOL, 6MWT, mortality
Molhoek[80] 2004b	Netherlands	Prospective cohort 6 mo. Effectiveness, safety	CRT, CRT+ICD	NA	74	NA	74 (CRT = 40, CRT+ICD = 34)	NA	0	Guidant Contak® TR, Contak® CD, Contak® Renewal™; Medtronic InSync® III, InSync® CD Transvenous	NYHA, QOL, 6MWT, LVEF, hospitalization, mortality
Molhoek[81] 2004c	Netherlands	Prospective cohort 6 mo. Effectiveness	CRT, CRT+ICD	NA	61	NA	61 (CRT = 33, CRT+ICD = 28)	NA	0	Guidant Contak® TR, Contak ®CD; Medtronic InSync® III, InSync® ICD Transvenous	NYHA, QOL, 6MWT, LVEF, QRS
Molhoek[82] 2005	Netherlands	Prospective cohort up to 3 yr. Effectiveness, safety	CRT, CRT+ICD	NA	NR	NA	125 (CRT = 42, CRT+ICD = 83)	NA	0	Guidant Contak® TR, Contak® CD; Medtronic InSync® III, InSync® CD Transvenous	Mortality, hospitalization, NYHA, QRS, QOL, 6MWT, LVEF
Navia[86] 2005	United States	Prospective cohort 9 mo. Effectiveness, safety	CRT, CRT+ICD	NA	41	NA	41 (CRT = 13, CRT+ICD = 28)	NA	0	NR Minithoracotomy, endoscopic	Mortality, NYHA

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Notabartolo[88] 2004	United States	Prospective cohort 3 mo. Effectiveness	CRT, CRT+ICD	NA	66	NA	49	NA	12	Guidant H115, H135; Medtronic InSync® 8040, InSync® 7272 Transvenous	NYHA, 6MWT, QOL, echocardiographic parameters
Pappone[92] 2003	Italy	Prospective cohort 28 mo. Effectiveness, safety	CRT, CRT+ICD		135	NA	135 (CRT = 47, CRT+ICD = 88)	NA	0	NR	Mortality, NYHA, LVEF
Pitzalis[94] 2005	Italy	Prospective cohort 14 mo. (median) Effectiveness, safety	CRT, CRT+ICD	NA	72	NA	72 (CRT = 42, CRT+ICD = 30)	NA	12	Guidant Contak® TR CHFD, Contak® CD CHFD, Contak® Renewal™; Medtronic InSync® III, InSync® ICD, InSync® Marquis™; St. Jude Medical Epic™ HFV-339 Transvenous	Mortality, hospitalization, LVEF, LV asynchrony. Septal-to-posterior wall motion delay
Pürerfellner[130] 2000a	Europe	Retrospective cohort 6 mo Safety	CRT, CRT+ICD	NA	47	NA	47	NA	0	Guidant Contak® TR, HF, CD Transvenous	LV pacing thresholds, LV lead impedance, LV R-wave amplitude, complications
Pürerfellner[130] 2000b	Europe	Registry data 6 mo Safety	CRT, CRT+ICD	NA	150	NA	150	NA	0	Guidant Contak® TR, HF, CD Transvenous	Complications,

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Purnode[98] 2004	France	Prospective cohort 12 mo. Effectiveness, safety	CRT, CRT+ICD	NA	43	NA	43 (CRT = 37, CRT+ICD = 6)	NA	0	ELA Chorum™ 7336; Guidant Contak® TR, Contak® CD, Renewal™ H135; Medtronic InSync® 8040, InSync® 7272; St. Jude Medical Trilogy™ DR, Affinity™ DR Transvenous	NYHA, 6MWT, QOL, mortality
Reuter[100] 2002	France	Prospective cohort 12 mo. Effectiveness, safety	CRT, CRT+ICD	NA	102	NA	102 (CRT = 93, CRT+ICD = 9)	NA	11	ELA Chorum™ 7336 MSP; Medtronic InSync® 8040, InSync® ICD; Transvenous	Mortality, NYHA, QOL, LVEF, O_2 uptake, hospitalization
Rossillo[103] 2004	United States, Italy	Prospective cohort 18 mo. Effectiveness, safety	CRT, CRT+ICD	NA	244	NA	233 (CRT = 68, CRT+ICD = 165)	NA	0	NR	NYHA, echocardiographic parameters, mortality
Salukhe[104] 2005	United Kingdom	Prospective cohort 6 mo. Effectiveness, safety	CRT, CRT+ICD	NA	43	NA	40 (CRT = 20, CRT+ICD = 20)	NA	0	NR	Mortality, NYHA, LVEF, efficiency of cardiac cycle

Table 8. Description of studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment*	Number in control*	Number of withdrawals		
Teo[111] 2003	Singapore, Indonesia, Thailand	Prospective cohort up to 28 mo. Effectiveness, safety	CRT, CRT+ICD	NA	29	NA	29 (CRT = 24, CRT+ICD = 5)	NA	0	Guidant Contak® TR, CD ICD; Medtronic InSync®, InSync® ICD Transvenous	Mortality, NYHA, LVEF, complications
Vidal[114] 2006	Spain	Prospective cohort 12 mo. Effectiveness	CRT, CRT+ICD	NA	64	NA	64	NA	0	Contak® HF, Contak® Renewal, Renewal II, Guidant	Mortality, transplant, 6MWT
Waggoner[115] 2006	United States	Prospective cohort Effectiveness	CRT, CRT+ICD	NA	57	NA	57	NA	0	NR Transvenous	Hospitalization for HF; cardiac transplantation; mortality
Yu[120] 2004	Hong Kong	Prospective cohort 3 mo. Effectiveness	CRT, CRT+ICD	NA	NR	NA	58 (CRT = 54, CRT+ICD = 4)	NA	0	Guidant Contak® CD, Contak® TR; Medtronic InSync®, InSync® III, InSync® ICD Transvenous	Echocardiographic parameters, 6MWT, QOL, NYHA

Table 9. Baseline characteristics of patients in studies included in the effectiveness or safety reviews: CRT alone or combined CRT-ICD devices

Author Year Trial Name	Study group	Males n (%)	Age, yr. Mean ± SD	Ischemic %	NYHA class II, %	NYHA class III, %	NYHA class IV, %	Other measures Atrial fibrillation %	Other measures QRS interval, msec mean ± SD	Other measures LVEF, % mean ± SD
CRT alone										
Abraham[4] 2002 MIRACLE	CRT	155 (68)	64 ± 11	50	0	90	10	0	167 ± 21	22 ± 6
	Control	153 (68)	65 ± 11	58	0	91	9	NR	165 ± 20	22 ± 6
Achilli[18] 2003	All	31 (60)	69.6 ± 9	40	0	III or IV = 100		0	152.6 ± 32.1	23.0 ± 4.6
Adamson[19] 2004 InSync III	All	169 (58.7)	65.8 ± 11.3	47	0	96	4	0	164.9 ± 22.2	22 ± 6
Albertsen[20] 2005	All	94 (78.3)	62 (4-8)	52	22	69	8	NR	NR	22.3 ± 8.6
Ansalone[23] 2002	All	NR	NR	0	0	III or IV = 100		NR	160.3 ± 27.3	31 ± 7
Aranda[24] 2005	All	30 (58)	63 ± 10	52	NR	NR	NR	NR	NR	18 ± 6
Auricchio[8] 2002a PATH-CHF	All	21 (50)	60 ± 7	29	0	86	14	0	175 ± 32	21 ± 7
Auricchio[25] 2002b	All	33 (66)	60 ± 9	40	II or III = 32		67	0	163 ± 25	22 ± 5
Baker[27] 2002	All	50 (83)	70 ± 12	57	0	57	43	NR	NR	21 ± 8
Bax[28] 2003	All	22 (88)	62 ± 9	44	0	76	24	NR	185 ± 35	22 ± 5
Bleeker[30] 2005a	< 70	80 (78)	59 ± 9	48	0	81	19	NR	175 ± 28	21 ± 8
	> 70	57(84)	76 ± 4	66	0	85	15	NR	171 ± 24	22 ± 8
	All	137 (80.6)	66 ± 11	55	0	83	17	NR	173 ± 27	21 ± 7

CRT = cardiac resynchronization therapy; ICD = implanted cardioverter defibrillator; IQR = interquartile range; NR = not reported

Table 9. Baseline characteristics of patients in studies included in the effectiveness or safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial Name	Study group	Males n (%)	Age, yr. Mean ± SD or median. (IQR)	Ischemic, %	NYHA class			Other measures		
					II, %	III, %	IV, %	Atrial fibrillation, %	QRS interval, msec mean ± SD or median (IQR)	LVEF, % mean ± SD or median (IQR)
Bleeker[31] 2005b	All	44 (78.6)	64 ± 11	52	0	89	11	13	176 ± 30	19 ± 6
Bleeker[32] 2006	NYHA II	47 (94)	65 ± 10	58	100	0	0	16	160 ± 30	25 ± 7
	NYHA III-IV	41 (82)	66 ± 11	56	0	86	14	12	168 ± 27	20 ± 7
	All	88 (88)	65.5 ± 10.5	57	50	43	7	14	164 ± 28.7	22.2 ± 7.4
Bonanno[34] 2004	All	32 (86.5)	73 ± 7	51	0	III or IV = 100		30	189.1 ± 35.4	27.4 ± 6.0
Bordachar[35] 2004	All	33 (80)	69 ± 6.5	56	0	III or IV = 100		0	170 ± 31	28 ± 6
Boriani[38] 2006c	All	22 (68.8)	65 median (61-74)	53	0	87.5	12.5	NR	168 median (142-180)	25.5 median (22.2-30.7)
Braunschweig[40] 2005	All	46 (82.1)	65 ± 11	55	20	66	14	0	170 ± 24	24 ± 7
Cazeau[5] 2001 MUSTIC-SR	All	50 (75)	63 ± 10	37	0	100	0	NR	1764 ± 19	23 ± 7
Cazeau[41] 2003	All	NR	NR	35	0	86	14	27	182 ± 33	28 ± 8
Chalil[42] 2006	All	58 (77)	67.8 ± 12.1	71	0	61	39	25	156.9 ± 21.7	32 ± 8.7
Chan[43] 2003	All	49 (78)	68.8	47	0	III or IV = 100		NR	182 ± 31	21.0 ± 5.9
Cleland[15] 2005 CARE-HF	OPT	293 (73)	66 median (59-72)	36	0	93	7	0	160 median, IQR 152-180	25 median IQR 22-29
	CRT + OPT	39 (74)	67 median (60-73)	40	0	94	6	0	160 median, IQR 152-180	25 median IQR 21-29
Daubert[46] 1998	All	42 (91)	68 ± 9	53	0	13	87	NR	187 ± 27	17 ± 4
De Martino[125] 2004	All	NR	NR	NR	0	III or IV = 100		NR	≥ 120 msec	NR
De Martino[126] 2005	All	NR	61.5 ± 6.5	50	0	III or IV = 100		NR	≥ 120 msec	24.5 ± 7

Table 9. Baseline characteristics of patients in studies included in the effectiveness or safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial Name	Study group	Males n (%)	Age, yr. Mean ± SD or median. (IQR)	Ischemic, %	NYHA class II, %	NYHA class III, %	NYHA class IV, %	Other measures Atrial fibrillation, %	Other measures QRS interval, msec mean ± SD or median (IQR)	Other measures LVEF, % mean ± SD or median (IQR)
Dixon[50] 2004	All	24 (89)	64 ± 9	52	0	III or IV = 100		NR	177 ± 21	< 30
Galvao[56] 2002	All	23 (82.1)	58.5 (36, 84)	46	0	43	57	NR	187 ± 18.35	34 ± 5.7
Gras[58] 2002	All	81 (78.6)	67 ± 10	48	0	68	32	NR	178 ± 28	22 ± 6
Hua[60] 2006	All	91 (64)	60 ± NR	31	0	III or IV = 100		NR	146.7 ± NR	28.7 ± NR
Kautzner[128] 2004	All	116 (84)	61 ± 8	NR	0	III or IV = 100		NR	≥150ms	21.8 ± 8.8
Kies[62] 2006	All	67 (90.5)	68 ± 8	43	0	82	18	100	176 ± 30	22 ± 7
Kindermann[13] 2006 HOBIPACE	All	23 (77)	69.6 ± 8.1	57	NR	NR	NR	37	174 ± 42	26.1 ± 7.8
Koos[63] 2004	All	52 (64.2)	65.4 ± 12.3	47	NR	NR	NR	NR	165.8 ± 21.1	23.6 ± 7.3
Leclercq[66] 2000	All	34 (92)	67.4 ± 7.2	38	0	70	30	41	181 ± 23	22.8 ± 5.3
Leclercq[7] 2002a MUSTIC-AF	All	35 (81)	65 ± 8	43	0	100	0	100	209 ± 18	26 ± 10
Leclercq[67] 2002b	All	81 (79)	67 ± 11	47	0	70	30	NR	177.9 ± 27.9	22 ± 7.1
Leclercq[10] 2003 RD-CHF	All	NR	73 ± 8	NR	0	III or IV = 100		23	206 ± 26	25 ± 9
Lecoq[68] 2005	All	113 (81)	68 ± 9	35	0	69	31	32	188 ± 28	21 ± 6
Leon[70] 2005	All	211 (58.8)	65.8 ± 10.8	46.2	0	91.6	8.4	89.7	163.9 ± 21.6	21.5 ± 6.9
Lindner[71] 2005	All	NR	62 ± 8.4	26	0	100	0	2	185.1 ± 19.3	22.2 ± 6.6
Macioce[72] 2005	All	26 (86.7)	74.1 ± 6.1	47	0	III or IV = 100		NR	140 ± 10	28 ± 8

Table 9. Baseline characteristics of patients in studies included in the effectiveness or safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial Name	Study group	Males n (%)	Age, yr. Mean ± SD or median. (IQR)	Ischemic, %	NYHA class II, %	NYHA class III, %	NYHA class IV, %	Other measures Atrial fibrillation, %	Other measures QRS interval, msec mean ± SD or median (IQR)	Other measures LVEF, % mean ± SD or median (IQR)
Mangiavacchi[74] 2006	All	116 (74.4)	65.6 ± 8.9	48.7	16.8	III or IV = 83.2		NR	171.7 ± 29.8	30.4 ± 6.9
Marai[75] 2006	All	84 (85.7)	69.8 ± 9.0	89.8	0	III or IV = 100		19.4	173.2 ± 35.1	22.3 ± 6.2
Mascioli[76] 2002	All	53 (77.9)	68 ± 8	51	NR	NR	NR	9	177 ± 30	NR
Mele[77] 2006	All	27 (73)	68 ± 8	43	0	86	14	0	161 ± 24	25 ± 5
Mortensen[83] 2004	All	137 (72.5)	66.3 ± 10.6	42	18	68	14	NR	176.3 ± 27.0	24.2 ± 6.9
Nagele[85] 2001	All	24 (75)	60 ± 10	47	NR	NR	NR	NR	185 ± 30	26.5 ± 7
Niu[87] 2006	All	86 (73.5)	53 ± NR	NR	0	III-IV = 100		NR	141.8 ± NR	25.8 ± NR
O'Donnell[89] 2005	All	NR	NR	NR	NR	NR	NR	0	NR	23
Oliva[90] 2005	All	213 (82)	62 ± 10	40	NR	NR	NR	NR	171 ± 31	26.1 ± 6.9
Ollitrault[91] 2003	All	50 (81)	71 ± 10	NR	0	III or IV = 100		NR	> 150	NR
Porciani[95] 2006a	All	28 (93.3)	73.7 ± 6.3	46.7	0	III or IV = 100		NR	140 ± 10	27 ± 8.0
Porciani[96] 2006b	All	51 (78)	73 ± 8	47.7	0	III or IV = 100		0	170 ± 30	28 ± 7
Puglisi[97] 2004	All	262 (83)	63 ± 10	40	0	85	15	NR	178 ± 34	26 ± 7
Reuter[99] 2000	All	38 (81)	64 ± 11	NR	8	47	47	40	173 ± 18	23 ± 7
Ricci[101] 2002	All	40 (83.3)	68 ± 8	40	0	III or IV = 100		15	154 ± 29	29 ± 9
Romeyer-Bouchard[131] 2005	All	86 (83.5)	71 ± 10	34	0	69	31	13	185 ± 25	≤35
Sawhney[105] 2004	All	28 (70)	59.8 ± 12.1	45	0	III or IV = 100		0	176 ± 22	25.6 ± 5.4

Table 9. Baseline characteristics of patients in studies included in the effectiveness or safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial Name	Study group	Males n (%)	Age, yr. Mean ± SD or median. (IQR)	Ischemic, %	NYHA class II, %	NYHA class III, %	NYHA class IV, %	Other measures Atrial fibrillation, %	Other measures QRS interval, msec mean ± SD or median (IQR)	Other measures LVEF, % mean ± SD or median (IQR)
Schuchert[132] 2004	All	71 (70)	67 ± 10	27	0	67	33	12	148.2 ± 18.3	< 35
Sogaard[107] 2002	All	22 (88)	61.2 ± 10	55	0	55	45	NR	189 ± 23	23.8 ± 6
Stahlberg[108] 2005	All	38 (95)	65 ± 10	65	0	88	12	30	173 ± 22	23 ± 9
St. Jude[16] 2005 VecTOR	All	90 (62.5)	67.1 ± 9.7	NR	29	65	6	NR	≥140	≤35
Taieb[109] 2002	All	33 (66)	71.4 ± 9.9	32	4	74	22	12	> 150 ± 35	< 35
Tedrow[110] 2006	All	53 (70.7)	65.5 ± 12.5	46.6	NR	73.3	9.3	50.1	171.1 ± 40.5	21 ± 9
Toussaint[113] 2003	All	31 (91.2)	64.5 ± 11	53	0	III or IV = 100		NR	179 ± 18	20.2 ± 8.1
Witte[116] 2006	All	NR	68.4 ± 17.7	52	NR	NR	NR	28	188.3 ± 31.4	20 ± 8.8
Yu[119] 2002b	All	21(70)	62 ± 14	40	0	60	40	NR	159.1 ± 25.8	25.1 ± 12.9
Yu[121] 2005	All	103 (73)	64 ± 11	48	9	75	16	NR	156.1 ± 37.4	24.8 ± 8
Zhang[122] 2006	All	36 (72)	66 ± 11	48	0	80	20	NR	151 ± 27	26.5 ± 9.3
Combined CRT-ICD										
Abraham[14] 2004 MIRACLE-ICD II	CRT/ICD on	75 (88)	63 ± 12.8	55	100	0	0	NR	166 ± 25	24.4 ± 6.6
	Control CRT off	91 (90)	63.1 ± 12.1	58	100	0	0	NR	165 ± 23	24.6 ± 6.7
Boriani[36] 2006a	CRT+ICD	100 (82.6)	67 ± 8.6	63	0.8	92.6	6.6	NR	175 ± 22	24.2 ± 5.8
Chugh[123] 2005	CRT + ICD	52 (67.5)	61 ± 11	56	NR	NR	NR	29	168 ± 24	19 ± 7
de Cock[124] 2004	All	NR	NR	NR	0	III or IV = 100		NR	≥140ms	≤ 35

Table 9. Baseline characteristics of patients in studies included in the effectiveness or safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial Name	Study group	Males n (%)	Age, yr. Mean ± SD or median. (IQR)	Ischemic, %	NYHA class			Other measures		
					II, %	III, %	IV, %	Atrial fibrillation, %	QRS interval, msec mean ± SD or median (IQR)	LVEF, % mean ± SD or median (IQR)
Gasparini[127] 2005	All	177 (91)	65.2 ± 8.5	70	Mean = 3.0 ± 0.5			NR	164 ± 31	29.3 ± 6.2
Higgins[9] 2003 CONTAK-CD	All	176 (77.5)	66 ± 11	68	13	72	15	0	158 ± 26.6	21.5 ± 7.0
Kuhlkamp[65] 2002	All	74 (91)	63.8 ± 8.8	57	32	59	9	6	170 ± 30	25 ± 7
Murphy[84] 2006	All	43 (80)	61 22-85	54	6	87	7	9	157 ± 34	26.6 ± 8.4
Ritter[102] 2006	All	32 (66.7)	71 ± 8	89.6	0	III or IV = 100		0	162 ± 27	23 ± 3.7
Saxon[106] 2006	All	142 (85)	70.7 ± 10.3	78	0	88	13	23	150 ± 25	22.6 ± 6.4
St. Jude[17] 2004a RHYTHM ICD	All	NR	NR	NR	6	87	6	0	168 ± 15	24.8 ± 7.7
St. Jude[17] 2004b RHYTHM ICD Quicksite®	All	132 (82)	68.8 ± 9.9	78	0	92	8	NR	166 ± 21	22.5 ± 6.7
Theuns[112] 2005	All	66 (77)	61 ± 10	59	26	74	0	27	174 ± 31	23 ± 8
Young[6] 2003 MIRACLE-ICD	CRT III-IV	142 (75.9)	66.6 ± 11.3	64	0	88	12	NR	165 ± 22	24.2 ± 6.5
	Control III-IV	141 (77.5)	67.6 ± 9.2	76	0	89	11	NR	162 ± 22	23.9 ± 6
Ypenburg[117] 2006	All	153 (79)	64 ± 11	56	0	III or IV = 100		28	163 ± 30	21 ± 7

Table 9. Baseline characteristics of patients in studies included in the effectiveness or safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial Name	Study group	Males n (%)	Age, yr. Mean ± SD or median. (IQR)	Ischemic, %	NYHA class II, %	NYHA class III, %	NYHA class IV, %	Other measures Atrial fibrillation, %	Other measures QRS interval, msec mean ± SD or median (IQR)	Other measures LVEF, % mean ± SD or median (IQR)
CRT or combined CRT-ICD										
Alonso[21] 1999	All	24 (92.3)	66 ± 7	35	0	69	31	23	178 ± 24	23 ± 8
Ammann[22] 2004	All	36 (83.7)	65 ± 10	47	0	III or IV = 100		16	172 median IQR 158-196	20 median IQR 15-25
Auricchio[12] 2003 PATH-CHF II	All	57 (66.3)	60 ± 9	38	II or III = 33		67	16	155 ± 20	23 ± 7
	Inactive first	27 (62.8)	58 ± 8	33	II or III = 28		72	7	157 ± 23	23 ± 8
	Active first	30 (69.8)	61 ± 9	44	II or III = 37		63	26	154 ± 18	23 ± 7
Azizi[26] 2006	All	200 (82)	64 ± 12	44	10	68	22	29	NR	24 ± 9
Bax[29] 2004	All	64 (75.3)	66 ± 12	55	0	80	20	0	178 ± 36	23 ± 7
Bocchiardo[33] 2000	All	45 (94)	63 ± 7	52	25	65	10	NR	NR	27 ± 5.5
Boriani[37] 2006b	All	383 (91)	65 ± 9	69	23	66	11	NR	168 ± 32	26 ± 7
Braun[39] 2005	OPT	40 (67.8)	63 ± 9	70	0	93	7	0	175 ± 22	21.5 ± 5
	CRT and CRT + ICD	45 (69.2)	65 ± 11	74	0	90	10	0	172 ± 19	20.9 ± 4
Bristow[11] 2004 COMPANION	CRT + OPT	415 (67)	67	54	0	87	13	NR	160	20
	CRT + ICD + OPT	401 (67)	66	55	0	86	14	NR	160	22
	OPT	213 (69)	68	59	0	82	18	NR	158	22
Cowburn[44] 2005	All	NR	67 ± 12	66	0	III or IV = 100	NR	NR	NR	19 ± 7
Da Costa[45] 2006	All	56 (83.6)	70 ± 10	34.3	0	59.7	40.3	26.9	190 ± 28	26 ± 5
Davis[47] 2005	All	75 (88)	66 ± 9	72	5	84	12	NR	168 ± 22	21 ± 6

Table 9. Baseline characteristics of patients in studies included in the effectiveness or safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial Name	Study group	Males n (%)	Age, yr. Mean ± SD or median. (IQR)	Ischemic, %	NYHA class			Other measures		
					II, %	III, %	IV, %	Atrial fibrillation, %	QRS interval, msec mean ± SD or median (IQR)	LVEF, % mean ± SD or median (IQR)
De Sisti[48] 2006	All	86 (84.3)	68 ± 10	51	13.7	65.7	20.6	28.4	187 ± 35	20 ± 9
Diaz-Infante[49] 2005	All	113 (79)	68.3 ± 7	34	17	80	3	23	165 ± 26	27 ± 7
Duncan[51] 2006	All	30 (77)	65 ± 10	59	0	95	5	0	154 ± 75	21 ± 5.6
Ellery[52] 2005	All	73 (76)	68 ± 9	38	0	83	17	NR	163 ± 30	NR
Ermis[53] 2004	All	96 (76.1)	69 ± 11.5	56	NR	III or IV = 87		NR	NR	22 ± 8.7
Fung[54] 2005	CRT	26 (72.2)	66.0 ± 10.4	36	NR	NR	NR	100	NR	31.7 ± 7.8
	Control	26 (72.2)	65.2 ± 8.1	33	NR	NR	NR	0	NR	32.8 ± 7
Gaita[55] 2000	All	88 (92)	66 ± 8	NR	II, III or IV = 100			NR	> 140 msec	22 ± 6
Gasparini[57] 2003a	All	121 (76.6)	65 ± 9	47	19	III or IV = 81		NR	173.7 ± 29.7	29.6 ± 7.0
Hernandez[59] 2004	All	21 (75)	66 ± 9	39	0	III or IV = 100		29	168 ± 23	30 ± 8
Kies[61] 2005	All	75 (77.3)	63.3 ± 10.6	62	0	84	16	NR	175.0 ± 23.4	22 ± 6
Krahn[64] 2002	All	37 (82)	65.3 ± 10.3	69	7	76	18	33	166 ± 20	19 ± 5
Lenom[69] 2005	All	25 (69)	76 ± 10	67	6	78	2	11	177 ± 27	24 ± 6
Lewicka-Nowak[129] 2005	All	73	62.6 ± 9.6	52	NR	NR	NR	16	170 ± 29	22 ± 7
Mair[73] 2005	All	NR	63.9 ± 9.8	31	II or III = 8	III or IV = 92		NR	182 ± 22	21.9 ± 6.9
Molhoek[78] 2002	All	31(78)	64 ± 10	48	0	III or IV = 100		NR	120-240 msec	24 ± 9
Molhoek[79] 2004a	All	51 (85)	65 ± 9	48	0	80	20	50	192.5 ± 26.7	21.5 ± 9.7
Molhoek[80] 2004b	All	57 (77)	64.5 ± 10.5	46	0	85	15	NR	176.6 ± 28.8	22.1 ± 11.3

Table 9. Baseline characteristics of patients in studies included in the effectiveness or safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year Trial Name	Study group	Males n (%)	Age, yr. Mean ± SD or median. (IQR)	Ischemic, %	NYHA class			Other measures		
					II, %	III, %	IV, %	Atrial fibrillation, %	QRS interval, msec mean ± SD or median (IQR)	LVEF, % mean ± SD or median (IQR)
Molhoek[81] 2004c	All	47 (77)	64 ± 11	46	0	84	16	NR	177 ± 30	28 ± 14
Molhoek[82] 2005	All	93 (74)	64 ± 10	54	0	89	11	10	176 ± 25	23 ± 8
Navia[86] 2005	All	31 (76)	68 ± 10	51	37	39	2	NR	186 ± 23	20.0 ± 9.2
Notabartolo[88] 2004	All	39 (80)	66 ± 10	69	0	III or IV = 100		16	158 ± 31	24 ± 9
Pappone[92] 2003	All	102 (76)	64 ± 11	43	0	III or IV = 100		4	153 ± 11	28 ± 6
Penicka[93] 2004	All	NR	71.3 ± 10.4	47	NR	NR	NR	NR	181.5 ± 30.0	25.3 ± 5.6
Pitzalis[94] 2005	All	32 (53.3)	62 ± 10	22	0	100	0	NR	171 ± 22	25 ± 5
Purerfellner[130] 2000a	All	31 (67)	70 ± 10	NR	NR	NR	NR	98	NR	NR
Purerfellner[130] 2000b	All	117 (78)	64 ± 10	30	8	70	21	NR	165 ± 35	NR
Purnode[98] 2004	All	31(72)	67 ± 11	53	7	72	21	79	182 ± 27	24.4 ± 7
Reuter[100] 2002	All	87 (85.3)	64 ± 11	NR	8	62	30	19	184 ± 38	24 ± 8
Rossillo[103] 2004	All	170 (73)	66.2 ± 5.8	61	0	89	11	NR	169.4 ± 33.4	19.0 ± 7.9
Salukhe[104] 2005	All	32 (80)	65 ± 10.5	58	10	83	7	NR	156.4 ± 18.3	35.6 ± 7.7
Teo[111] 2003	All	26 (90)	59.6 ± 12.8	62	0	III or IV = 100		NR	161 ± 21	22 ± 9
Vidal[114] 2006	All	52 (81)	70 ± 8	48	24	65	11	NR	176 ± 26	23 ± 6
Waggoner[115] 2006	All	43 (75)	61 ± 12	33		III or IV = 100		0	180 ± 27	25.5 ± 5
Yu[118] 2002a	All	18 (72)	65 ± 12	36	0	44	56	NR	162 ± 30	27.9 ± 10.2
Yu[120] 2004	All	38 (66)	66.1 ± 11.6	41	0	74	26	NR	154.3 ± 26.6	27.1 ± 10.6

Table 10. Description of studies included in the effectiveness and safety reviews: ICD

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment Primary vs. secondary prevention	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals		
Alter[144] 2005	Germany	Prospective cohort 46 mo. Effectiveness, safety	ICD Primary and secondary	NA	440	NA	440	NA	0	Guidant, Medtronic Transvenous, epicardial	Inappropriate shocks, adverse events, mortality
Antiarrhyth-mics vs. Implantable Defibrillators (AVID) In-vestigators[141] 1997 AVID	United States	RCT parallel 18 mo. Efficacy, safety	ICD Secondary	Amio-darone, Sotalol	1,885	1,016	505	509	2	Guidant, Medtronic, Ventritex, Sulzer Intermedics Transvenous, epicardial	All-cause mortality, QOL, cost, adverse events, time to rehospitalization
Backenkohler[145] 2005	Germany	Prospective cohort 4 yr. Effectiveness, safety	ICD Primary and secondary	NA	245	NA	245	NA	0	NR Transvenous	Inappropriate therapy, incidence of VA therapy, mortality
Bansch[136] 2002 CAT	Germany	RCT parallel 66 mo. Efficacy, safety	ICD Primary	Usual care	104	104	50	54	0	Guidant Ventak® P2, P3, PrX II, CPI Transvenous	All-cause mortality, sustained VT, VT requiring treatment, adverse events, inappropriate shocks

DER = defibrillation energy requirement; EPS = electrophysiological study; ICD = implanted cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; NA = not applicable; NR = not reported; OPT = optimal pharmacological therapy; QOL = quality of life; RCT = randomized controlled trial; RV = right ventricular; VO2 max = maximal oxygen consumption; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia

Table 10. Description of studies included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment Primary vs. secondary prevention	Control	Participants Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals	Device Method of implant	Outcomes
Bardy[140] 2005 SCD-HeFT	United States, Canada	RCT parallel, 3 arms 46 mo. (median) Efficacy	ICD Primary	Amiodarone placebo	NR	2521	829	Amio-daron e = 845, place bo = 847	50	Medtronic 7223 NR	All-cause mortality, inappropriate shocks
Bigger[134] 1997 CABG-Patch	United States, Germany	RCT parallel 32 mo. Efficacy, safety	CABG + ICD Primary	CABG + usual care	1,055	900	446	454	70	Guidant Epicardial	All-cause mortality, time to shock, adverse events
Blangy[146] 2003	France	Retrospective cohort 25 mo. Effectiveness	ICD Primary	NA	283	NA	144 LVEF < 35%	NA	0	NR	All-cause mortality
Bode-Schnurbus[147] 2003	Germany	Prospective cohort 24 mo. Effectiveness, safety	ICD Primary and secondary	NA	603	NA	165	NA	0	Biotronik Phylax 06; Guidant P2/P3/PRx, Mini ™ II; Medtronic 7216, 7218, 7219; Jewel Plus, Ventritex V-100, Contour®; Telectronic Guardian ATP2/3 Transvenus epicardial	Mortality, QRS duration

Table 10. Description of studies included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment Primary vs. secondary prevention	Control	Participants Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals	Device Method of implant	Outcomes
Bokhari[148] 2004 CIDS	Canada	Prospective cohort up to 11 yr. Effectiveness, safety	ICD Secondary	Amiodarone	120	120	120	NA	0	NR	All-cause mortality, side effects of amiodarone, VA recurrence, composite endpoint of total mortality, VA recurrence, discontinuation of amiodarone
Bristow[11] 2004 COMPANION	USA	RCT parallel (OPT vs OPT+CRT vs OPT+CRT+ICD Efficacy, safety	OPT+CRT or OPT+CRT+ ICD Primary	OPT	1520	1520	CRT = 617 CRT+ICD = 595	308	159	Guidant: Contak® TR Contak® CD Transvenous	Time to mortality or hospitalization from any cause
Bruch[149] 2006	Germany	Prospective cohort 1 yr. Effectiveness	ICD Primary and secondary	NA	98	NA	98	NA	0	NR	Cardiac event Mortality from pump failure and/or appropriate therapy
Brunckhorst[150] 2004	Germany	Prospective cohort 12 mo. Effectiveness	ICD Primary	NA	104	NA	104	NA	0	St Jude, Guidant, Medtronic NR	Mortality

Table 10. Description of studies included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment Primary vs. secondary prevention	Control	Participants Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals	Device Method of implant	Outcomes
Buxton[151] 1999 MUSTT	United States, Canada	RCT parallel (antiarrythmic vs. no antiarrythmic therapy) 39 mo. (median) Effectiveness	OPT + EP guided therapy (anti-arrhythmic drug therapy or ICD if drug therapy failed) Primary	OPT	2,202	704	351	353	NR	NR	Cardiac arrest, arrhythmic death, all-cause mortality, sustained VT
Capoferri[152] 2004	Switzerland	Prospective cohort 20 mo. Effectiveness, safety	ICD Primary and secondary	NA	100	NA	100	NA	0	NR	Mortality, inappropriate shocks
Carlsson[192] 2003	Germany	RCT (pooled analysis) NR Safety	ICD Secondary	NA	96	NA	96	NA	0	Guidant Ventak® Mini™ IV, Ventak® VR, Ventak ® Prizm™ VR, Ventak® Prizm™ DR, Ventak® AV III DR; Medtronic Gem VR, Gem DR Transvenous	Success of DER+5J and DER+10J safety margins
Chan[153]	United States	Prospective cohort 5 yr. Effectiveness	ICD Primary and secondary	NA	6,996	NA	1,442	5,554	0	NR	All-cause mortality, cardiovascular mortality

Table 10. Description of studies included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment Primary vs. secondary prevention	Control	Participants Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals	Device Method of implant	Outcomes
Chan[154]	United States (7 centers)	Prospective cohort 27 ± 12 mo. Effectiveness	ICD Primary	NA	395	NA	395	NA	0	NR	All-cause mortality, cause specific mortality, appropriate shock therapy, symptomatic VA
Connolly[142] 2000 CIDS	Canada	RCT parallel 35 mo. Efficacy, safety	ICD Secondary	Amiodarone	NR	659	328	331	NR	NR Transvenous thoracotomy	All-cause mortality, arrhythmic death, adverse events
Cuesta[155] 2003	Spain	Prospective cohort 30 mo. Effectiveness, safety	ICD Primary and secondary	NA	120	NA	120	NA	0	NR Abdominal, transvenous	Antiarrhythmia recurrence, mortality, adverse events
Dorian[193] 2004a ASTRID Investigators	Canada	RCT parallel 12 mo. Effectiveness, safety	ICD Primary	NA	149	149	149	NA	0	Guidant Ventak® 1810, 1820, 1821, 1831 Transvenous	Time to first inappropriate therapy, mortality
Dorian[156] 2004b SHIELD Investigators	United States, Canada, Germany, United Kingdom, Poland, France, Spain, Netherlands, Belgium, Italy	RCT parallel (placebo arm only) 12 mo. Safety	ICD + placebo Primary and secondary	NA	214	214	214	NA	2	NR	All-cause shocks, appropriate shocks for VT/VF

Table 10. Description of studies included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment Primary vs. secondary prevention	Control	Participants Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals	Device Method of implant	Outcomes
Dubner[157] 2005	Argentina, Uruguay, Brazil, Mexico, Chile, Cuba, Venezuela	Retrospective cohort 27 mo. Effectiveness, safety	ICD Secondary	NA	770	NA	770	NA	0	Biotronik NR	All-cause mortality, sudden cardiac death
Duray[158] 2005	Germany	Retrospective cohort 2.2 ± 1.5 yr Effectiveness, safety	ICD Primary and secondary	NA	375	NA	375	NA	0	NR	Mortality, first appropriate therapy
Elhendy[159] 2005	United States	Prospective cohort 2.8 yr. Effectiveness	ICD Primary and secondary	NA	90	NA	90	NA	0	NR	Mortality
Ellenbogen[160] 2003	United States	Prospective cohort 68.6 mo. Effectiveness, safety	ICD NR	NA	74	NA	74	NA	0	Medtronic 7227, 7229, 7271, 7273 NR	Lead failure, mortality
Ermis[161] 2003	United States	Retrospective cohort 15 mo. Effectiveness, safety	ICD Primary and secondary	OPT	310	NA	59	251	0	NR	All-cause mortality
Evonich[162] 2004	United States	Retrospective cohort 6 yr. Effectiveness, safety	ICD Primary and secondary	NA	153	NA	153	NA	0	NR Tranvenous	Appropriate treatment, mortality

Table 10. Description of studies included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment Primary vs. secondary prevention	Control	Participants Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals	Device Method of implant	Outcomes
Friedman[194] 2006	United States	RCT parallel 6 mo. Safety	ICD dual chamber Primary and secondary	ICD ventricular only pacing	400	400	201	199	51	St. Jude Medical	Inappropriately detected SVT episodes; inappropriate treatment, VT/VF sensitivity; arrhythmia-related hospitalizations or clinic visits; early termination rate
Gatzoulis[163] 2005	Greece	Prospective cohort 33 mo. Effectiveness	ICD Primary and secondary	NA	169	NA	169	NA	0	NR Tranvenous	Occurrence of electrical storm, mortality
Greenberg[164] 2002	Israel	Retrospective cohort 2.6 yr. Effectiveness, safety	ICD Primary and secondary	NA	732	NA	732	NA	0	NR	Mortality
Grimm[165] 2002	Germany	Prospective cohort 35 mo. Effectiveness, safety	ICD Primary	NA	101	NA	101	NA	0	Guidant Ventak® P2, Mini™ 2, Mini™ 4, Prizm®, Ventak® AV; Medtronic 7202, 7219-7221, 7223, 7227, 7229, 7271-7273 Transvenous	Appropriate interventions, mortality

Table 10. Description of studies included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment Primary vs. secondary prevention	Control	Participants Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals	Device Method of implant	Outcomes
Grimm[195] 2006	Germany	Retrospective cohort 3.2 ± 2.3 yr Safety	ICD Primary	NA	93	NA	93	NA	0	Medtronic 7220/21/23/27/29/30/31/71/72/74/75/79. Guidant Mini/Prizm/VentakAV/ Contak® H135 Transvenous	To decrease rapid VT using antitachycardia pacing (ATP), inappropriate shocks
Ho[166] 2005	United States	Retrospective cohort 4.4 yr. Effectiveness	ICD Primary and secondary	NA	360	NA	360	NA	0	NR	All-cause mortality
Hohnloser[139] 2004 DINAMIT	Europe, Canada, United States	RCT parallel 30 mo. Efficacy, safety	ICD Primary	OPT	NR	674	332	342	24	NR	All-cause mortality, adverse events
Hreybe[196] 2006	United States	Prospective cohort 4 yr. Safety	ICD Primary and secondary	NA	230	NA	230	NA	0	NR	Inappropriate ICD shocks
Kadish[138] 2004 DEFINITE	United States, Israel	RCT parallel 29 mo. Efficacy, safety	ICD Primary	OPT	NR	458	229	229	6	NR	All-cause mortality, adverse events
Koplan[167] 2006	United States	Retrospective cohort 3.3 yrs Effectiveness	ICD Primary and secondary	NA	348	NA	348	NA	0	NR	All-cause mortality

Table 10. Description of studies included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment Primary vs. secondary prevention	Control	Participants Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals	Device Method of implant	Outcomes
Kuck[143] 2000 CASH	Germany	RCT parallel 3 arms 57 mo. Efficacy, safety	ICD Secondary	Metoprolol, amio-darone	293	288	99	Meto-prolol = 97, Amio-darone = 92	NR	Guidant Ventak® AID, Ventak® AICD, Ventak® P, Ventak® PRx, Ventak® Mini™ Epicardial, endocardial	All-cause mortality, sudden cardiac death
Lampert[168] 2004	United States	Retrospective cohort 2.5 yr Effectiveness	ICD Primary and secondary	NA	650	NA	399	NA	0	Guidant 1705 and beyond NR	Mortality, VT/VF events, differences by sex
Leosdottir[169] 2006	Iceland	Retrospective cohort 10 yr Effectiveness, safety	ICD Secondary	NA	62	NA	62	NA	0	NR Transvenous	Review all ICD implant experience since first implant in 1992
Lickfett[197] 2004	Germany	Retrospective cohort 47 mo. Safety	ICD NR	NA	105	NA	105	NA	0	NR Transvenous	Incidence of venous obstruction
Moss[133] 1996 MADIT	United States, Germany, Italy	RCT parallel 27 mo. Efficacy, safety	ICD Primary	OPT	253	196	95	101	18	Guidant Transthoracic, transvenous	All-cause mortality, arrhythmic death
Moss[135] 2002 MADIT II	United States, Europe	RCT parallel 20 mo. Efficacy, safety	ICD Primary	OPT	NR	1,232	742	490	3	NR Transvenous	All-cause mortality, adverse events
Nazarian[170] 2005	United States	Retrospective cohort 3 yr. Effectiveness	ICD Primary and secondary	NA	94	NA	94	NA	0	NR	Time to rehospitalization and death

Table 10. Description of studies included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment Primary vs. secondary prevention	Control	Participants					Device Method of implant	Outcomes
					Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals		
Niehaus[198] 2003	Germany	Retrospective cohort 12 mo. Safety	ICD Secondary	NA	25	NA	25	NA	0	NR Tranvenous	Implant success, adverse events
Noseworthy[171] 2004	Canada	Retrospective cohort 7 yr. Effectiveness, safety	ICD Primary and secondary	NA	637	NA	212	NA	0	NR Tranvenous epicardial	All-cause mortality, cause specific mortality, inappropriate shocks, adverse events
Parkash[172] 2006	United States	Retrospective cohort 3.2 yr. Effectiveness	ICD Primary and secondary	NA	469	NA	469	NA	0	NR	Mortality
Pires[173] 2002	United States	Retrospective cohort 24 mo. Effectiveness	ICD Primary and secondary	NA	2,030	NA	2,030	NA	0	Angstrom Contour® MD, Photon DR Transvenous	Mortality, arrhythmic events
Pires[174] 2006	United States	Retrospective cohort 22 ± 14 mo. Effectiveness	ICD NR	NA	861	NA	861	NA	26	Medtronic, Guidant, St. Jude Medical, Biotronik Transvenous	Success of anti-tachycardia therapies, mortality
Raitt[175] 2005	United States	RCT (placebo arm only) 10 yr. Effectiveness	ICD Primary	NA	NR	100	100	NA	26	NR	Time to first VT/VF leading to therapy, mortality, hospitalization

Table 10. Description of studies included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment Primary vs. secondary prevention	Control	Participants Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals	Device Method of implant	Outcomes
Raviele[176] 2005 BEST ICD	Italy	RCT (analyzed as prospective cohort) 24 mo. Effectiveness, safety	EPC guided or ICD Secondary	OPT	143	138	79	59	0	NR	All-cause mortality, appropriate/inap-propriate shocks, non-fatal sustained VT
Robin[177] 2006	United States	Retrospective cohort 11 yr. Effectiveness	ICD Primary	NA	585	NA	585	NA	0	NR	First appropriate ICD therapy for VT/VF, mortality
Russo[178] 2003	United States	Prospective cohort 15.7mo. Effectiveness, safety	ICD Primary	NA	51	NA	51	NA	0	NR	Treatment events, inappropriate therapy, mortality
Saba[179] 2003	United States	Retrospective cohort 4 yr. Effectiveness, safety	ICD Primary and secondary	NA	35	NA	35	NA	0	NR	Mortality, adverse events
Saeed[199] 2003	United States	Prospective cohort 8.4 mo. Safety	ICD NR	NA	229	NA	48	NA	0	Guidant Ventak® 1810, 1831, 1820, 1821 NR	Sensing abnormalities in dual-chamber ICD
Sanchez[180] 2005	United States	Case-control NR Effectiveness, safety	ICD Primary and secondary	OPT	102	NA	19	32	0	NR	Mortality, cardiac arrest, appropriate therapy
Sanchez[181] 2006	United States	Retrospective cohort 22 ± 14 mo. Effectiveness, safety	ICD Primary	NA	123	NA	123	NA	0	NR Transvenous	Survival free of appropriate ICD therapy

Table 10. Description of studies included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment Primary vs. secondary prevention	Control	Participants Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals	Device Method of implant	Outcomes
Schaer[182] 2006	Switzerland	Prospective cohort 18 m0. Effectiveness	ICD Primary and secondary	NA	58	NA	58	NA	0	NR	Appropriate therapy, mortality, drug therapy, LVEF
Sears[183] 2004	United States	Prospective cohort 14.3 mo. Effectiveness	ICD Primary	NA	88	NA	88	NA	0	NR	QOL, mortality
Takahashi[184] 2002	United States	Retrospective cohort 12 mo. Effectiveness, safety	ICD NR	NA	178	NA	178	NA	0	Guidant Ventak® Mini™, Ventak® AV; Medtronic Micro Juel, Gem Gem DR; Ventritex Angstrom™, Contour®, Profile Tranvenous	Adverse events requiring surgical correction, comparison of dual vs. single-chamber ICD, mortality
Tandri[185] 2006	United States	Retrospective cohort 23 yr. Effectiveness	ICD Primary and secondary	NA	1382	NA	1382	NA	0	NR Thoracotomy, abdominal, transvenous, endocardial	Appropriate ICD therapy, mortality
Telfer[186] 2002	United States	Retrospective cohort 2.2 yr. Effectiveness, safety	ICD Primary	NA	379	NA	29	NA	2	NR	Mortality, inappropriate therapy

Table 10. Description of studies included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment Primary vs. secondary prevention	Control	Participants Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals	Device Method of implant	Outcomes
Theuns[200] 2004	Netherlands	RCT parallel 12 mo. Safety	ICD Primary and secondary	ICD	NR	60		NA	0	Biotronik achos DR; Guidant Prizm DR NR	Inappropriate ICD therapy for atrial arrhythmias, comparison of dual vs. single-chamber ICD
Theuns[187] 2005b	Netherlands	Prospective cohort 5 yr. Effectiveness, safety	ICD Primary and secondary	NA	127	NA	127	NA	0	Biotronik Guidant ELA Medical Medtronic Transvenous	Mortality
Theuns[201] 2005a	Netherlands	Prospective cohort 4 yr. Safety	ICD Primary and secondary	NA	326	NA	260	NA	0	Biotronik Phylax AV, Tachos DR, Belos® VR-T; ELA Defender IV, Alto DR; Guidant Mini™ IV, Contak® CD, Renewal™ I, Renewal™ II; Medtronic 7227, 7250, 7271, 7272 Transvenous	Inappropriate shocks
Tiroke[202] 2003	Germany	Retrospective cohort 5 yr. Safety	ICD NR	NR	149	NA	149	NA	NR	NR	Inappropriate shocks

Table 10. Description of studies included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial name	Study location	Design Duration Type of outcomes	Treatment Primary vs. secondary prevention	Control	Participants Number enrolled	Number randomized	Number in treatment	Number in control	Number of withdrawals	Device Method of implant	Outcomes
Trappe[188] 2002	Germany	Prospective cohort 28 mo. Effectiveness, safety	ICD NR	NA	410	NA	410	NA	0	NR Epicardial, non-thoracotomy	Mortality, inappropriate shocks
Wase[189] 2004	United States	Retrospective cohort 4 yr. Effectiveness, safety	ICD Primary and secondary	NA	256	95	93	NA	0	NR Transvenous	Mortality
Wilkoff[190] 2006	United States	RCT parallel 12 mo. Effectiveness	ICD EMPIRIC Primary and secondary	ICD TAIL-ORED	900	900	455	455	0	Medtronic	Shock related morbidity [health-care utilization, death, syncope, ED visits]
Zecchin[191] 2004	Italy	Retrospective cohort 24 mo. Effectiveness, safety	ICD Primary and secondary	NA	54	NA	54	NA	0	Biotronik Belos®; Guidant Ventak® Mini™ II, AV II-IV, Prizm™ I, Prizm™ II, Vitality™, Renewal™; Medtronic Jewel II, ATK Gem III, Defender II; St. Jude Medical/ Ventitrex Contour® II NR	Mortality, effectiveness for primary prevention, inappropriate shocks

Table 11. Baseline characteristics of patients in trials included in the effectiveness and safety reviews: ICD

Author Year Trial Name	Study group	Males, n (%)	Age, yr. mean ± SD	Ischemic, %	NYHA class			Other measures			Baseline measures pre/post implantation
					II, %	III, %	IV, %	Atrial fibrillation, %	QRS interval, msec mean ± SD	LVEF, % mean ± SD	
Alter[144] 2005	ICD	357 (81.1)	58 ± 14	48	49	37.3	2	NR	NR	34 ± 15	Pre
Anti-arrhythmics vs. Implantable Defibrillators[141] 1997 AVID	ICD	395 (78)	65 ± 11	81	I or II = 48	7	0	21	116 ± 26	32 ± 13	Pre
	Antiarrhythmics	412 (81)	65 ± 10	81	I or II = 48	12	0	26	117 ± 26	31 ± 13	
Backenkohler[145] 2005	All participants	196 (80)	62.8 ± 0.8	75.1	NR	NR	NR	15.9	NR	35.6 ± 15.4	Pre
	Secondary prevention	157 (78)	63 ± 11	73.8	NR	NR	NR	16	52% ≥ 120 msec	36 ± 16	
	Primary prevention	39 (91)	62 ± 10	81	NR	NR	NR	14	49% ≥ 120 msec	34 ± 12	
Bänsch[136] 2002 CAT	All participants	83 (79.8)	52 ± 11	0	65.3	34.6	0	15.7	108 ± 29	24 ± 7	Pre
	ICD	43 (86)	52 ± 12	0	66.7	33.3	0	20.4	102 ± 29	24 ± 6	
	Control	40 (74.1)	52 ± 10	0	64.1	35.8	0	11.3	114 ± 29	25 ± 8	
Bardy[140] 2005 SCD-HeFT	ICD	639 (77)	60.1 median IQR 51.9-69.2	52	57.4	21.0	Exc	16	NR	24.0 median IQR 19.0-30.0	Pre
	Amiodarone	639 (76)	60.4 median IQR 61.7-68.3	50	54.2	21.5	Exc	17	NR	25.0 median IQR 20.0-30.0	
	Placebo	655 (77)	59.7 median IQR 51.2-67.8	53	60.7	21.4	Exc	14	NR	25.0 median IQR 20.0-30.0	

ICD = implanted cardioverter defibrillator; IQR = interquartile range; NR = not reported

Table 11. Baseline characteristics of patients in trials included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial Name	Study group	Males, n (%)	Age, yr. mean ± SD	Ischemic, %	NYHA class II, %	NYHA class III, %	NYHA class IV, %	Other measures Atrial fibrillation, %	Other measures QRS interval, msec mean ± SD	Other measures LVEF, % mean ± SD	Baseline measures taken pre/post implantation
Bigger[134] 1997 CABG-Patch	CABG+ICD	386 (86.5)	64 ± 9	100	II or III = 71		0	NR	71% ≥100 msec	27 ± 6	Pre
	CABG	373 (82.2)	63 ± 9	100	II or III = 74		0	NR	74% ≥ 100 msec	27 ± 6	
Blangy[146] 2003	Participants with LVEF ≤35%	124 (86.1)	60.5 ± 11.9	72.9	NR	NR	NR	18	NR	27 ± 5	Unclear
Bode-Schnurbus[147] 2003	All participants	132 (80)	61.8 ± 9.7	72.7	0	100	0	NR	85% < 150 msec	32.5 ± 13.6	Unclear
Bokhari[148] 2004 CIDS	ICD	50 (83)	64 ± 9.2	80	I or II = 95	III or IV = 5		NR	NR	33.9 ± 12.5	Pre
	Amiodarone	50 (83)	64 ± 8.7	80	I or II = 95	III or IV = 5		NR	NR	32.1 ± 11.1	
Bristow[11] 2004 COMPANION	CRT + OPT	413 (67)	Median 67	54	Exc	87	13	NR	≥ 120 msec	Median 20	Pre
	CRT+ICD +OPT	399 (67)	Median 66	55	Exc	86	14	NR	≥ 120 msec	Median 22	Pre
	OPT only	213 (69)	Median 68	59	Exc	82	18	NR	≥ 120 msec	Median 22	Pre
Bruch[149] 2006	All participants	67 (80)	60 ± 12	74	2.7 ± 0.5			0	153 ± 39	29 ± 10	Post
Brunckhorst[150] 2004	All participants	97 (93.3)	67 ± 10	100	NR	NR	NR	NR	383 ± 195	35 ± 15	Unclear
Buxton[151] 1999 MUSTT	EP-Antiarrhythmics	316 (90)	67 median IQR 60-72	96	39	24	0	NR	NR	30 median IQR 20-35	Pre
	No Antiarrhythmics	318 (90)	66 median IQR 58-72	93	38	25	0	NR	NR	29 median IQR 22-35	
Capoferri[152] 2004	Secondary prevention	NR	55 ± 13	70	NR	NR	NR	NR	NR	35 ± 13	Pre
	Primary prevention	NR	49 ± 15	67	NR	NR	NR	NR	NR	36 ± 13	

Table 11. Baseline characteristics of patients in trials included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial Name	Study group	Males, n (%)	Age, yr. mean ± SD	Ischemic, %	NYHA class II, %	NYHA class III, %	NYHA class IV, %	Other measures: Atrial fibrillation, %	Other measures: QRS interval, msec mean ± SD	Other measures: LVEF, % mean ± SD	Baseline measures taken pre/post implantation
	All participants	NR	53 ± 13.9	69	NR	NR	NR	NR	NR	35.3 ± 12.9	
Carlsson[192] 2003	All participants	86 (90)	61 ± 10.3	67.7	NR	NR	NR	NR	NR	34.1 ± 13.2	Pre
Chan[153]	ICD	NR	66.2	100	NR	NR	NR	NR	NR	NR	Pre
	Control	NR	68.6	100	NR	NR	NR	NR	NR	NR	
Chan[154]	ICD	339 (86)	66 ± 9.9	100	NR	NR	NR	0	39% > 120ms	26.2 ± 6.0	Pre
Connolly[142] 2000 CIDS	ICD	280 (85.4)	63.3 ± 9.2	82.2	I or II = 37.8	III or IV = 11		NR	NR	34.3 ± 14.5	Pre
	Amiodarone	277 (83.7)	63.8 ± 9.9	82.9	I or II = 39.9	III or IV = 10.6		NR	NR	33.3 ± 14.1	
Cuesta[155] 2003	All participants	115 (95.8)	63.3 ± 9	66.7	NR	III or IV = 22.5		NR	NR	33.7 ± 10.9	Pre
Dorian[193] 2004a ASTRID Investigators	All participants	124 (83.2)	60 ± 13	71.1	51.7	9.5	0	10.7	NR	35 ± 15	Pre
Dorian[156] 2004b SHIELD Investigators	Placebo group	199 (93)	62 ± 12	NR	43	9	Exc	NR	NR	34 ± 14	Pre
Dubner[157] 2005	All participants	578 (75)	60 ± 13	39.7	I or II = 81	III or IV = 19		NR	NR	37.7 ± 14.3	Pre
Duray[158] 2005	All participants	309 (82)	63.6 ± 10	84	43.5	III or IV = 23.5		NR	NR	32.8 ± 11.4	Pre
Elhendy[159] 2005	ICD	63 (70)	65 ± 13	48.9	NR	NR	NR	15.6	NR	33.7 ± 11.9	Post
Ellenbogen[160] 2003	ICD	58 (78.4)	62 ± 16	65	NR	NR	NR	NR	NR	34 ± 11	Unclear

Table 11. Baseline characteristics of patients in trials included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial Name	Study group	Males, n (%)	Age, yr. mean ± SD	Ischemic, %	NYHA class II, %	NYHA class III, %	NYHA class IV, %	Other measures: Atrial fibrillation, %	Other measures: QRS interval, msec mean ± SD	Other measures: LVEF, % mean ± SD	Baseline measures taken pre/post implantation
Ermis[161] 2003	All participants	231 (74.5)	49.3 ± 11.9	45.2	15.8	58.4	18.7	NR	NR	NR	Unclear
	ICD	40 (67.8)	51.1 ± 9.9	44.1	13.6	61	25.4	NR	NR	18.7 ± 6.8	
	No ICD	191 (76.1)	48.9 ± 12.3	45.4	16.3	57.8	17.1	NR	NR	20.8 ± 9.8	
Evonich[162] 2004	All participants	122 (79.7)	65.6 ± 12.6	64.4	34	44	0	NR	NR	25.4 ± 9.01	Pre
Friedman[194] 2006	ICD (dual chamber)	163 (81)	64.3 ± 11.3	81	NR	NR	NR	18	NR	32 ± 13	Pre
	ICD (ventricular only)	156 (78)	65.1 ± 11.3	81	NR	NR	NR	20	NR	32 ± 13	
Gatzoulis[163] 2005	All participants	142 (84)	59.9 ± 12.5	60	NR	NR	NR	NR	NR	34.2 ± 14	Pre
	Primary prevention	18 (100)	57 ± 18	78	NR	NR	NR	NR	NR	28 ± 10	
	Secondary prevention	124 (82.1)	61 ± 12	58	NR	NR	NR	NR	NR	35 ± 14	
Greenberg[164] 2002	All participants	630 (86)	62.6 ± 12.4	79	NR	NR	NR	NR	NR	29.2 ± 11.2	Unclear
Grimm[165] 2002	All participants	82 (81)	51 ± 14	NR	61	35	0	21	NR	25 ± 8	Unclear
Grimm[195] 2006	All participants	83 (89)	56 ± 13	34.4	38	58	4	22 ± 7	NR	NR	Pre
Ho[166] 2005	ICD	288 (80)	62 ± 13	68	NR	NR	NR	23	NR	33 ± 17	Unclear
Hohnloser[139] 2004 DINAMIT	ICD	252 (75.9)	61.5 ± 10.9	100	95	40	Exc	NR	107 ± 24	28 ± 5	Pre
	CMT	262 (76.6)	62.1 ± 10.6	100	98	49	Exc	NR	105 ± 23	28 ± 5	
Hreybe[196] 2006	All participants	181(79)	63 ± 14	75	NR	III or IV = 45		17	123 ± 34	26 ± 13	Pre

Table 11. Baseline characteristics of patients in trials included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial Name	Study group	Males, n (%)	Age, yr. mean ± SD	Ischemic, %	NYHA class II, %	NYHA class III, %	NYHA class IV, %	Other measures: Atrial fibrillation, %	Other measures: QRS interval, msec mean ± SD	Other measures: LVEF, % mean ± SD	Baseline measures taken pre/post implantation
Kadish[138] 2004 DEFINITE	All participants	326 (71.2)	58.3 range 20.3 - 83.9	0	57	21	Exc	24.5	115.1 range 78-196	21.4 range 7-35	Pre
	ICD	166 (72.5)	58.4 range 20.3-83.9	0	54	21	Exc	22.7	114.7 range 78-196	20.9 range 7-35	
	Control	160 (69.9)	58.1 range 21.8-78.7	0	61	21	Exc	26.2	115 range 79-192	21.8 range 10-35	
Koplan[167] 2006	All participants	285 (82)	70 ± 8	80.6	NR	NR	NR	NR	51% > 120ms	30 ± 11	Pre
Kuck[143] 2000 CASH	ICD	78 (79)	58 ± 11	73	59	18	0	NR	NR	46 ± 19	Pre
	Antarrhythmics	152 (80)	57.5 ± 10	74	59	18	0	NR	NR	46 ± 17	
Lampert[168] 2004	All participants	340 (85)	67.4 SE ± 1.3	100	NR	NR	NR	NR	> 120 = 24%	31.6 SE ± 1.7	Pre
Leosdottir[169] 2006	All participants	44 (71)	58 ± 14	62	NR	NR	NR	NR	NR	40% ≤ 40	Pre
Lickfett[197] 2004	All participants	87 (83)	NR	65	NR	NR	NR	NR	NR	31 ± 7	Unclear
Moss[133] 1996 MADIT	ICD	87 (92)	62 ± 9	34	II or III = 63		0	NR	NR	27 ± 7	Pre
	CMT	93 (92)	64 ± 9	29	II or III = 67		0	NR	NR	25 ± 7	
Moss[135] 2002 MADIT II	ICD	623 (84)	64 ± 10	100	35	25	5	9	≥ 120 = 50%	23 ± 5	Pre
	Conventional treatment	417 (85)	65 ± 10	100	34	23	4	8	≥ 120 = 51%	23 ± 6	
Nazarian[170] 2005	All participants	69(73)	55 ± 11	45	20	35	33	27	NR	25 ± 10	Pre
Niehaus[198] 2003	All participants	20 (80)	60.8 ± 12	72	NR	NR	NR	28	NR	35 ± 14	Pre

Table 11. Baseline characteristics of patients in trials included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial Name	Study group	Males, n (%)	Age, yr. mean ± SD	Ischemic, %	NYHA class II, %	NYHA class III, %	NYHA class IV, %	Other measures Atrial fibrillation, %	Other measures QRS interval, msec mean ± SD	Other measures LVEF, % mean ± SD	Baseline measures taken pre/post implantation
Noseworthy[171] 2004	All participants	169 (80)	74.9 ± 4.4	80	I or II = 90.1	NR	NR	NR	NR	34.1 ± 12.1	Pre
Parkash[172] 2006	All participants	356 (76)	65 ± 15	62	≤ II = 81	III or IV = 19		31	NR	35 ± 16	Pre
Pires[173] 2002	ICD	1654 (81.5)	64.4 ± 12.4	78	55	III or IV = 19		NR	NR	33.7 ± 13.8	Pre
Piers[174] 2006	All participants	641 (77)	65.4 ± 12.7	57	NR	NR	NR	NR	NR	24.1 ± 10.4	
Raitt[175] 2005	ICD (placebo arm)	86 (86)	62 ± 13	71	14	50	8	NR	NR	34 ± 15	Pre
Raviele[176] 2005 BEST-ICD	All participants	98 (71)	66.5 ± 9.6	100	NR	NR	Exc	22	> 114 msec	31.1 ± 4.1	Pre
Robin[177] 2006	All participants	462 (79)	63 ± 15	60	NR	NR	NR	10	NR	33 ± 15	Pre
Russo[178] 2003	All participants	41 (92)	70 ± 9 range 41-98	100	NR	NR	NR	NR	NR	29 ± 9	Pre
Saba[179] 2003	ICD	29 (82.9)	51 ± 12	20	Exc	III or IV = 100		17	NR	21.9 ± 6.8	Unclear
	Control	114 (71.7)	51 ± 12	73	Exc	III or IV = 100		26	NR	22.1 ± 9.7	
Saeed[199] 2003	All participants	38 (79)	64 ± 12	63	42	23	0	NR	NR	33.6 ± 14.8	Unclear
Sanchez[180] 2005	ICD	15 (79)	60 ± 16	47	NR	NR	Exc	NR	NR	27 ± 7	Unclear
	Conventional therapy	26 (81)	61 ± 13	59	NR	NR	Exc	NR	NR	27 ± 6	
Sanchez[181] 2006	All participants	93 (89)	66.7 ± 9.3	100	NR	NR	NR	NR	119 ± 12	26.6 ± 7.7	Pre
Schaer[182] 2006	All participants	50 (86)	56.4 ± 12.7	0	NR	NR	NR	NR	NR	25 ± 8.8	Pre

Table 11. Baseline characteristics of patients in trials included in the effectiveness and safety reviews: ICD (continued)

Author Year Trial Name	Study group	Males, n (%)	Age, yr. mean ± SD	Ischemic, %	NYHA class II, %	NYHA class III, %	NYHA class IV, %	Other measures: Atrial fibrillation, %	Other measures: QRS interval, msec mean ± SD	Other measures: LVEF, % mean ± SD	Baseline measures taken pre/post implantation
Sears[183] 2004	All participants	73 (83)	65 ± 13	69	NR	NR	NR	NR	NR	30.5 ± 16.4	Unclear
Strickberger[137] 2003 AMIOVIRT	All	72 (70)	59 ± 11	0	64	19	0	NR	NR	22.5 ± 9	Pre
	ICD	34 (67)	58 ± 11	0	64	16	0	NR	NR	22 ± 10	
	Amiodarone	38 (74)	60 ± 12	0	63	24	0	NR	NR	23 ± 8	
Takahashi[184] 2002	All participants	144 (81)	64	61	NR	NR	NR	NR	NR	33 ± 15	Unclear
Tandri[185] 2006	All participants	1050 (76)	62 ± 11	72	38	III or IV = 23		NR	NR	33 ± 11	Pre
Telfer[186] 2002	ICD	26 (96)	59 ± 13	NR	NR	NR	NR	NR	NR	22 ± 7	Pre
Theuns[200] 2004	ICD-single	24 (83)	57 ± 17	72	NR	NR	NR	27.6	NR	29 ± 11	Pre
	ICD-dual	23 (74)	61 ± 10	84	NR	NR	NR	22.6	NR	31 ± 10	
	All participants	47 (78)	59 ± 14	78	NR	NR	NR	25	NR	30 ± 10.5	
Theuns[201] 2005a	All participants	216 (83)	60 ± 13	71	NR	NR	NR	29	NR	31 ± 14	Pre
Theuns[187] 2005b	All participants	105 (83)	59 ± 11	72	≤II = 72	III or IV = 28		0	NR	35 ± 15	Pre
Tiroke[202] 2003	All participants	136 (91.3)	62 range 51-72	77	42	38	2	NR	NR	NR	Unclear
Trappe[188] 2002	All participants	368 (89.8)	57 ± 11	NR	I or II = 12 II = 37	II or III = 29 III = 22	0	NR	NR	NR	Pre
Wase[189] 2004	ICD	66 (71)	66.5 ± 12.2	NR	NR	NR	NR	NR	NR	29 ± 12.5	Pre (at implantation)
Wilkoff[190] 2006	All participants	731 (81.2)	65 ± 12.6	69.4	≤II = 47	III or IV = 14.5		0	NR	32.0 ± 12.7	Post
Zecchin[191] 2004	All participants	43 (79.6)	52.5 ± 17.2	0	I or II = 76	NR	NR	NR	NR	26.5 ± 7.6	Pre (at implantation)

Table 12. Description of additional studies included in the ICD safety review for peri-implant complications only

Author Year	Study location	Design Duration	Intervention	Participants Treatment (n)	Participants Control (n)	Device Method of implant	Data or patient source	Primary or Secondary prevention
Al-khatib[204] 2005	United States	Retrospective cohort Registry data 2 yr. 9 mo.	ICD	9,854	NA	Defender III, IV ELA Medical	20% of Part B Medicare files & 100% MEDPAR files January 1999-September 2001	NR (61% urgent or emergency implants)
Bänsch[205] 2004	Germany	RCT crossover 1 yr.	Dual-chamber vs. single-chamber ICD	102	NA	NR	Multiple centers in Germany	Mixed
Boriani[206] 2003	Italy	RCT crossover 6 mo.	ICD-atrial enhancements on v. off	89	NA	Guidant NR	Multiple centers in Europe and Canada	Primary
Brockes[207] 2002	Switzerland	Retrospective cohort 5 yr.	ICD	130	NA	NR Thoracotomy, subxiphoid, transvenous	One center	Secondary
Gradaus[208] 2003	Germany	Retrospective cohort Registry data 2yr. 10 mo.	ICD	3,344	NA	NR Transvenous	European Registry of Implantable Defibrillators (EURID)	Mixed
Hlatky[209] 2002	United States	Retrospective cohort Registry data 9 yr.	ICD	22,565	NA	NR	Health Care Finance Administration for Medicare Beneficiaries files Jan. 1984-Sept. 1995; California Statewide Health Planning and Development hospital discharge database, 1991-1995	Mixed
Nademanee[210]	Thailand, United States	RCT parallel 3 yr.	ICD vs. propanalol	47	Not included	NR Guidant Transvenous	NR	Secondary

ICD = implanted cardioverter defibrillator; MEDPAR = Medicare Provider Analysis and Review; NA = not applicable; NR = not reported; RCT = randomized controlled trial

Table 12. Description of additional studies included in the ICD safety review for peri-implant complications only (continued)

Author Year	Study location	Design Duration	Intervention	Participants Treatment (n)	Participants Control (n)	Device Method of implant	Data or patient source	Primary or Secondary prevention
Reynolds[203] 2006	United States	Retrospective cohort 1 yr.	ICD	30,984	NA	NR	MEDPAR files fiscal yr. 2003	Mixed
Rosenqvist[211] 1998	Europe	Prospective cohort 4 mo.	ICD	778	NA	Medtronic 7219 C & D Pectoral or abdominal	63 European centers	Mixed
Schläpfer[212] 2002	Switzerland	Prospective cohort 63 ± 30 mo.	ICD vs. amiodarone	41	Not included	NR Epicardial, non-thoracotomy	One center	Secondary
Vollmann[213] 2003	Europe, United States, Canada	RCT parallel 1 year	ICD Single-chamber vs. dual-chamber	542	NA combined groups	Medtronic 6942 or 6944 Pectoral	48 centers	Mixed
Wiegand[214] 2004	Germany	Retrospective cohort 12 yr.	ICD	372	Not included	NR Sub-pectoral	Single center	Mixed

Table 13. Baseline characteristics of patients in additional studies included in the ICD safety review for peri-implant complications only

Author Year Trial name	Study Group	Males, n (%)	Mean age, yr. mean ± SD	Ischemic, %	NYHA class				Other measures		Inclusion criteria
					I%	II, %	III, %	IV, %	Atrial fibrillation %	LVEF, mean ± SD	
Al-khatib[204] 2005	ICD	7,724 (78.4)	NR	NR	NR	NR	NR	NR	NR	NR	ICD for any indication
Bänsch[205] 2004	ICD	NR	NR	82.4	24.5	58.8	16.6	0	NR	37.5 ± 13.5	Spontaneous or inducible monomorphic VTs with a cycle length > = 300 ms
Boriani[206] 2003	ICD	69 (77.5)	64.1 ± 12.5	60	32	60	NR	NR	100	46 ± 16	History of persistent or paroxysmal AF or AT in past yr.
Brockes[207] 2002	ICD	115 (88.5)	61 ± 11	100	NR	NR	NR	NR	NR	36 ± 12	CAD patients undergoing ICD implant
Gradaus[208] 2003	ICD	2,682 (80.2)	61.1 ± 12.1	64.6	19.3	54.3	20.9	1.1	NR	70.6% > 30	ICD patients in EURID registry Jan. 1998–Oct. 2000
Hlatky[209] 2002	ICD	18,255 (80.9)	71.5 ± NR	6	NR	NR	NR	NR	NR	NR	≥65 yr, ICD9 37.94 (implantation or replacement of ICD).
Nademanee[210] 2003 DEBUT	ICD	45 (95.7)	40.9 ± 11	NR	100	0	0	0	NR	66.1 ± 10.3	SUDS survivor or probable SUDS patient
Reynolds[203] 2006	ICD	24,401 (78.8)	NR	NR	NR	NR	NR	NR	NR	NR	ICD9 37.94 (implantation or replacement of ICD) or ICD9 00.51 (CRT+ICD)
Rosenqvist[211] 1998	ICD	635 (81.6)	58 ± 13	58	22.6	53.3	23.1	0.9	NR	39 ± 17	Patients with abdominal or pectoral ICD implant

AF = atrial fibrillation; AT = atrial tachycardia; CAD = coronary artery disease; CRT = cardiac resychronization therapy; EURID = European Registry of Implantable Defibrillators; ICD = implanted cardioverter defibrillator; ICD9 = International Classification of Diseases, 9th Revision; MI = myocardial infarction; NR = not reported, SUDS = Sudden Unexplained Death Syndrome, VF = ventricular fibrillation; VT = ventricular tachycardia,

Table 13. Baseline characteristics of patients in additional studies included in the ICD safety review for peri-implant complications only (continued)

Author Year Trial name	Study Group	Males, n (%)	Mean age, yr. mean ± SD	Ischemic, %	NYHA class				Other measures		Inclusion criteria
					I%	II, %	III, %	IV, %	Atrial fibrillation %	LVEF, mean ± SD	
Schläpfer[212] 2002	ICD	78 (93)	60 ± 10	NR	NR	NR	III or IV = 23		NR	36 ± 11	Age 20-80 yr. with MI and first episode of sustained VT or VF
Vollmann[213] 2003	ICD	452 (83.4)	64.8 ± 10.9	79	NR	NR	NR	NR	NR	35.5 ± 14.4	Indication for conventional ICD; pectoral implantation was possible
Wiegand[214] 2004	ICD	306 (82.3)	62.5 ± 11	71	NR	NR	NR	NR	28	NR	Pectoral implantation; generator replacements or lead revision

Table 14. Methodological quality of randomized trials included in the efficacy review: CRT alone or combined CRT-ICD devices

Author Year Trial name	Randomization		Double-blinding		Description of withdrawals/ dropouts	Jadad score	Allocation concealment
	Stated	Method described	Stated	Method described			
Abraham 2002[4] MIRACLE	Yes	Adequate	Yes	Adequate	Adequate	5	Clear
Cazeau 2001[5] MUSTIC-SR	Yes	Adequate	No	NR	Adequate	3	Unclear
Young 2003[6] MIRACLE-ICD	Yes	Unclear	Yes	Adequate	Adequate	4	Unclear
Leclercq 2002[7] MUSTIC-AF	Yes	Adequate	No	NR	Adequate	3	Unclear
Auricchio 2002[8] PATH-CHF	Yes	Unclear	Yes	Adequate	Adequate	4	Unclear
Higgins[9] 2003 CONTAK-CD	Yes	Unclear	No	NR	Adequate	2	Unclear
Leclercq[10] 2003 RD-CHF	Yes	NA	No	NA	NA	1	NA
Bristow[11] 2004 COMPANION	Yes	Unclear	No	NR	Adequate	2	Unclear
Auricchio[12] 2003 PATH-CHF II	Yes	Unclear	No	NR	Adequate	2	Unclear
Kindermann[13] 2006 HOBIPACE	Yes	Unclear	No	NR	Adequate	2	Unclear
Abraham[14] 2004 MIRACLE ICD II	Yes	Unclear	Yes	Adequate	Adequate	4	Clear
Cleland[15] 2005 CARE-HF	Yes	Unclear	No	NR	Adequate	2	Unclear
St. Jude[16] 2005 VecTOR	Yes	Unclear	Yes	Unclear	Adequate	3	Unclear
St. Jude[17] 2004a RHYTHM ICD	Yes	Unclear	Yes	Unclear	Adequate	3	Unclear

NA = not available; NR = not reported

Table 15. Methodological quality of randomized trials included in the efficacy review: ICD

Author Year Trial name	Randomization		Double blinding		Description of withdrawals/ dropouts	Jadad score	Allocation concealment
	Stated	Method described	Stated	Method described			
Moss[133] 1996 MADIT	Yes	Clear	No	NR	Unclear	2	Unclear
Bigger[134] 1997 CABG-Patch	Yes	Clear	No	NR	Adequate	3	Adequate
Moss[135] 2002 MADIT II	Yes	Unclear	No	NR	Adequate	2	Unclear
Bänsch[136] 2002 CAT	Yes	Unclear	No	NR	Unclear	1	Adequate
Strickberger[137] 2003 AMIOVIRT	Yes	Unclear	No	NR	Adequate	2	Unclear
Kadish[138] 2004 DEFINITE	Yes	Unclear	No	NR	Adequate	2	Unclear
Bristow[11] 2004 COMPANION	Yes	Unclear	No	NR	Adequate	2	Unclear
Hohnloser[139] 2004 DINAMIT	Yes	Clear	No	NR	Adequate	3	Adequate
Bardy[140] 2005 SCD-HeFT	Yes	Unclear	Yes	NR	Adequate	3	Unclear
AVID Investigators[141] 1997 AVID	Yes	Unclear	No	NR	Unclear	1	Unclear
Connolly[142] 2000 CIDS	Yes	Clear	No	NR	Unclear	2	Unclear
Kuck[143] 2000 CASH	Yes	Unclear	No	NR	Unclear	1	Unclear

NR = not reported

Table 16. Methodological quality assessment of included studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices

Author Year	Downs and Black quality score						Funding
	Reporting	External validity	Internal validity (bias)	Internal validity (confounding)	Power	Overall	
	Maximum 11	Maximum 3	Maximum 7	Maximum 6	Maximum 2	Maximum 29	
Achilli[18] 2003	11	3	6	4	1	25	NR
Adamson[19] 2004	11	1	5	3	1	21	NR
Albertsen[20] 2005	11	3	5	3	1	23	Foundation
Alonso[21] 1999	10	3	5	4	1	23	NR
Ammann[22] 2004	10	3	5	4	1	23	NR
Ansalone[23] 2002	6	1	5	2	1	15	NR
Aranda[24] 2005	9	3	5	4	1	22	NR
Auricchio[25] 2002b	10	1	5	3	1	20	Private industry
Azizi [26] 2006	8	3	5	3	1	20	NR
Baker[27] 2002	11	1	4	4	1	21	Private industry
Bax[28] 2003	8	2	5	3	1	19	Foundation
Bax[29] 2004	9	3	6	4	1	23	NR
Bleeker[30] 2005a	9	3	6	4	1	23	Foundation
Bleeker[31] 2005b	10	3	6	3	1	23	Foundation
Bleeker[32] 2006	9	3	6	4	1	23	Foundation
Bocchiardo[33] 2000	8	1	3	4	1	17	NR
Bonanno[34] 2004	10	1	4	4	0	19	NR
Bordachar[35] 2004	11	2	5	4	1	23	NR
Boriani[36] 2006a	11	2	5	5	2	25	Private industry
Boriani[37] 2006b	9	3	5	4	1	22	None
Boriani[38] 2006c	10	2	5	4	1	22	Foundation
Braun[39] 2005	10	2	5	4	1	22	None
Braunschweig[40] 2005	9	1	5	2	1	18	Private industry
Cazeau[41] 2003	6	0	3	3	1	13	NR
Chalil[42] 2006	10	3	5	4	1	23	Private industry
Chan[43] 2003	7	2	5	4	1	19	NR
Chugh[123] 2005	10	3	4	4	1	22	NR
Cowburn[44] 2005	8	3	4	4	1	20	Foundation
Da Costa[45] 2006	11	1	6	4	1	23	NR
Daubert[46] 1998	11	1	4	3	1	20	NR
Davis[47] 2005	10	3	5	4	1	23	NR

NR = not reported

Table 16. Methodological quality assessment of included studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Downs and Black quality score							
Author Year	**Reporting**	**External validity**	**Internal validity (bias)**	**Internal validity (confounding)**	**Power**	**Overall**	**Funding**
	Maximum 11	**Maximum 3**	**Maximum 7**	**Maximum 6**	**Maximum 2**	**Maximum 29**	
de Cock[124] 2004	4	3	5	3	1	16	NR
De Martino[125] 2004	9	3	5	5	2	24	NR
De Martino[126] 2005	10	3	5	4	1	23	NR
De Sisti[48] 2005	11	1	5	2	1	20	NR
Diaz-Infante[49] 2005	11	3	5	4	1	24	Private industry
Dixon[50] 2004	10	1	5	4	1	21	NR
Duncan[51] 2006	10	1	6	3	1	21	Internal
Ellery[52] 2005	8	1	4	2	1	16	Private industry
Ermis[53] 2004	11	3	5	4	1	24	NR
Fung[54] 2005	10	3	5	4	1	23	NR
Gaita[55] 2000	8	2	4	4	1	19	NR
Galvao[56] 2002	10	3	5	4	1	23	NR
Gasparini[57] 2003a	9	2	5	2	1	19	NR
Gasparini[127] 2005	10	3	5	3	0	21	NR
Gras[58] 2002	9	1	5	1	1	17	NR
Hernandez[59] 2004	8	1	3	1	0	13	Private industry
Hua[60] 2006	8	1	5	2	1	17	NR
Kautzner[128] 2004	10	2	5	4	1	22	Government
Kies[128] 2005	9	3	5	4	1	22	Private industry
Kies[62] 2006	9	3	5	2	1	20	Foundation
Koos[63] 2004	11	1	5	4	1	22	NR
Krahn[64] 2002	10	3	5	4	0	22	Foundation
Kuhlkamp[65] 2002	11	1	5	3	0	20	Private industry
Leclercq[66] 2000	10	2	5	2	0	19	NR
Lecoq[68] 2005	10	2	4	4	1	21	NR
Lenom[69] 2005	5	0	2	0	0	7	NR
Leon[70] 2005	11	1	5	3	1	21	Private industry
Lindner[71] 2005	9	2	5	4	1	21	NR
Macioce[72] 2005	9	1	5	1	1	17	NR
Mair[73] 2005	10	1	4	4	1	20	NR
Mangiavacchi[74] 2006	9	1	5	3	1	19	NR
Marai[75] 2006	9	3	5	1	1	19	NR
Mascioli[76] 2002	8	2	5	4	1	20	NR
Mele[77] 2006	10	1	6	2	1	20	Private industry

Table 16. Methodological quality assessment of included studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year	Downs and Black quality score						Funding
	Reporting	External validity	Internal validity (bias)	Internal validity (confounding)	Power	Overall	
	Maximum 11	Maximum 3	Maximum 7	Maximum 6	Maximum 2	Maximum 29	
Molhoek[78] 2002	10	2	5	3	1	21	NR
Molhoek[79] 2004a	9	3	5	4	1	22	NR
Molhoek[80] 2004b	9	3	5	4	1	22	NR
Molhoek[81] 2004	9	3	5	4	0	21	NR
Molhoek[82] 2005	10	1	5	3	1	20	NR
Mortensen[83] 2004	10	1	5	4	2	22	Private industry
Murphy[84] 2006	9	1	5	4	1	20	NR
Navia[86] 2005	11	3	5	4	1	24	NR
Niu[87] 2006	5	3	5	1	1	15	NR
Notabartolo[88] 2004	10	3	5	4	1	23	NR
O'Donnell[89] 2005	7	3	6	4	1	21	NR
Oliva[90] 2005	7	1	2	1	1	12	NR
Ollitrault[91] 2003	7	1	4	0	1	13	NR
Pappone[92] 2003	10	3	5	4	1	23	NR
Penicka[93] 2004	10	3	6	4	1	24	Foundation
Pitzalis[94] 2005	9	3	5	4	1	22	NR
Porciani[95] 2006a	9	1	5	3	1	19	NR
Porciani[96] 2006b	8	3	5	3	1	20	NR
Puglisi[97] 2004	11	3	5	3	1	23	NR
Purerfellner[130] 2000	7	2	5	3	1	23	NR
Purnode[98] 2004	4	1	2	0	1	8	NR
Reuter[99] 2000	9	1	5	2	1	18	NR
Reuter[100] 2002	11	3	5	3	1	23	NR
Ricci[101] 2002	8	1	3	2	1	15	NR
Ritter[102] 2006	10	1	5	4	1	21	NR
Romeyer-Bouchard[131] 2005	10	1	5	1	0	17	NR
Rossillo[103] 2004	10	3	5	3	1	22	NR
Salukhe[104] 2005	10	3	7	4	1	25	NR
Sawhney[105] 2004	11	2	6	5	1	25	NR
Saxon[106] 2006	10	1	5	2	0	18	Private industry
Schuchert[132] 2004	10	1	5	4	1	21	NR
Sogaard[107] 2002	9	3	5	4	1	22	NR
Stahlberg[108] 2005	11	3	5	4	1	24	Foundation
St Jude[17] 2004	11	2	5	4	0	22	Private industry
Taieb[109] 2002	3	0	0	1	1	5	NR

Table 16. Methodological quality assessment of included studies in the effectiveness and safety reviews: CRT alone or combined CRT-ICD devices (continued)

Author Year	Downs and Black quality score						Funding
	Reporting	External validity	Internal validity (bias)	Internal validity (confounding)	Power	Overall	
	Maximum 11	Maximum 3	Maximum 7	Maximum 6	Maximum 2	Maximum 29	
Tedrow[110] 2006	9	3	5	4	1	22	NR
Teo[111] 2003	10	3	4	3	1	21	NR
Theuns[112] 2005	9	1	5	2	1	18	NR
Toussaint[113] 2003	10	3	5	4	1	23	NR
Vidal[114] 2006	9	1	6	3	1	20	Spanish Society of Cardiology
Waggoner[115] 2006	8	1	5	4	1	19	Government
Witte[116] 2006	8	1	6	3	1	19	Private industry
Ypenburg[117] 2006	11	3	5	4	1	24	NR
Yu[118] 2002	9	3	5	3	1	21	Private industry
Yu[119] 2003	10	1	5	4	1	21	NR
Yu[120] 2004	9	1	5	4	1	20	NR
Yu[121] 2005	10	1	6	3	1	21	NR
Zhang[122] 2006	10	1	5	2	1	19	Li Ka Shing Institute of Health Sciences

Table 17. Methodological quality assessment of included studies in the effectiveness and safety reviews: ICD alone

Author Year	Downs and Black quality score						Funding
	Reporting	External validity	Internal validity (bias)	Internal validity (confounding)	Power	Overall	
	Maximum 11	Maximum 3	Maximum 7	Maximum 6	Maximum 2	Maximum 29	
Alter[144] 2005	10	3	4	4	1	22	NR
Backenkohler[145] 2005	10	3	5	4	1	23	NR
Blangy[146] 2003	4	0	2	0	1	7	NR
Bode-Schnurbus[147] 2004	10	3	5	4	1	23	Foundation
Bokhari[148] 2004	10	2	5	5	1	23	NR
Bruch[149] 2006	8	3	6	4	1	22	NR
Brunckhorst[150] 2004	0	2	0	0	0	2	NR
Buxton[151] 1999	10	3	6	5	2	26	Private industry
Capoferri[152] 2004	9	2	5	4	1	21	NR
Carlsson[192] 2003	10	3	5	5	2	25	NR
Chan[153] 2005	8	3	5	4	1	21	NR
Chan[154] 2006	10	3	5	3	1	22	Private industry, government
Cuesta[155] 2003	10	3	5	4	0	22	Foundation
Dorian[193] 2004a	11	2	7	6	2	28	Private industry
Dorian[156] 2004b	11	2	7	5	2	27	Private industry
Dubner[157] 2005	10	3	5	4	1	23	NR
Duray[158] 2005	10	3	5	4	1	23	NR
Elhendy[159] 2005	11	3	5	4	1	24	NR
Ellenbogen[160] 2003	10	1	5	4	0	20	Private industry
Ermis[161] 2003	10	3	5	4	1	23	Foundation
Evonich[162] 2004	11	3	5	4	1	24	NR
Friedman[194] 2006	10	1	6	6	2	25	Private industry
Gatzoulis[163] 2005	10	3	5	4	1	23	NR
Greenberg[164] 2002	9	3	5	4	1	22	NR
Grimm[165] 2002	11	1	5	4	1	22	NR
Grimm[195] 2006	10	1	5	3	1	20	NR
Ho[166] 2005	10	3	5	4	1	23	NR

NR = not reported

Table 17. Methodological quality assessment of included studies in the effectiveness and safety reviews: ICD alone (continued)

Author Year	Downs and Black quality score						Funding
	Reporting	External validity	Internal validity (bias)	Internal validity (confounding)	Power	Overall	
	Maximum 11	Maximum 3	Maximum 7	Maximum 6	Maximum 2	Maximum 29	
Hreybe[196] 2006	9	3	5	4	1	22	NR
Koplan[167] 2006	9	3	5	4	1	22	NR
Lampert[168] 2004	9	3	5	4	1	22	NR
Leosdottir[169] 2006	9	3	5	4	1	22	NR
Lickfett[197] 2004	11	3	4	3	1	22	NR
Nazarian[170] 2005	7	3	5	4	1	20	NR
Niehaus[198] 2003	10	1	5	3	1	20	Private industry
Noseworthy[171] 2004	11	3	5	4	1	24	NR
Parkash[172] 2006	9	3	5	4	1	22	NR
Pires[173] 2002	9	1	5	2	1	18	NR
Pires[174] 2006	10	3	5	4	1	23	NR
Raitt[175] 2005	10	2	7	5	2	26	Private industry, government
Raviele[176] 2005	10	2	5	5	1	23	Private industry
Robin[177] 2006	10	2	5	4	1	22	Private industry, government
Russo[178] 2003	7	2	5	4	0	18	NR
Saba[179] 2003	10	3	5	4	1	23	NR
Saeed[199] 2003	11	2	4	2	1	20	NR
Sanchez[180] 2005	8	3	5	4	1	21	NR
Sanchez[181] 2006	11	3	6	4	1	25	NR
Schaer[182] 2006	7	3	5	4	1	20	NR
Sears[183] 2004	6	1	4	3	1	15	NR
Takahashi[184] 2002	11	3	4	4	1	23	NR
Tandri[185] 2006	10	3	5	4	1	23	Private industry
Telfer[186] 2002	10	1	5	2	0	18	NR
Theuns[200] 2004	9	3	4	6	2	24	Private industry
Theuns[201] 2005a	10	2	5	4	1	22	NR
Theuns[187] 2005b	9	3	5	4	1	22	NR
Wase[189] 2004	9	3	5	4	1	22	NR
Wilkoff[190] 2006	10	3	6	6	2	27	Private industry
Zecchin[191] 2004	10	1	5	3	1	20	NR

Table 18. Methodological quality assessment of additional studies included in the ICD safety review for peri-implant complications only

Author Year	Downs and Black quality score: Reporting	External validity	Internal validity (bias)	Internal validity (confounding)	Power	Overall	Funding
	Maximum 11	Maximum 3	Maximum 7	Maximum 6	Maximum 2	Maximum 29	
Al-Khatib[204] 2005	10	3	5	3	1	22	Private Industry
Bänsch[205] 2004	9	1	6	4	2	22	Private Industry
Boriani[206] 2003	10	2	5	3	0	20	NR
Brockes[207] 2002	9	1	5	3	0	18	NR
Gradaus[208] 2003	9	3	5	2	1	20	NR
Hlatky[209] 2002	5	3	3	1	0	12	Government
Nademanee[210] 2003	10	1	5	4	2	22	Foundation
Reynolds[203] 2006	10	3	5	4	1	23	NR
Rosenqvist[211] 1998	10	1	5	3	0	19	NR
Schlapfer[212] 2002	11	3	5	4	1	24	Foundation
Vollmann[213] 2003	11	1	5	4	1	22	Private Industry
Wiegand[214] 2004	11	3	5	4	1	24	NR

NR = not reported

Quantitative Results: Efficacy Review

CRT Alone

All-Cause Mortality. Based on data pooled from all 14 RCTs (n = 544 deaths/3,825 patients), CRT alone significantly reduced all-cause mortality (RR = 0.78; 95% CI, 0.67 to 0.91, Figure 4). There was negligible statistical heterogeneity among trials (I^2 = 0 percent). The results were identical when the analysis was restricted to trials which enrolled only those patients with NYHA class III or IV symptoms (n = 498 deaths/2,778 patients, RR = 0.78; 95% CI, 0.67 to 0.91; I^2 = 0 percent). All-cause mortality in the control patients with symptomatic heart failure (NYHA class II-IV) was 15 percent and the number needed to treat (NNT) to prevent one death was 29 over a median followup of 6 months in patients with symptomatic heart failure. All-cause mortality in the control patients with NYHA class III or IV symptoms was 20 percent and the NNT to prevent one death was 23 over a median followup of 3 months. Although no differences were detected in all-cause mortality (RR = 0.86; 95% CI, 0.54 to 1.39) in the four trials[6,9,14,17] that included an ICD in both the experimental and control arms (i.e., combined CRT-ICD vs. ICD alone), this analysis is based on just 88 deaths in 1,224 patients. Thus, while the data from the other 10 trials comparing CRT alone vs. medical therapy conclusively demonstrated reduced mortality (RR = 0.77; 95% CI, 0.66 to 0.91) with CRT, the difference between the pooled effect estimates from the CRT+ICD vs. ICD alone trials and the pooled effect estimates from the CRT alone vs. medical therapy trials was not statistically significant (p = 0.67),

Progressive Heart Failure Mortality. Eight trials reported progressive heart failure mortality in NYHA class II to IV patients (n = 203 deaths/3,004 patients); CRT alone conferred a statistically significant reduction in this endpoint (RR = 0.64; 95% CI, 0.49 to 0.84) with negligible heterogeneity (I^2 = 0 percent; Figure 5). Restricting this analysis to patients with NYHA class III or IV symptoms provided similar results (n = 103 deaths/1,408 patients, RR = 0.56; 95% CI, 0.38 to 82; I^2 = 0 percent). In the two trials which tested combined CRT-ICD vs. ICD alone and reported this outcome, the benefits of CRT were similar (n = 13 deaths/671 patients, RR = 0.44; 95% CI, 0.14 to 1.42; p = 0.53 for comparison with non-ICD trials).

Sudden Cardiac Death. Using data pooled from the 11 trials that reported this outcome, the incidence of sudden cardiac death (n = 165 deaths/3503 patients) was no different between CRT recipient and control groups (RR = 1.07; 95% CI, 0.79 to 1.46; Figure 6). This result demonstrated no statistical heterogeneity (I^2 = 0 percent) and was similar if restricted to trials of 6 months or longer (RR = 1.02; 95% CI, 0.75 to 1.40; I^2 = 0 percent) or if restricted to patients with NYHA class III or IV symptoms (n = 85 deaths/1,452 patients, RR = 0.91; 95% CI, 0.60 to 1.38, I^2 = 0 percent). Although results were slightly more favorable toward control for the three trials which tested combined CRT-ICD vs. ICD alone and reported this outcome, they were still nonsignificant (RR = 1.45; 95% CI, 0.43 to 4.91; p = 0.62 for comparison with non-ICD trials).

Noncardiac Death. Pooled data from the six trials (n = 40/1,738 patients) reporting this outcome did not demonstrate any significant differences in noncardiac deaths between patients with CRT alone vs. controls (RR = 0.81; 95% CI, 0.43 to 1.52; Figure 7). This result was not statistically heterogeneous (I^2 = 0 percent).

Heart Failure Hospitalizations. Pooled results from the seven trials that reported HF hospitalizations demonstrated a significant reduction in the number of patients hospitalized at least once for HF (n = 514/2,270 patients, RR = 0.63; 95% CI, 0.43 to 0.93; Figure 8) in favor of CRT alone compared to control. This result was substantially heterogeneous (I^2 = 74 percent). Restricting the analysis to patients with more advanced HF (those with NYHA class III or IV symptoms) revealed greater reductions (n = 280 hospitalized for HF/1,411 patients, RR = 0.51; 95% CI, 0.41 to 0.64) and was statistically homogeneous (I^2 = 0 percent). However, no benefits were seen in the two combined CRT-ICD vs. ICD trials which reported this outcome (RR = 1.00; 95% CI, 0.80 to 1.24; $p < 0.0001$ for comparison with non-ICD trials), and the presence of an ICD in both arms of these studies seemed to be the main cause of the heterogeneity present in this outcome for the seven CRT trials.

6-minute Walk Test. CRT was associated with an improved 6-minute walk test distance (WMD = 24m; 95% CI, 13m to 35m; Figure 9) compared to controls, although there was substantial heterogeneity in this estimate (I^2 = 53 percent). This improvement was similar in those patients with more advanced HF, i.e., NYHA class III or IV symptoms (WMD = 32m; 95% CI, 13 to 51; I^2 = 64 percent). The magnitude of change for the 6-minute walk test of 24m is difficult to interpret in light of other trials that have shown a weak correlation between this and other functional testing (e.g., NYHA class, LVEF, VO_2 max.). Importantly, the change in 6-minute walk test is highly dependent on age and less so on NYHA class.[265] Subgrouping by the presence of an ICD showed that those trials without an ICD (WMD = 31m; 95% CI, 16m to 46m; I^2 = 56 percent) showed greater improvement than those with an ICD (WMD = 12m; 95% CI, 0m to 25m; I^2 = 0 percent). However, the difference was not statistically significant (p = 0.06) and did not explain all the heterogeneity as the ICD group still contained substantial heterogeneity.

New York Heart Association Functional Class. Functional class data from three studies were combined in a meta-analysis (although 10 studies reported NYHA class at baseline and at conclusion of followup, only three reported it in a format which permitted pooling of data across studies). Combining these three studies showed improvements in NYHA class in 59 percent of CRT patients and 37 percent of controls (CRT was associated with a 1.55 times increased chance of improving at least one NYHA class; 95% CI, 1.25 to 1.92; Figure 10). This result was heterogeneous (I^2 = 59 percent). In patients with NYHA class III or IV symptoms, the relative risk of improving at least one NYHA class was greater (RR = 1.69; 95% CI, 1.47 to 1.94) and demonstrated less heterogeneity (I^2 = 0 percent). The data from MIRACLE-ICD[6] were not reported in a format that permitted pooling with the other three trials; however, the median NYHA Class for both groups was III at baseline and was II in the CRT group vs. III in the control group at the end of the study. This improvement in NYHA Class was significant (p = 0.01) and favored CRT; the specific statistical test used was not reported. Although the data from CARE-HF[15] were not reported in a format that permitted pooling with the other trials, the CARE-HF investigators documented statistically significantly improved NYHA class 90 days after randomization in patients receiving CRT alone compared to controls (mean NYHA class 2.7 vs. 2.1, $p < 0.001$). This was also true for the PATH-CHF II, HOBIPACE, and RHYTHM-ICD trials (mean changes of 0.25, 0.6, and 0.2 respectively in favor of CRT).[12,13,17] Only the PATH-CHF Trial[8] (which also could not be combined with the other trials due to the manner in which the data were reported) failed to identify a difference between treatment arms; however,

both arms demonstrated significant improvements from baseline and the sample was underpowered to detect a difference.

Quality of Life. Quality of life was measured by the Minnesota Living With Heart Failure Instrument[266-268] for 11 trials; pooled results showed a significant improvement in favor of CRT (WMD = –8.0 points; 95% CI, -10.4 to -5.6 points; Figure 11). Although this result demonstrated substantial heterogeneity (I^2 = 61 percent), the results were consistent in direction across studies. Restricting the analysis to only those patients with NYHA class III or IV symptoms slightly increased the difference between the CRT and control groups (WMD = –8.6 points; 95% CI, –12.1 to –5.1 points; I^2 = 73 percent). Subgrouping by presence of ICD also did not explain the heterogeneity as the no ICD group (WMD = -8.1 points; 95% CI, -11.2 to -5.0) and ICD group (WMD = -7.8 points; 95% CI, -12.1 to -3.5) were nearly identical. These differences are clinically significant since the minimal clinically important difference for the Minnesota Living with Heart Failure Questionnaire has been established to be 5 points.[266-268]

Left Ventricular Ejection Fraction. Ejection fraction significantly improved in the CRT alone arm compared to the control arm in the 5 trials in which it was reported (WMD = 3.0 percent; 95% CI, 0.9 to 5.1 percent**;** I^2 = 75 percent; Figure 12).

Sensitivity Analyses. Many a priori subgroup and sensitivity analyses (including examining any interactions between the effects of CRT in patients with different etiologies of heart failure, or by ethnic background, gender, age, comorbidities, and baseline medication use) could not be performed due to our inability to obtain individual patient-level data from these trials. None of the CRT trials reported definitive subgroup effects. For example, although the PATH CHF II Investigators[12] reported significantly larger improvements in exercise capacity in patients with QRS duration > 150 msec at baseline than those with shorter QRS width, this was based on only 16 patients; similarly, the report from the HOBIPACE Investigators[13] that the functional improvements with CRT were greater in those patients with septal coronary sinus leads outside of the anterolateral region was based on 17 patients. Further, while a post hoc analysis of the MIRACLE trial suggested that patients with an ischemic etiology demonstrated less improvements in LVEF and ventricular volumes with CRT than those patients with nonischemic disease,[216] mortality benefits with CRT did not differ between ischemic and nonischemic patients in the COMPANION, CARE-HF, or CONTAK CD Trials (i.e., those trials which specifically examined for this interaction in analyses specified a priori).[9] However, it should be noted that these trials were not powered to detect such subgroup effects.[11,15]

A series of univariate meta-regressions on our three most important outcomes (all-cause mortality, HF hospitalizations, and quality of life as assessed by the Minnesota Living With Heart Failure Instrument) revealed that while no factors influenced the all-cause mortality results, several factors (presence of an ICD in both controls and CRT patients, NYHA class II at baseline, and higher LVEF) were significantly associated with a reduced magnitude of beneficial effects from CRT (see table below). It should be noted that these analyses are based on aggregate level data from a small number of relatively homogenous trials.

Table 19. Univariate meta-regression subgroup analyses: CRT

Covariate	All-cause mortality (p-values)	Heart failure hospitalizations (p-values)	Quality of life (p-values)
Presence of ICD	0.68	0.001	0.93
Length of followup	0.28	0.17	0.14
Ischemic etiology (%)	0.71	0.54	0.12
NYHA class IV (%)	0.85	0.26	0.55
NYHA class II (%)	0.76	0.003	0.31
Mean age (years)	0.27	0.78	0.02
Mean LVEF (%)	0.42	0.004	0.72
Randomization after implantation	0.50	0.07	0.14

The COMPANION trial[11] provides the only direct comparison between combined CRT-ICD vs. CRT alone devices. Although this was not a primary pre-specified comparison within this trial (which was designed to compare both arms against optimal medical therapy alone), the chi-square test for all-cause mortality was not significant [p = 0.13] and the reductions in HF hospitalizations were similar in the combined CRT-ICD vs. CRT alone arms.[269]

When the data were pooled for all-cause mortality from the four trials[6,9,14,17] that included an ICD in both the experimental and control arms (i.e., combined CRT-ICD vs. ICD alone), no differences were detected (RR = 0.86; 95% CI, 0.54 to 1.39), but this analysis is based on just 88 deaths in 1,224 patients. On the other hand, pooling data from the other 10 trials comparing CRT alone vs. medical therapy demonstrated reduced mortality (RR = 0.77; 95% CI, 0.66 to 0.91) with CRT (Figure 13). However, this difference between the pooled effect estimates from the combined CRT-ICD vs. ICD alone trials and the pooled effect estimates from the CRT alone vs. medical therapy trials was not statistically significant (p = 0.67), supporting the assertion arising from the COMPANION trial data that the benefits of CRT (at least on all-cause mortality) are not appreciably altered by addition of an ICD. However, using the same meta-regression model revealed that CRT appeared to have less impact on HF hospitalizations when it was added to patients with an ICD (RR = 1.00; 95% CI, 0.80 to 1.24 in the 2 trials [234 of 859 patients hospitalized] comparing combined CRT-ICD devices with ICD alone) than when CRT was compared to patients treated with medical therapy alone (RR = 0.51, 95% CI 0.41 to 0.64 in the five non-ICD trials reporting this outcome [280 of 1411 patients hospitalized]); p < 0.0001 for comparison between those trials with/without ICD in both arms of the trial.

Publication Bias. Publication bias was examined for our primary outcome, all cause mortality. The funnel plot (Figure 14) did appear somewhat asymmetric indicating possible publication bias. Both Begg's rank correlation test (p = 0.06) and Egger's test (p = 0.06) just failed to achieve statistical significance. Using the trim and fill correction added four studies to our meta-analysis, but the new estimate was largely unchanged from the original (RR = 0.77, 95% CI, 0.62 to 0.92). Interestingly, the bias indicated in all of these tests was that studies which favoured CRT were less likely to be published — the opposite of what one usually would expect in funnel

plot asymmetry. This would imply that if publication bias truly did exist, the true relative risk reduction with CRT could be even greater than that observed.

Combined CRT-ICD Devices

Only one trial compared combined CRT-ICD to medical therapy alone.[11] Its effect on all-cause mortality was statistically significant (hazard ratio = 0.64; 95% CI, 0.48 to 0.86), and although larger than the effect size reported for the CRT alone vs. medical therapy comparison (hazard ratio = 0.76; 95% CI, 0.58 to 1.01), this difference was not statistically significant (p = 0.13). The effects of the combined CRT-ICD device in COMPANION for nonmortality outcomes were similar to the results reported in those trials which compared CRT alone vs. medical therapy: statistically significant improvements were seen in six minute walk test (Mean Difference = 45m; 95% CI, 27 to 63), NYHA functional class (RR = 1.49; 95% CI, 1.23 to 1.81, for improving at least one NYHA class), and quality of life (Mean difference = -14 points; 95% CI, -18 to -10, on the Minnesota Living with Heart Failure Instrument).

ICD Alone

All-Cause Mortality. Based on data pooled from all 12 randomized controlled trials (1851 deaths in 8,516 patients), ICD alone significantly reduced all-cause mortality (RR = 0.80; 95% CI, 0.71 to 0.90; Figure 15 in patients with left ventricular systolic dysfunction). All-cause mortality in the control patients with left ventricular systolic dysfunction was 25 percent, so the NNT to prevent one death was 20 over a median followup of 35 months in these patients. There was moderate statistical heterogeneity among trials (I^2 = 44 percent). The results were similar (but more homogeneous) when the analysis was restricted to patients with NYHA Class II or III symptoms (RR = 0.77; 95% CI, 0.65 to 0.90; I^2 = 0 percent). All-cause mortality in the control patients with left ventricular systolic dysfunction and NYHA class II or III symptoms was 29 percent and the NNT to prevent one death was 15 over a median followup of 72 months in these patients.

Mode of Death Analysis. Unlike the CRT trials (in which the majority of trials classified deaths into those due to progressive heart failure mortality vs. sudden cardiac death vs. non-cardiac death), the ICD trials focused almost exclusively on all-cause mortality and sudden cardiac death**.** Two trials reported progressive heart failure mortality and the data was not conclusive (n = 125 deaths/1668 patients; RR = 0.99; 95% CI, 0.70 to 1.38; I^2 = 0 percent) (Figure 16). Ten ICD trials reported rates of sudden cardiac death and confirmed the benefits of ICD for this outcome (n = 414 deaths/5608 patients; RR = 0.46; 95% CI, 0.37 to 0.57; Figure 17). This result was not statistically heterogeneous (I^2 = 0 percent). All studies enrolled patients with NYHA class I to III, thus without individual patient data no sub-analysis by NYHA class could be performed. Pooled data from 8 trials reporting non-cardiac deaths did not demonstrate any significant differences between patients with ICD compared to controls (n = 183/4304 patients; RR = 1.27; 95% CI, 0.95 to 1.69; Figure 18). This result was not statistically heterogeneous (I^2 = 0 percent).

Heart Failure Hospitalizations. Pooled results from the two trials that reported HF hospitalizations suggested no difference between ICD and control, but was not conclusive due to

the small number of events (810 of 2,248 patients hospitalized for HF; RR = 1.10; 95% CI, 0.76 to 1.59; Figure 19).

6-Minute Walk Test. One study comparing ICD to control had data on 6-minute walk test. ICD patients did not appear to walk further than control patients, although the data was not conclusive (MD = 6 m; 95% CI, -8 m to 19 m).[11]

New York Heart Association Functional Class. One study reported data on NYHA functional class and there was no statistically significant difference between ICD and control patients during followup (RR = 0.93; 95% CI, 0.84 to 1.04).[11]

Quality of Life. Quality of life as measured by the Minnesota Living with Heart Failure Instrument was reported in one trial and there was no significant difference between ICD and control (MD = -1.0 points; 95% CI, -4.5 to 2.5).[11] One other trial used a generic quality of life score and found no difference between ICD and control.[137]

Sensitivity Analyses. Many a priori subgroup and sensitivity analyses (including examining any interactions between the effects of ICD in patients with different etiologies of HF, or by ethnic background, gender, age, comorbidities, NYHA class, and baseline medication use) could not be performed due to our inability to obtain individual patient-level data from these trials. Although only one trial reported a significant subgroup effect (the SCD-HeFT Investigators[140] reported that the mortality benefits of ICD were greater in patients with NYHA class II symptoms than those with NYHA class III symptoms at baseline – $p<0.001$), it should be noted that these trials were not powered to detect such subgroup effects. A series of univariate meta-regression sensitivity analyses on the primary outcome (all-cause mortality) were performed. As shown in the table below, none of the covariates we examined contributed to the moderate heterogeneity observed in our meta-analysis of all-cause mortality. As with our meta-regressions with the CRT trials, it should be noted these analyses are based on aggregate level data from a small number of relatively homogenous trials. There were too few studies reporting HF hospitalizations or any of the other secondary outcomes to do meta-regressions on those outcomes.

Table 20. Univariate meta-regression subgroup analyses: ICD alone

Covariate	All-cause mortality (p-values)
Presence of CRT	0.92
Length of followup	0.90
Ischemic etiology (%)	0.46
NYHA class IV (%)	0.62
NYHA class II (%)	0.81
NYHA Class I (%)	0.13
Mean age (years)	0.995
Mean QRS interval (msec)	0.82
Mean LVEF (%)	0.84
Secondary vs. primary prevention	0.56

Although the single trial that included CRT in the two study arms for its comparison of ICD vs. control failed to achieve statistical significance for all-cause mortality (RR = 0.83; 95% CI, 0.66 to 1.05), the point estimate was almost identical to that reported in the remainder of the studies which did not contain CRT in either arm (RR = 0.79; 95% CI, 0.69 to 0.91). The difference between this single trial and the other CRT trials was not statistically significant (p = 0.93), supporting the assertion that the benefits of ICD on all-cause mortality are not appreciably altered by addition of a CRT. ICDs were equally beneficial in reducing all-cause mortality in both primary prevention trials (RR = 0.81; 95% CI, 0.69 to 0.95) and secondary prevention trials (RR = 0.77; 95% CI, 0.65 to 0.91)—see Figure 20 (p-value for comparison = 0.59).

Publication Bias. There was no indication of any publication bias for our primary outcome (all-cause mortality) when comparing ICD to control. The funnel plot did not appear asymmetric (Figure 21), and Begg's rank correlation test (p = 0.54), Egger's regression test (p = 0.81) and Duval's trim and fill (no studies added) all indicated that there was little possibility that publication bias influenced these results.

Quantitative Results: Effectiveness Review

CRT Alone

All-Cause Mortality. As shown in Figure 22, mortality over time was similar in the randomized trials and the observational studies for patients who received CRT devices. One observational study had contemporaneous control group permitting calculation of a relative risk for all-cause mortality and mode of death analyses—the effectiveness point estimates were almost identical to the efficacy estimates, although none were statistically significant due to the small number of events (all-cause mortality RR = 0.64; 95% CI, 0.26 to 1.56; Figure 4; progressive HF mortality RR = 0.68; 95% CI, 0.16 to 2.92; Figure 5; and sudden cardiac death RR = 0.61; 95% CI, 0.18 to 2.04; Figure 6).

Left Ventricular Ejection Fraction. The effectiveness estimate from the one controlled observational study that reported this outcome was consistent with our findings in the efficacy trials (WMD = 4.6 percent; 95% CI, 2.68 to 6.34 percent; Figure 12).

Other Endpoints. No controlled observational studies reported non-cardiac deaths, heart failure hospitalizations, New York Heart Association functional class, 6-minute walk test results, or quality of life assessments.

Nonresponse Rates. As outlined in Table 21, 22 studies reported on response rates in CRT recipients. Since the definitions varied between studies, these data were not meta-analyzed. The reported response rates varied between 63 percent and 82 percent in those studies using definitions of response based on functional status and between 55 percent and 69 percent in those studies employing echocardiographic definitions for response. Various parameters have been reported in some of these studies to predict response to CRT, but no factors were found to be independent predictors consistently across studies (Table 21). Without access to individual

patient data from these studies it was not possible to perform multivariate analyses to define predictors of response in the pooled data.

Table 21. Response rates reported in observational studies: CRT alone or combined CRT-ICD devices

Author Year	Definition of responder	Followup	Sample size	Proportion of responders, %	Independent predictors of positive response
Functional definition of response					
CRT alone					
Bleeker[30] 2005a	Improved ≥1 NYHA class	6 mo.	170	78	Analysis by age < 70 vs. ≥ 70 yrs. (NS)
Chan[43] 2003	6MWT increased 10%	3 mo.	63	67	Not done
Lecoq[68] 2004	Alive, no CHF hospitalizations, improved ≥1 NYHA class or > 10% increase VO_2 max during 6MWT	6 mo.	139	72	Δ QRS (step of 20 msec)
Lenom[69] 2005	Improved NYHA class	6 mo.	36	71	Not done
Molhoek[82] 2005	Improved ≥1 NYHA class	6 mo.	74	68	Analysis by etiology (NS)
Sawhney[105] 2004	Improved ≥1 NYHA class	3 mo.	40	63	Acute response to CRT by aortic Doppler VTI
Stahlberg[108] 2005	Alive, no CHF hospitalizations, improved ≥1 NYHA class and/or 10% increase in 6MWT distance	6 mo.	35	66	Not done
Combined CRT-ICD					
Alonso[21] 1999	Alive, improved ≥1 NYHA class, 10% increase in peak VO2	6 mo.	26	73	Not done
Bax[29] 2004	Improved ≥1 NYHA class, improved 6MWT ≥25%	6 mo.	85	74	Baseline LV dyssynchrony of ≥ 65ms
Diaz-Infante[49] 2005	Alive, no heart transplant, 10% increase in 6MWT	6 mo.	143	80	Etiology, mitral regurgitation, LVEDD < 75mm
Hernandez[59] 2004	Improved 6MWT ≥10%	6 mo.	28	79	BNP level, etiology, baseline NYHA
Kies[61] 2005	Improved ≥1 NYHA class	6 mo.	97	74	Analysis by diabetes mellitus vs. no diabetes mellitus (NS)
Molhoek[79] 2004a	Improved ≥1 NYHA class	6 mo.	60	72	Not done
Molhoek[80] 2004b	Improved ≥1 NYHA class	6 mo.	117	78	NYHA = III vs. IV
Molhoek[81] 2004c	Improved ≥1 NYHA class	6 mo.	61	74	Analysis by baseline QRS (NS)
Reuter[100] 2002	Improved NYHA class associated with improved QOL score	12 mo.	102	82	Etiology, cardiac output
Echocardiographic definition of response					
CRT alone					
Bax[28] 2003	Absolute Increase in LVEF ≥ 5%	6 mo.	25	68	Septal to lateral delay
Penicka[93] 2004	Relative Increase in LVEF ≥ 25%	6 mo.	49	55	Tissue doppler imaging derived indices of asynchrony

Table 21. Response rates reported in observational studies: CRT alone or combined CRT-ICD devices (continued)

Author Year	Definition of responder	Followup	Sample size	Proportion of responders, %	Independent predictors of positive response
Yu[118] 2002a	LV reverse modeling (reduction in LV end-systolic volume > 10%)	3-6 mo.	141	62	Reduced LVESV ≥9.5% (significant predictor of all-cause mortality)
Multiple definitions of response					
CRT alone					
Mascioli[76] 2002	Improved ≥ 1 NYHA class, LVEF increased by ≥ 10%	6 mo.	68	69	Analysis performed but none found
Yu[120] 2004	LV reverse modeling (reduction in LV end-systolic volume > 15%)	3 mo.	30	57	Systolic dyssynchrony by tissue doppler imaging
Combined CRT-ICD					
Notabartolo[88] 2004	2 of 3: Improved ≥ 1 NYHA class; > 50 meter increase in 6MWT; decrease QOL score = 15 pts; or reduction in LV end-systolic volume >15%	3 mo.	49	Echocard-iographic response = 59 clinical response = 75	PVD predicted echocardiographic response; no significant predictors of clinical response

CRT = cardiac resynchronization therapy; CRT+ICD = CRT with implanted cardioverter defibrillator; LV = left ventricular; LVEF = left ventrular ejection fraction; NS = not significant; NYHA = New York Heart Association class; QOL = Quality of life; 6MWT = 6-minute walk test; VO_2 max = maximal oxygen consumption

Combined CRT-ICD Devices

There were no controlled effectiveness studies which compared combined CRT-ICD to contemporaneous controls.

ICD Alone

All-Cause Mortality. The benefit of ICD on all-cause mortality was greater in the 11 observational studies with contemporaneous control groups than in the RCTs (Figure 15). The pooled relative risk was 0.54 (95% CI, 0.43 to 0.68), although heterogeneity was substantial (I^2 = 60 percent). As shown in Figure 23, mortality over time was similar in the randomized trials and the observational studies for patients who received ICD devices.

Progressive Heart Failure Mortality. Three observational controlled studies reported this outcome, although the result was not significant (RR = 1.15; 95% CI, 0.50 to 2.66; I^2 = 30 percent).

Sudden Cardiac Death. The effectiveness estimate derived from eight observational studies with control groups was greater than the estimate from the RCTs (RR = 0.33; 95% CI, 0.23 to 0.46; I^2 = 0 percent; Figure 17).

Non-Cardiac Death. The effectiveness estimate derived from the eight observational studies with control groups revealed a benefit in favor of ICD (RR = 0.74; 95% CI, 0.65 to 0.85; I^2 = 0 percent; Figure 18). This unexpected result suggests that clinicians do select healthier patients for ICD insertion since ICD alone should not impact noncardiac deaths.

No controlled observational studies reported HF hospitalizations, quality of life, or changes in NYHA functional class or 6-minute walk test with ICD.

Mortality Comparison Across Devices and Study Types

We evaluated all-cause mortality vs. length of followup in all studies that followed patients with CRT alone, ICD alone, or combined CRT-ICD. Mortality increased as length of followup increased; however, we were interested in differences in rates of increase in each of the three groups. A weighted regression was performed for each group. The plots, along with best fitting regression line, are represented in Figures 22, 23, and 24.

The CRT studies had an increase in mortality of approximately 5.9 percent with each followup year. This was slightly higher for the combined CRT-ICD device group with a per annum increase of 6.2 percent. However, the ICD alone group had the smallest increase in annual mortality at 3.7 percent. It should be noted that the ICD studies tended to be much longer in duration than the CRT studies and this may have skewed these results.

Quantitative Results: Safety Review

CRT Alone

Fifty-four studies (n = 6,123 patients) reported data which permitted us to examine the safety of CRT. Table 22 reports peri-implantation and post-implantation risks from individual studies as well as pooled results for CRT alone devices. During data pooling, studies that did not report any data for particular outcomes were excluded.

Peri-Implantation Risks. Twenty-four studies reported data on deaths while undergoing implantation of a biventricular pacemaker. There were 8 deaths in 2,571 patients (pooled risk = 0.3 percent, 95% CI, 0.1 to 0.6 percent). Implants of devices were successful in 93 percent (95% CI, 92.2 to 93.7 percent) of attempts in 4,625 patients from 41 studies. Twenty-one studies that reported on peri-implantation mechanical complications showed a frequency of 4.3 percent (95% CI, 3.6 to 5.1 percent) in 3,139 patients. Of note, implant success rates and peri-implantation risks were no different in the CRT RCTs as in the observational studies conducted in non-trial settings.

Post-Implantation Risks. Post-implant mechanical malfunction was reported to be 4.0 percent (95% CI 3.0 to 5.2 percent) over a median followup of 12 months in 9 studies (1,316 patients), with no appreciable difference between the frequencies reported in observational studies vs. RCTs (Table 17). The device malfunction frequency was 5.4 percent (95% CI, 4.2 to 6.7 percent) over a median followup of 6 months in 20 studies (1,339 patients), post-implant lead problems were reported in 6.6 percent (95% CI, 5.8 to 7.4 percent) of patients over a median followup of 11 months in 32 studies (3,649 patients), and post-implant infections occurred in 1.8 percent (95% CI, 1.3 to 2.5 percent) of patients as reported in 16 studies (2,088 patients)—none of these outcomes differed between the CRT RCTs and the observational studies. The frequency of post-implant arrythmias attributed to the CRT device occurred in a far higher proportion of patients in

the CRT RCTs (12 percent; 95% CI, 9.5 to 14.9 percent) than in the observational studies (5.4 percent; 95% CI, 2.4 to 10.4 percent), likely reflecting the closer followup in RCTs.

Combined CRT-ICD Devices

Thirty-six studies (5,199 patients) reported data which permitted the examination of the safety of combined CRT-ICD. Table 21 report peri-implantation and post-implantation risks from individual studies as well as pooled results. During data pooling, studies that did not report any data for particular outcomes were excluded.

Peri-Implantation Risks. Twenty studies reported data on deaths while undergoing implantation of a CRT and ICD: there were 13 deaths in 2,731 patients (pooled risk = 0.5 percent; 95% CI, 0.2 to 0.8 percent). Implants of devices were successful in 93.7 percent (95% CI, 92.9 to 94.4 percent) of attempts in 4,163 patients from 28 studies. Ten studies that reported on peri-implantation mechanical complications showed a frequency of 4.6 percent (95% CI, 3.7 to 5.6 percent) in 1,889 patients. Of note, implant success rates and peri-implantation risks were no different in the combined CRT-ICD RCTs as in the observational studies of these devices conducted in non-trial settings (Table 21).

Post-Implantation Risks. Post-implant mechanical malfunction was reported in 4.6 percent (95% CI, 3.5 to 6.0 percent) of patients from five studies (n = 1,102 patients), the device malfunction frequency was 5.0 percent (95% CI, 4.0 to 6.3 percent) over 12 months in nine studies (1,411 patients), and the frequency of post-implant infections was 1.1 percent (95% CI, 0.7 to 1.7 percent) over 12 months in 10 studies (1,791 patients)—none of these outcomes differed between the combined CRT-ICD RCTs and the observational studies. Post-implant lead problems were reported in 9.8 percent (95% CI, 8.2 to 11.6 percent) of RCT participants compared to 5.7 percent (95% CI, 4.8 to 6.8 percent) of patients in observational studies, again likely reflecting closer scrutiny in the RCT setting or a publication bias in the observational data. While post-implant arrythmias occurred in 6.4 percent (95% CI, 4.6 to 8.7 percent) of patients in two studies (609 patients) which recorded this outcome, inappropriate shocks occurred in 6.0 percent (95% CI, 4.8 to 7.5 percent) of patients over 12 months in the nine studies (1,210 patients) which evaluated this outcome.

ICD Alone

As previously described, 49 studies were used to examine the safety of ICD alone. Table 22 reports peri-implantation and post-implantation risks from individual studies as well as pooled results. During data pooling, studies that did not report any data for particular outcomes were excluded.

Peri-Implantation Risks. Twenty-eight studies reported data on deaths while undergoing implantation of an ICD: there were 59 deaths in 4,902 patients (pooled risk 1.2 percent, 95% CI, 0.9 to 1.5 percent). Implants of devices were successful in 99.0 percent (95% CI, 98.8 to 99.3 percent) of attempts in 6,189 patients from 24 studies. Eighteen studies that reported on peri-implantation mechanical complications showed a frequency of 5.3 percent (95% CI, 4.6 to 6.2 percent) in 3,299 patients. Of note, implantation success rates were significantly lower and peri-

implantation death rates were significantly higher in the ICD RCTs compared to the observational studies. This difference likely reflects closer scrutiny in the RCT setting or a publication bias in the observational data.

We also examined peri-implant deaths and success rates for studies that enrolled all patients undergoing ICD implant, not just those patients with left ventricular systolic dysfunction. Ten studies (34,956 patients) demonstrated a peri-implant death rate of 1.3 percent (95% CI, 1.2 to 1.4 percent). Seven studies (4,940 patients) reported an implant success rate of 98.6 percent (95% CI, 98.3, 98.9). Both of these frequencies (for implant success and peri-implant death) were very similar to the rates reported in studies restricted to patients with left ventricular systolic dysfunction.

Post-Implantation Risks. Implantation mechanical malfunction was reported in 18 studies representing 3,299 patients. The malfunction frequency was 5.3 percent (95% CI, 4.6 to 6.2 percent). The frequency of post-implant mechanical malfunction from 9 studies (2,190 patients) was 2.0 percent (95% CI, 1.5 to 2.7 percent; 0.6 per 100 patient-years [95% CI 0.5 to 0.8]) and the frequency of post-implant device malfunction from 10 studies (2,569 patients) was 5.8 percent (95% CI, 4.9 to 6.7 percent; 1.4 per 100 patient-years [95% CI 1.2 to 1.6])—both frequencies were similar in RCTs as in observational studies. Post-implant lead problems were reported in 16 studies (3,713 patients) and although the pooled rate was 4.3 percent (95% CI, 3.7 to 5.0 percent; 1.5 per 100 patient-years [95% CI 1.3 to 1.8]), the rate was far lower in RCT data (1.7 percent, 95% CI 1.2 to 2.3 percent) compared to observational data (8.7 percent, 95% CI 7.3 to 10.3 percent). The frequency of post-implant infections was 1.8 percent (95% CI, 1.4 to 2.2 percent; 0.6 per 100 patient-years [95% CI 0.5 to 0.8]) as reported in 17 studies of 4,232 patients, but was lower in observational studies (1.1 percent, 95% CI, 0.6 to 1.7 percent) than RCTs (2.3 percent, 95% CI 1.7 to 2.9 percent). The different direction for these two outcomes (one more frequent in RCTs, the other more frequent in observational studies) raises the possibility that lead infections may have been classified as “lead problems” in some studies but “lead infections” in other studies. The frequency of inappropriate shocks was substantially higher in RCT participants—38.8 percent, 95% CI, 33.9 to 43.7 percent, or 19.1 per 100 patient years [95% CI, 16.5 to 22.0] over 24 months of followup vs. 16.3 percent, 95% CI, 15.0 to 17.7 percent, or 4.7 per 100 patient-years [95% CI, 4.3 to 5.1] over 24 months of followup in the observational studies (pooled 5.8 per 100 patient-years [95% CI, 5.4 to 6.2]).

Table 22. Peri- and post-implantation risks: CRT alone

Trial name, Author Study year	n/N	Simple pool risk, % [95% CI]
Peri-implant deaths: RCT		
COMPANION[11] 2004	2/699	0.3 [0.0, 1.0]
MUSTIC-AF[7] 2002	0/59	0.0 [0.0, 5.0]
MUSTIC-SR[5] 2001	1/58	1.7 [0.0, 9.2]
PATH-CHF[8] 2002a	0/41	0.0 [0.0, 7.0]
Sub-Total:	3/857	0.4 [0.1, 1.0]
Peri-implant deaths: Observational studies		
Bleeker[31] 2005b	0/56	0.0 [0.0, 5.2]
Bordachar[35] 2004	0/41	0.0 [0.0, 7.0]
Cazeau[41] 2003	0/66	0.0 [0.0, 4.4]
Daubert[46] 1998	0/47	0.0 [0.0, 6.2]
De Martino[125] 2004	0/34	0.0 [0.0, 8.4]
Galvao[56] 2002	3/28	10.7 [2.3, 28.2]
Kautzner[128] 2004	0/46	0.0 [0.0, 6.3]
Koos[63] 2004	0/81	0.0 [0.0, 3.6]
Leclercq[67] 2002b	0/139	0.0 [0.0, 2.1]
Lecoq[68] 2005	0/158	0.0 [0.0, 1.9]
Leon[70] 2005	1/422	0.2 [0.0, 1.3]
Mair[73] 2005	0/80	0.0 [0.0, 3.7]
Molhoek[79] 2004a	0/74	0.0 [0.0, 4.0]
Nagele[85] 2001	0/32	0.0 [0.0, 8.9]
Niu[87] 2006	0/117	0.0 [0.0, 2.5]
Ollitrault[91] 2003	0/62	0.0 [0.0, 4.7]
Penicka[93] 2004	1/55	1.8 [0.0, 9.7]
Schuchert[132] 2004	0/102	0.0 [0.0, 2.9]
Stahlberg[108] 2005	0/40	0.0 [0.0, 7.2]
Toussaint[113] 2003	0/34	0.0 [0.0, 8.4]
Sub Total	5/1714	0.3 [0.1, 0.7]
Total [N=24]	8/2571	0.3 [0.1, 0.6]
Implant success rate: RCT		
COMPANION[11] 2004	617/699	88.3 [85.6, 90.6]
MIRACLE[4] 2002	528/571	92.5 [90.0, 94.5]
MUSTIC-AF[7] 2002	54/59	91.5 [81.3, 97.2]
MUSTIC-SR[5] 2001	58/64	90.6 [80.7, 96.5]
PATH-CHF[8] 2002a	41/41	100.0 [93.0, 100.0]
PATH-CHF II[12] 2003	86/89	96.6 [90.5, 99.3]
Sub-Total:	1384/1523	90.9 [89.3, 92.3]
Implant success rate: Observational studies		
Albertsen[20] 2005	120/120	100.0 [97.5, 100.0]
Baker[27] 2002	54/60	90.0 [79.5, 96.2]
Bleeker[30] 2005a	170/170	100.0 [98.3, 100.0]
Bleeker[31] 2005b	56/56	100.0 [94.8, 100.0]
Bleeker[32] 2006	100/100	100.0 [97.0, 100.0]
Bordachar[35] 2004	41/41	100.0 [93.0, 100.0]
Daubert[46] 1998	35/47	74.5 [59.7, 86.1]
De Martino[126] 2005	82/83	98.8 [93.5, 100.0]
De Martino[125] 2004	30/34	88.2 [72.5, 96.7]
Dixon[50] 2004	27/27	100.0 [89.5, 100.0]
Galvao[56] 2002	28/28	100.0 [89.9, 100.0]
Gras[58] 2002	125/139	89.9 [83.7, 94.4]

RCT=randomized control trial

Table 22. Peri- and post-implantation risks: CRT alone (continued)

Trial name, Author Study year	n/N	Simple pool risk, % [95% CI]
Implant success rate: Observational studies (continued)		
Hua[60] 2006	142/149	95.3 [90.6, 98.1]
Kautzner[128] 2004	42/46	91.3 [79.2, 97.6]
Leclercq[67] 2002b	125/139	89.9 [83.7, 94.4]
Lecoq[68] 2005	139/158	88.0 [81.9, 92.6]
Leon[70] 2005	397/422	94.1 [91.4, 96.1]
Lewika-Nowak[129]2005	80/92	87.0 [78.3, 93.1]
Mair[73] 2005	80/80	100.0 [96.3, 100.0]
Mascioli[76]2002	95/96	99.0 [94.3, 100.0]
Molhoek[80] 2004b	74/74	100.0 [96.0, 100.0]
Molhoek[78] 2002	40/40	100.0 [92.8, 100.0]
Mortensen[83] 2004	189/198	95.5 [91.5, 97.9]
Nagele[85] 2001	28/32	87.5 [71.0, 96.5]
Niu[87] 2006	111/117	94.9 [89.2, 98.1]
O'Donnell[89] 2005	58/63	92.1 [82.4, 97.4]
Ollitrault[91] 2003	38/62	61.3 [48.1, 73.4]
Penicka[93] 2004	53/55	96.4 [87.5, 99.6]
Romeyer-Bouchard[131] 2005	99/103	96.1 [90.4, 98.9]
Sawhney[105] 2004	40/40	100.0 [92.8, 100.0]
Schuchert[132] 2004	96/102	94.1 [87.6, 97.8]
Stahlberg[108] 2005	35/40	87.5 [73.2, 95.8]
Tousaint[113]2003	34/34	100.0 [91.6, 100.0]
Yu[119] 2002b	30/30	100.0 [90.5, 100.0]
Yu[118] 2002a	25/25	100.0 [88.7, 100.0]
Sub-Total:	2918/3102	94.1 [93.2, 94.9]
Total [N=41]	4302/4625	93.0 [92.2, 93.7]
Implantation mechanical complication: RCT		
CARE-HF[15] 2005	16/409	3.9 [2.3, 6.3]
COMPANION[11] 2004	12/617	1.9 [1.0, 3.4]
PATH CHF II[12] 2003	6/98	6.1 [2.3, 12.9]
Sub-Total:	34/1124	3.0 [2.1, 4.2]
Implantation mechanical complication: Observational studies		
Albertsen[20]2005	2/120	1.7 [0.2, 5.9]
Baker[27] 2002	1/60	1.7 [0.0, 8.9]
de Cock[124] 2004	7/103	6.8 [2.8, 13.5]
De Martino[126] 2005	4/83	4.8 [1.3, 11.9]
De Martino[125] 2004	4/34	11.8 [3.3, 27.5]
Dixon[50] 2004	0/27	0.0 [0.0, 10.5]
Kautzner[128] 2004	9/46	19.6 [9.4, 33.9]
Koos[63] 2004	3/81	3.7 [0.8, 10.4]
Lecoq[68] 2005	2/102	2.0 [0.2, 6.9]
Lenom[69] 2005	1/36	2.8 [0.1, 14.5]
Leon[70] 2005	28/422	6.6 [4.5, 9.4]
Mortensen[83] 2004	3/189	1.6 [0.3, 4.6]
Nagele[85] 2001	7/32	21.9 [9.3, 40.0]
Niu[87] 2006	9/117	7.7 [3.6, 14.1]
Puglisi[97] 2004	10/315	3.2 [1.5, 5.8]
Purnode[98] 2004	1/43	2.3 [0.1, 12.3]
Romeyer-Bouchard[131] 2005	1/103	1.0 [0.0, 5.3]
Schuchert[132] 2004	10/102	9.8 [4.8, 17.3]
Sub Total	102/2015	5.1 [4.1, 6.1]
Total [N=21]	136/3139	4.3 [3.6, 5.1]

Table 22. Peri- and post-implantation risks: CRT alone (continued)

Trial name, Author Study year	n/N	Simple pool risk, % [95% CI]
Post-implant mechanical malfunction: RCT		
CARE-HF[15] 2005	8/409	2.0 [0.8, 3.8]
MUSTIC-AF[7] 2002	2/54	3.7 [0.5, 12.7]
MUSTIC-SR[5] 2001	2/58	3.4 [0.4, 11.9]
Sub-Total	12/521	2.3 [1.2, 4.0]
Post-implant mechanical malfunction: Observational studies		
Dixon[50] 2004	0/27	0.0 [0.0, 10.5]
Gras[58] 2002	4/103	3.9 [1.1, 9.6]
Koos[63] 2004	1/81	1.2 [0.0, 6.7]
Leclercq[66] 2000	3/37	8.1 [1.7, 21.9]
Leclercq[67] 2002b	25/125	20.0 [13.4, 28.1]
Leon[70] 2005	8/422	1.9 [0.8, 3.7]
Sub Total	41/795	5.2 [3.7, 6.9]
Total [N=9]	53/1316	4.0 [3.0, 5.2]
Post-implant device malfunction: RCT		
MUSTIC-SR[5] 2001	2/67	3.0 [0.4, 10.4]
VECTOR[16] 2005	11/120	9.2 [4.7, 15.8]
Kindermann[13] 2006	1/30	3.3 [0.1, 17.2]
Sub-Total:	14/217	6.5 [3.6, 10.6]
Post-implant device malfunction: Observational studies		
Albertsen[20] 2005	11/120	9.2 [4.7, 15.8]
Bordachar[35] 2004	1/41	2.4 [0.1, 12.9]
Braun[39] 2005	1/65	1.5 [0.0, 8.3]
Chalil[42] 2006	0/75	0.0 [0.0, 3.9]
Dixon[50] 2004	0/27	0.0 [0.0, 10.5]
Galvao[56] 2002	3/28	10.7 [2.3, 28.2]
Kautzner[128] 2004	2/46	4.3 [0.5, 14.8]
Lecoq[68] 2005	18/102	17.6 [10.8, 26.4]
Lenom[69] 2005	1/36	2.8 [0.1, 14.5]
Lewicka-Nowak[129] 2005	2/92	2.2 [0.3, 7.6]
Mortensen[83] 2004	2/189	1.1 [0.1, 3.8]
Ollitrault[91] 2003	2/62	3.2 [0.4, 11.2]
Penicka[93] 2004	1/55	1.8 [0.0, 9.7]
Purnode[98] 2004	1/43	2.3 [0.1, 12.3]
Romeyer-Bouchard[131] 2005	1/10	10.0 [0.3, 44.5]
Schuchert[132] 2004	8/96	8.3 [3.7, 15.8]
Stahlberg[108]2005	4/35	11.4 [3.2, 26.7]
Sub Total	58/1122	5.2 [3.9, 6.6]
Total [N=20]	72/1339	5.4 [4.2, 6.7]
Post-implant lead problems: RCT		
CARE-HF[15] 2005	24/409	5.9 [3.8, 8.6]
MIRACLE[4] 2002	30/524	5.7 [3.9, 8.1]
MUSTIC-AF[7] 2002	5/54	9.3 [3.1, 20.3]
MUSTIC-SR[5] 2001	8/67	11.9 [5.3, 22.2]
VECTOR[16] 2005	8/120	6.7 [2.9, 12.7]
Kindermann[13] 2006	2/30	6.7 [0.8, 22.1]
Sub-Total:	77/1204	6.4 [5.1, 7.9]
Post-implant lead problems: Observational studies		
Albertsen[20] 2005	6/120	5.0 [1.9, 10.6]
Baker[27] 2002	1/60	1.7 [0.0, 8.9]
Braun[39] 2005	1/65	1.5 [0.0, 8.3]
Chalil[42] 2006	5/75	6.7 [2.2, 14.9]
Dixon[50] 2004	0/27	0.0 [0.0, 10.5]
Galvao[56] 2002	1/28	3.6 [0.1, 18.3]

Table 22. Peri- and post-implantation risks: CRT alone (continued)

Trial name, Author Study year	n/N	Simple pool risk, % [95% CI]
Gras[58] 2002	10/103	9.7 [4.8, 17.1]
Kautzner[128] 2004	5/46	10.9 [3.6, 23.6]
Koos[63] 2004	18/81	22.2 [13.7, 32.8]
Leclercq[66] 2000	2/37	5.4 [0.7, 18.2]
Leclercq[67] 2002b	15/125	12.0 [6.9, 19.0]
Lecoq[68] 2005	7/102	6.9 [2.8, 13.6]
Lenom[69] 2005	1/36	2.8 [0.1, 14.5]
Leon[70] 2005	22/422	5.2 [3.3, 7.8]
Lewicka-Nowak[129] 2005	12/92	13.0 [6.9, 21.7]
Molhoek[78] 2002	3/40	7.5 [1.6, 20.4]
Mortensen[83] 2004	12/189	6.3 [3.3, 10.8]
Nagele[85] 2001	2/32	6.3 [0.8, 20.8]
Niu[87] 2006	2/117	1.7 [0.2, 6.0]
Ollitrault[91] 2003	2/62	3.2 [0.4, 11.2]
Puglisi[97] 2004	12/315	3.8 [2.0, 6.6]
Purnode[98] 2004	1/43	2.3 [0.1, 12.3]
Romeyer-Bouchard[131] 2005	7/103	6.8 [2.8, 13.5]
Sawhney[105] 2004	2/40	5.0 [0.6, 16.9]
Stahlberg[108] 2005	4/35	11.4 [3.2, 26.7]
Taieb[109] 2002	10/50	20.0 [10.0, 33.7]
Sub Total	163/2445	6.7 [5.7, 7.7]
Total [N=32]	240/3649	6.6 [5.8, 7.4]
Post-implant infections: RCT		
MIRACLE[4] 2002	7/524	1.3 [0.5, 2.7]
Sub-Total:	7/524	1.3 [0.5, 2.7]
Post-implant infections: Observational studies		
Albertsen[20] 2005	3/120	2.5 [0.5, 7.1]
Baker[27] 2002	3/60	5.0 [1.0, 13.9]
Daubert[46] 1998	0/47	0.0 [0.0, 6.2]
Dixon[50] 2004	0/26	0.0 [0.0, 10.9]
Galvao[56] 2002	1/28	3.6 [0.1, 18.3]
Gras[58] 2002	2/103	1.9 [0.2, 6.8]
Koos[63] 2004	0/79	0.0 [0.0, 3.7]
Leclercq[67] 2002b	15/125	12.0 [6.9, 19.0]
Leon[70] 2005	3/422	0.7 [0.1, 2.1]
Lewicka-Nowak[129] 2005	1/92	1.1 [0.0, 5.9]
Mortensen[83] 2004	0/189	0.0 [0.0, 1.6]
Ollitrault[91] 2003	1/38	2.6 [0.1, 13.8]
Romeyer-Bouchard[131] 2005	1/99	1.0 [0.0, 5.5]
Schuchert[132] 2004	0/102	0.0 [0.0, 2.9]
Toussaint[113] 2003	1/34	2.9 [0.1, 15.3]
Sub Total	31/1564	2.0 [1.4, 2.8]
Total [N=16]	38/2088	1.8 [1.3, 2.5]
Post-implant arrhythmias: RCT		
CARE-HF[15] 2005	64/409	15.6 [12.3, 19.5]
MUSTIC-AF[7] 2002	1/54	1.9 [0.0, 9.9]
PATH-CHF[8] 2002a	4/41	9.8 [2.7, 23.1]
PATH-CHF II[12] 2003	2/86	2.3 [0.3, 8.1]
Sub-Total:	71/590	12.0 [9.5, 14.9]

Table 22. Peri- and post-implantation risks: CRT alone (continued)

Trial name, Author Study year	n/N	Simple pool risk, % [95% CI]
Post-implant arrhythmias: Observational studies		
Dixon[50] 2004	0/27	0.0 [0.0, 10.5]
Koos[63] 2004	7/81	8.6 [3.5, 17.0]
Molhoek[78] 2002	1/40	2.5 [0.1, 13.2]
Sub Total	8/148	5.4 [2.4, 10.4]
Total [N=7]	79/738	10.7 [8.6, 13.2]

Table 23. Peri- and post-implantation risks: combined CRT-ICD devices

Study, Author Year	n/N	Simple pool risk, % [95% CI]
Peri-implant deaths: RCT		
COMPANION[11] 2004	3/595	0.5 [0.1, 1.5]
CONTAK-CD[9] 2003	2/490	0.4 [0.0, 1.5]
Sub-Total	5/1085	0.5 [0.1, 1.1]
Peri-implant deaths: Observational studies		
Ammann[22] 2004	0/43	0.0 [0.0, 6.7]
Azizi[26] 2006	0/244	0.0 [0.0, 1.2]
Bax[29] 2004	0/85	0.0 [0.0, 3.5]
Bocchiardo[33] 2000	0/48	0.0 [0.0, 6.1]
Cowburn[44] 2005	0/68	0.0 [0.0, 4.3]
Da Costa[45] 2006	0/67	0.0 [0.0, 4.4]
de Sisti[48] 2005	0/102	0.0 [0.0, 2.9]
Diaz-Infante[49] 2005	2/147	1.4 [0.2, 4.8]
Ellery[52] 2005	0/85	0.0 [0.0, 3.5]
Ermis[53] 2004	0/62	0.0 [0.0, 4.7]
Molhoek[81] 2004c	0/61	0.0 [0.0, 4.8]
Navia[86] 2005	0/41	0.0 [0.0, 7.0]
Pitzalis[94] 2005	0/63	0.0 [0.0, 4.6]
Reuter[100] 2002	0/102	0.0 [0.0, 2.9]
Salukhe[104] 2005	0/40	0.0 [0.0, 7.2]
Saxon[106] 2006	5/168	3.0 [1.0, 6.8]
Teo[111] 2003	0/29	0.0 [0.0, 9.8]
Ypenburg[117] 2006	1/191	0.5 [0.0, 2.9]
Sub Total	8/1646	0.5 [0.2, 1.0]
Total [N=20]	13/2731	0.5 [0.3, 0.8]
Implant success rate: RCT		
COMPANION[11] 2004	541/595	90.9 [88.3, 93.1]
CONTAK-CD[9] 2003	501/501	100.0 [99.4, 100.0]
MIRACLE-ICD[6] 2003	379/429	88.3 [84.9, 91.2]
Sub-Total	1421/1525	93.2 [91.8, 94.4]
Implant success rate: Observational studies		
Ammann[22] 2004	43/47	91.5 [79.6, 97.6]
Azizi[26] 2006	240/244	98.4 [95.9, 99.6]
Bax[29] 2004	85/85	100.0 [96.5, 100.0]
Bocchiardo[33] 2000	48/51	94.1 [83.8, 98.8]
Boriani[36] 2006a	118/127	92.9 [87.0, 96.7]
Cowburn[44] 2005	63/68	92.6 [83.7, 97.6]
Da Costa[45] 2006	68/71	95.8 [88.1, 99.1]
Diaz-Infante[49] 2005	147/177	83.1 [76.7, 88.3]
Ellery[52] 2005	85/96	88.5 [80.4, 94.1]
Ermis[53] 2004	126/158	79.7 [72.6, 85.7]
Gasparini[57] 2003a	158/159	99.4 [96.5, 100.0]
Krahn[64] 2002	40/45	88.9 [75.9, 96.3]
Kuhlkamp[270] 2002	81/84	96.4 [89.9, 99.3]
Molhoek[82] 2005	125/125	100.0 [97.6, 100.0]
Molhoek[81] 2004c	61/61	100.0 [95.2, 100.0]
Navia[86] 2005	41/41	100.0 [93.0, 100.0]
Pitzalis[94] 2005	63/65	96.9 [89.3, 99.6]
Pürerfellner[130] 2000a	36/44	81.8 [67.3, 91.8]
Pürerfellner[130] 2000b	135/150	90.0 [84.0, 94.3]

Table 23. Peri- and post-implnantation risks: combined CRT-ICD (continued)

Study, Author Year	n/N	Simple pool risk, % [95% CI]
Reuter[100] 2002	89/102	87.3 [79.2, 93.0]
Ritter[102] 2006	48/48	100.0 [93.9, 100.0]
Rossillo[103] 2004	233/244	95.5 [92.1, 97.7]
Salukhe[104] 2005	40/40	100.0 [92.8, 100.0]
Teo[111] 2003	29/29	100.0 [90.2, 100.0]
Theuns[112] 2005	86/86	100.0 [96.6, 100.0]
Ypenburg[117] 2006	191/191	100.0 [98.4, 100.0]
Sub-Total:	2479/2638	94.0 [93.0, 94.9]
Total [N=28]	3900/4163	93.7 [92.9, 94.4]
Implantation mechanical complication: RCT		
COMPANION[11] 2004	10/595	1.7 [0.8, 3.1]
MIRACLE ICD II[14] 2004	6/210	2.9 [1.1, 6.1]
RHYTHM-ICD[17] 2005	33/205	16.1 [11.3, 21.9]
Sub-Total:	49/1010	4.9 [3.6, 6.4]
Implantation mechanical complication: Observational studies		
Ammann[22] 2004	1/47	2.1 [0.1, 11.3]
Azizi[26] 2006	13/285	4.6 [2.5, 7.7]
Boriani[36] 2006a	3/121	2.5 [0.5, 7.1]
Pürerfellner[130] 2000a	2/44	4.5 [0.6, 15.5]
RHYTHM ICD[17] 2005	8/162	4.9 [2.2, 9.5]
Teo[111] 2003	1/29	3.4 [0.1, 17.8]
Ypenburg[117] 2006	9/191	4.7 [2.2, 8.8]
Sub Total	37/879	4.2 [3.0, 5.8]
Total [N=10]	86/1889	4.6 [3.7, 5.6]
Post-implant mechanical malfunction: RCT		
CONTAK-CD[9] 2003	22/448	4.9 [3.1, 7.3]
MIRACLE-ICD[6] 2003	25/364	6.9 [4.5, 10.0]
Sub-Total:	47/812	5.8 [4.3, 7.6]
Post-implant mechanical malfunction: Observational studies		
Kuhlkamp[270] 2002	1/84	1.2 [0.0, 6.5]
Pürerfellner[130] 2000a	1/44	2.3 [0.1, 12.0]
RHYTHM ICD[17] 2005	2/162	1.2 [0.1, 4.4]
Sub Total	4/290	1.4 [0.4, 3.5]
Total [N=5]	51/1102	4.6 [3.5, 6.0]
Post-implant device malfunction: RCT		
RHYTHM-ICD[17] 2005	20/205	9.8 [6.1, 14.7]
Sub-Total:	20/205	9.8 [6.1, 14.7]
Post-implant device malfunction: Observational studies		
Azizi[26] 2006	5/285	1.8 [0.6, 4.0]
Bocchiardo[33] 2000	2/42	4.8 [0.6, 16.2]
Boriani[36] 2006a	8/121	6.6 [2.9, 12.6]
Ellery[52] 2005	7/95	7.4 [3.0, 14.6]
Gasparini[57] 2003a	2/142	1.4 [0.2, 5.0]
RHYTHM ICD[17] 2005	25/162	15.4 [10.2, 21.9]
Saxon[106] 2006	1/168	0.6 [0.0, 3.3]
Ypenburg[117] 2006	1/191	0.5 [0.0, 2.9]
Sub Total	51/1206	4.2 [3.2, 5.5]
Total [N=9]	71/1411	5.0 [4.0, 6.3]

Table 23. Peri- and post-implnantation risks: combined CRT-ICD (continued)

Study, Author Year	n/N	Simple pool risk, % [95% CI]
Post-implant lead problems: RCT		
CONTAK-CD[9] 2003	31/448	6.9 [4.7, 9.7]
MIRACLE ICD[6] 2003	46/364	12.6 [9.4, 16.5]
MIRACLE ICD II[14] 2004	19/191	9.9 [6.1, 15.1]
RHYTHM ICD[17] 2005	22/205	10.7 [6.8, 15.8]
Sub-Total:	118/1208	9.8 [8.2, 11.6]
Post-implant lead problems: Observational studies		
Ammann[22] 2004	3/47	6.4 [1.3, 17.5]
Azizi[26] 2006	13/285	4.6 [2.5, 7.7]
Bocchiardo[33] 2000	3/42	7.1 [1.5, 19.5]
Boriani[36] 2006a	31/121	25.6 [18.1, 34.4]
Cowburn[44] 2005	4/68	5.9 [1.6, 14.4]
Da Costa[45] 2006	3/67	4.5 [0.9, 12.5]
Diaz-Infante[49] 2005	2/177	1.1 [0.1, 4.0]
Ellery[52] 2005	5/95	5.3 [1.7, 11.9]
Ermis[53] 2004	1/126	0.8 [0.0, 4.3]
RHYTHM ICD[17] 2005	4/162	2.5 [0.7, 6.2]
Gasparini[127] 2005	5/194	2.6 [0.8, 5.9]
Krahn[64] 2002	4/40	10.0 [2.8, 23.7]
Kuhlkamp[270] 2002	7/84	8.3 [3.4, 16.4]
Molhoek[82] 2005	10/117	8.5 [4.2, 15.2]
Pürerfellner[130] 2005a	4/44	9.1 [2.5, 21.7]
Pürerfellner[130] 2005b	1/150	0.7 [0.0, 3.7]
Reuter[100] 2002	4/91	4.4 [1.2, 10.9]
Ritter[102] 2006	7/48	14.6 [6.1, 27.8]
Salukhe[104] 2005	2/40	5.0 [0.6, 16.9]
Saxon[106] 2006	11/168	6.5 [3.3, 11.4]
Teo[111] 2003	2/29	6.9 [0.8, 22.8]
Sub Total	126/2195	5.7 [4.8, 6.8]
Total [N=25]	244/3403	7.2 [6.3, 8.1]
Post-implant infections: RCT		
CONTAK CD[9] (Knight 2004)	5/443	1.1 [0.4, 2.6]
MIRACLE-ICD[6] 2003	2/364	0.5 [0.1, 2.0]
Sub-Total:	7/807	0.9 [0.3, 1.8]
Post-implant infections: Observational studies		
Azizi[26] 2006	2/285	0.7 [0.1, 2.5]
Cowburn[44] 2005	1/68	1.5 [0.0, 7.9]
Da Costa[45] 2006	1/67	1.5 [0.0, 8.0]
Ellery[52] 2005	0/85	0.0 [0.0, 3.5]
Kuhlkamp[270] 2002	2/84	2.4 [0.3, 8.3]
Molhoek[82] 2005	0/125	0.0 [0.0, 2.4]
Reuter[100] 2002	0/102	0.0 [0.0, 2.9]
Saxon[106] 2006	7/168	4.2 [1.7, 8.4]
Sub Total	13/984	1.3 [0.7, 2.2]
Total [N=10]	20/1791	1.1 [0.7, 1.7]
Post-implant arrhythmias: RCT		
CONTAK-CD[9] 2003	36/245	14.7 [10.5, 19.8]
MIRACLE-ICD[6] 2003	3/364	0.8 [0.2, 2.4]
Total [N=2]	39/609	6.4 [4.6, 8.7]

Table 23. Peri- and post-implnantation risks: combined CRT-ICD (continued)

Study, Author Year	n/N	Simple pool risk, % [95% CI]
Inappropriate shocks: RCT		
RHYTHM ICD[17] 2005	10/205	4.9 [2.4, 8.8]
Sub-Total:	10/205	4.9 [2.4, 8.8]
Inappropriate shocks: Observational studies		
Bocchiardo[33] 2000	6/42	14.3 [5.4, 28.5]
Boriani[36] 2006	4/121	3.3 [0.9, 8.2]
Chugh[123] 2005	12/77	15.6 [8.3, 25.6]
Ermis[53] 2004	3/62	4.8 [1.0, 13.5]
RHYTHM ICD[17] 2005	1/162	0.6 [0.0, 3.4]
Gaita[55] 2000	4/96	4.2 [1.1, 10.3]
Saxon[106] 2006	1/168	0.6 [0.0, 3.3]
Theuns[112] 2005	18/86	20.9 [12.9, 31.0]
Sub Total	63/1005	6.3 [4.9, 7.9]
Total [N=9]	73/1210	6.0 [4.8, 7.5]

Table 24. Peri- and post-implantation risks: ICD alone

Study, Author Year	n/N	Simple pool risk,% [95% CI]
Peri-implant deaths: RCT		
AVID[141] 1997	4/492	0.8 [0.2, 2.1]
CABG-Patch[134] 1997	24/434	5.5 [3.6, 8.1]
CASH[143] 2000	5/99	5.1 [1.7, 11.4]
CAT[136] 2002	0/50	0.0 [0.0, 5.8]
CIDS[142] 1999	2/310	0.6 [0.1, 2.3]
DEFINITE[138] 2004	0/229	0.0 [0.0, 1.3]
DINAMIT[139] 2004	0/310	0.0 [0.0, 1.0]
MADIT[133] 1996	0/90	0.0 [0.0, 3.3]
Sub-Total:	35/2014	1.7 [1.2, 2.4]
Peri-implant deaths: Observational studies		
Alter[144] 2005	1/440	0.2 [0.0, 1.3]
Backenkohler[145] 2005	0/245	0.0 [0.0, 1.2]
Bode-Schnurbus[147] 2003	5/165	3.0 [1.0, 6.9]
Bokhari[148] 2004	0/60	0.0 [0.0, 4.9]
Carlsson[192] 2003	0/96	0.0 [0.0, 3.1]
Cuesta[155] 2003	0/120	0.0 [0.0, 2.5]
Duray[158] 2005	0/375	0.0 [0.0, 0.8]
Ermis[161] 2003	0/59	0.0 [0.0, 5.0]
Evonich[162] 2004	0/153	0.0 [0.0, 1.9]
Grimm[165] 2002	0/101	0.0 [0.0, 2.9]
Leosdottir[169] 2006	1/62	1.6 [0.0, 8.7]
Niehaus[198] 2003	0/25	0.0 [0.0, 11.3]
Noseworthy[171] 2004	0/209	0.0 [0.0, 1.4]
Raviele[176] 2005	0/24	0.0 [0.0, 11.7]
Russo[178] 2003	0/51	0.0 [0.0, 5.7]
Takahashi[184] 2002	0/178	0.0 [0.0, 1.7]
Telfer[186] 2002	0/22	0.0 [0.0, 12.7]
Theuns[187] 2005b	0/127	0.0 [0.0, 2.3]
Trappe[188] 2002	12/410	2.9 [1.5, 5.1]
Wase[189] 2004	5/93	5.4 [1.8, 12.1]
Sub Total	24/3015	0.8 [0.5, 1.2]
Total [N=28]	59/5029	1.2 [0.9, 1.5]
Implant success rate: RCT		
AVID[141] 1997	488/492	99.2 [97.9, 99.8]
CABG-Patch[134] 1997	434/446	97.3 [95.3, 98.6]
CASH[143] 2000	99/99	100.0 [97.0, 100.0]
CIDS[142] 2000	310/328	94.5 [91.5, 96.7]
DEFINITE[138] 2004	227/229	99.1 [96.9, 99.9]
DINAMIT[139] 2004	310/332	93.4 [90.1, 95.8]
Dorian[193] 2004a	149/149	100.0 [98.0, 100.0]
MADIT[133] 1996	90/90	100.0 [96.7, 100.0]
MADIT II[135] 2002	739/739	100.0 [99.6, 100.0]
SCD-HeFT[140] 2005	811/812	99.9 [99.3, 100.0]
Sub-Total:	3657/3716	98.4 [98.0, 98.8]
Implant success rate: Observational studies		
Alter[144] 2005	440/440	100.0 [99.3, 100.0]
Bode-Schnurbus[147] 2003	165/165	100.0 [98.2, 100.0]
Bokhari[148] 2004	60/60	100.0 [95.1, 100.0]
Capoferri[152] 2004	100/100	100.0 [97.0, 100.0]

RCT=randomized control trial

Table 24. Peri- and post-implantation risks: ICD alone (continued)

Study, Author Year	n/N	Simple pool risk, % [95% CI]
Implant success rate: Observational studies (continued)		
Carlsson[192] 2003	96/96	100.0 [96.9, 100.0]
Cuesta[155] 2003	120//120	100.0 [97.5, 100.0]
Dubner[157] 2005	761/761	100.0 [99.6, 100.0]
Duray[158] 2005	375/375	100.0 [99.2, 100.0]
Ermis[161] 2003	59/59	100.0 [95.0, 100.0]
Niehaus[198] 2003	25/25	100.0 [88.7, 100.0]
Raviele[176] 2005	24/24	100.0 [88.3, 100.0]
Russo[178] 2003	51/51	100.0 [94.3, 100.0]
Sanchez[180] 2005	19/19	100.0 [85.4, 100.0]
Takahashi[184] 2002	178/178	100.0 [98.3, 100.0]
Sub-Total:	2473/2473	100.0 [99.9, 100.0]
Total [N=24]	6130/6189	99.0 [98.8, 99.3]
Implantation mechanical complication: RCT		
AVID[141] 1997	28/507	5.5 [3.7, 7.9]
CASH[143] 2000	11/99	11.1 [5.7, 19.0]
DEFINITE[138] 2004	3/227	1.3 [0.3, 3.8]
MADIT[133] 1996	5/95	5.3 [1.7, 11.9]
SCD-HeFT[140] 2005	41/812	5.0 [3.6, 6.8]
Sub-Total:	88/1740	5.1 [4.1, 6.2]
Implantation mechanical complication: Observational studies		
Alter[144] 2005	26/440	5.9 [3.9, 8.5]
Bokhari[148] 2004	3/60	5.0 [1.0, 13.9]
Carlsson[192] 2003	0/96	0.0 [0.0, 3.1]
Cuesta[155] 2003	8/120	6.7 [2.9, 12.7]
Evonich[162] 2004	17/153	11.1 [6.6, 17.2]
Grimm[165] 2002	2/101	2.0 [0.2, 7.0]
Leosdottir[169] 2006	13/62	21.0 [11.7, 33.2]
Noseworthy[171] 2004	12/212	5.7 [3.0, 9.7]
Raviele[176] 2005	0/24	0.0 [0.0, 11.7]
Russo[178] 2003	1/51	2.0 [0.0, 10.4]
Saba[179] 2003	0/35	0.0 [0.0, 8.2]
Takahashi[184] 2002	6/178	3.4 [1.2, 7.2]
Telfer[186] 2002	0/27	0.0 [0.0, 10.5]
Sub Total	88/1559	5.6 [4.6, 6.9]
Total [N=18]	176/3299	5.3 [4.6, 6.2]
Post-implant mechanical malfunction: RCT		
CAT[136] 2002	4/104	3.8 [1.1, 9.6]
DEFINITE[138] 2004	3/227	1.3 [0.3, 3.8]
Friedman[194] 2006	4/400	1.0 [0.3, 2.5]
Sub-Total:	11/731	1.5 [0.8, 2.7]
Post-implant mechanical malfunction: Observational studies		
Alter[144] 2005	2/440	0.5 [0.1, 1.6]
Duray[158] 2005	22/375	5.9 [3.7, 8.7]
Evonich[162] 2004	4/153	2.6 [0.7, 6.6]
Grimm[165] 2002	2/101	2.0 [0.2, 7.0]
Noseworthy[171] 2004	1/212	0.5 [0.0, 2.6]
Post-implant mechanical malfunction: Observational studies		
Takahashi[184] 2002	2/178	1.1 [0.1, 4.0]
Sub Total	33/1459	2.3 [1.6, 3.2]
Total [N=9]	44/2190	2.0 [1.5, 2.7]

Table 24. Peri- and post-implantation risks: ICD alone (continued)

Study, Author Year	n/N	Simple pool risk, % [95% CI]
Post-implant device malfunction: RCT		
CASH[143] 2000	5/99	5.1 [1.7, 11.4]
CAT[136] 2002	8/104	7.7 [3.4, 14.6]
CIDS[142] 2000	2/328	0.6 [0.1, 2.2]
MADIT[133] 1996	3/95	3.2 [0.7, 9.0]
SCD-HeFT[140] 2005	73/812	9.0 [7.1, 11.2]
Sub-Total:	91/1438	6.3 [5.1, 7.7]
Post-implant device malfunction: Observational studies		
Alter[144] 2005	26/440	5.9 [3.9, 8.5]
Duray[158] 2005	15/375	4.0 [2.3, 6.5]
Evonich[162] 2004	9/153	5.9 [2.7, 10.9]
Grimm[165] 2002	4/101	4.0 [1.1, 9.8]
Leosdottir[169] 2006	3/62	4.8 [1.0, 13.5]
Sub Total	57/1131	5.0 [3.8, 6.5]
Total [N=10]	148/2569	5.8 [4.9, 6.7]
Post-implant lead problems: RCT		
AVID[141] 1997	3/507	0.6 [0.1, 1.7]
CASH[143] 2000	3/99	3.0 [0.6, 8.6]
CIDS[142] 2000	8/328	2.4 [1.1, 4.7]
DEFINITE[138] 2004	6/227	2.6 [1.0, 5.7]
Friedman[194] 2006	5/400	1.3 [0.4, 2.9]
MADIT II[135] 2002	13/742	1.8 [0.9, 3.0]
Sub-Total	38/2303	1.7 [1.2, 2.3]
Post-implant lead problems: Observational		
Alter[144] 2005	52/440	11.8 [9.0, 15.2]
Bokhari[148] 2004	18/60	30.0 [18.8, 43.2]
Ellenbogen[160] 2003	19/74	25.7 [16.2, 37.2]
Evonich[162] 2004	2/153	1.3 [0.2, 4.6]
Grimm[165] 2002	8/101	7.9 [3.5, 15.0]
Leosdottir[169] 2006	10/62	16.1 [8.0, 27.7]
Niehaus[198] 2003	1/25	4.0 [0.1, 20.4]
Noseworthy[171] 2004	1/212	0.5 [0.0, 2.6]
Sanchez[181] 2006	1/105	1.0 [0.0, 5.2]
Takahashi[184] 2002	11/178	6.2 [3.1, 10.8]
Sub-Total	123/1410	8.7 [7.3, 10.3]
Total [N=16]	161/3713	4.3 [3.7, 5.0]
Post-implant infections: RCT		
AVID[141] 1997	10/492	2.0 [1.0, 3.7]
CABG-Patch[134] 1997	19/434	4.4 [2.7, 6.8]
CASH[143] 2000	3/99	3.0 [0.6, 8.6]
CIDS[142] 2000	15/310	4.8 [2.7, 7.9]
DEFINITE[138] 2004	1/229	0.4 [0.0, 2.4]
Dorian[193] 2004a	3/141	2.1 [0.4, 6.1]
MADIT[133] 1996	2/90	2.2 [0.3, 7.8]
MADIT II[135] 2002	5/739	0.7 [0.2, 1.6]
Sub-Total:	58/2534	2.3 [1.7, 2.9]
Post-implant infections: Observational studies		
Alter[144] 2005	2/440	0.5 [0.1, 1.6]
Bokhari[148] 2004	3/60	5.0 [1.0, 13.9]
Cuesta[155] 2003	2/120	1.7 [0.2, 5.9]
Duray[158] 2005	1/375	0.3 [0.0, 1.5]
Evonich[162] 2004	4/153	2.6 [0.7, 6.6]
Grimm[165] 2002	0/101	0.0 [0.0, 2.9]
Leosdottir[169] 2006	1/62	1.6 [0.0, 8.7]

Table 24. Peri- and post-implantation risks: ICD alone (continued)

Study, Author Year	n/N	Simple pool risk, % [95% CI]
Noseworthy[171] 2004	2/209	1.0 [0.1, 3.4]
Takahashi[184] 2002	3/178	1.7 [0.3, 4.8]
Sub Total	18/1698	1.1 [0.6, 1.7]
Total [N=17]	76/4232	1.8 [1.4, 2.2]
Inappropriate shocks: RCT		
AVID[141] 1997	106/171	62.0 [54.3, 69.3]
DEFINITE[138] 2004	49/229	21.4 [16.3, 27.3]
Sub-Total:	155/400	38.8 [33.9, 43.7]
Inappropriate shocks: Observational studies		
Alter[144] 2005	54/440	12.3 [9.4, 15.7]
Backenkohler[145] 2005	6/245	2.4 [0.9, 5.3]
Bokhari[148] 2004	30/44	68.2 [52.4, 81.4]
Capoferri[152] 2004	19/90	21.1 [13.2, 31.0]
Dorian[193] 2004a	51/141	36.2 [28.3, 44.7]
Dorian[156] 2004b	57/212	26.9 [21.0, 33.4]
Ermis[161] 2003	4/17	23.5 [6.8, 49.9]
Evonich[162] 2004	37/153	24.2 [17.6, 31.8]
Grimm[165] 2002	16/101	15.8 [9.3, 24.4]
Grimm[195] 2006	8/93	8.6 [3.8, 16.2]
Hreybe[196] 2006	32/230	13.9 [9.7, 19.1]
Leosdottir[169] 2006	10/62	16.1 [8.0, 27.7]
Niehaus[198] 2003	2/25	8.0 [1.0, 26.0]
Noseworthy[171] 2004	1/212	0.5 [0.0, 2.6]
Raviele[176] 2005	4/24	16.7 [4.7, 37.4]
Russo[178] 2003	5/51	9.8 [3.3, 21.4]
Saeed[199] 2003	5/48	10.4 [3.5, 22.7]
Sanchez[180] 2005	4/17	23.5 [6.8, 49.9]
Sanchez[181] 2006	7/105	6.7 [2.7, 13.3]
Takahashi[184] 2002	3/176	1.7 [0.4, 4.9]
Telfer[186] 2002	7/22	31.8 [13.9, 54.9]
Theuns[200] 2004	37/98	37.8 [28.2, 48.1]
Theuns[201] 2005a	18/60	30.0 [18.8, 43.2]
Tiroke[202] 2003	38/149	25.5 [18.7, 33.3]
Zecchin[191] 2004	11/46	23.9 [12.6, 38.8]
Sub Total	466/2861	16.3 [15.0, 17.7]
Total [N=27]	621/3261	19.0 [17.7, 20.4]

Table 25. Peri- and post-implantation risks with ICD in studies that were not restricted to patients with left ventricular systolic dysfunction

Trial name, Author Study year	n/N	Simple pool risk, % [95% CI]
Peri-implant deaths: RCT		
Bansch[205] 2004	0/50	0.0 [0.0, 5.8]
Boriani[206] 2003	0/89	0.0 [0.0, 3.3]
Nademanee[210] 2003	0/47	0.0 [0.0, 6.2]
Vollman[213] 2003	0/539	0.0 [0.0, 0.6]
Sub-Total:	0/725	0.0 [0.0, 0.4]
Peri-implant deaths: Observational studies		
Al-Khatib[204] 2005	237/9854	2.4 [2.1, 2.7]
Brockes[207] 2002	3/76	3.9 [0.8, 11.1]
Reynolds[203] 2006	208/23110	0.9 [0.8, 1.0]
Rosenqvist[211] 1998	6/778	0.8 [0.3, 1.7]
Schlapfer[212] 2002	0/41	0.0 [0.0, 7.0]
Wiegand[214] 2004	0/372	0.0 [0.0, 0.8]
Sub Total	454/34231	1.3 [1.2, 1.5]
Total [N=10]	454/34956	1.3 [1.2, 1.4]
Implant success rate: RCT		
Bansch[205] 2004	102/102	100.0 [97.1, 100.0]
Boriani[206] 2003	88/89	98.9 [93.9, 100.0]
Nademanee[210] 2003	47/47	100.0 [93.8, 100.0]
Vollman[213] 2003	529/539	98.1 [96.6, 99.1]
Sub-Total:	766/777	98.6 [97.5, 99.3]
Implant success rate: Observational studies		
Gradaus[208] 2003	3294/3344	98.5 [98.0, 98.9]
Rosenqvist[211] 1998	772/778	99.2 [98.3, 99.7]
Schapfer[212] 2002	41/41	100.0 [93.0, 100.0]
Sub Total	4107/4163	98.7 [98.3, 99.0]
Total [N=7]	4873/4940	98.6 [98.3, 98.9]

Figure 4. Metagraph of all-cause mortality: CRT alone

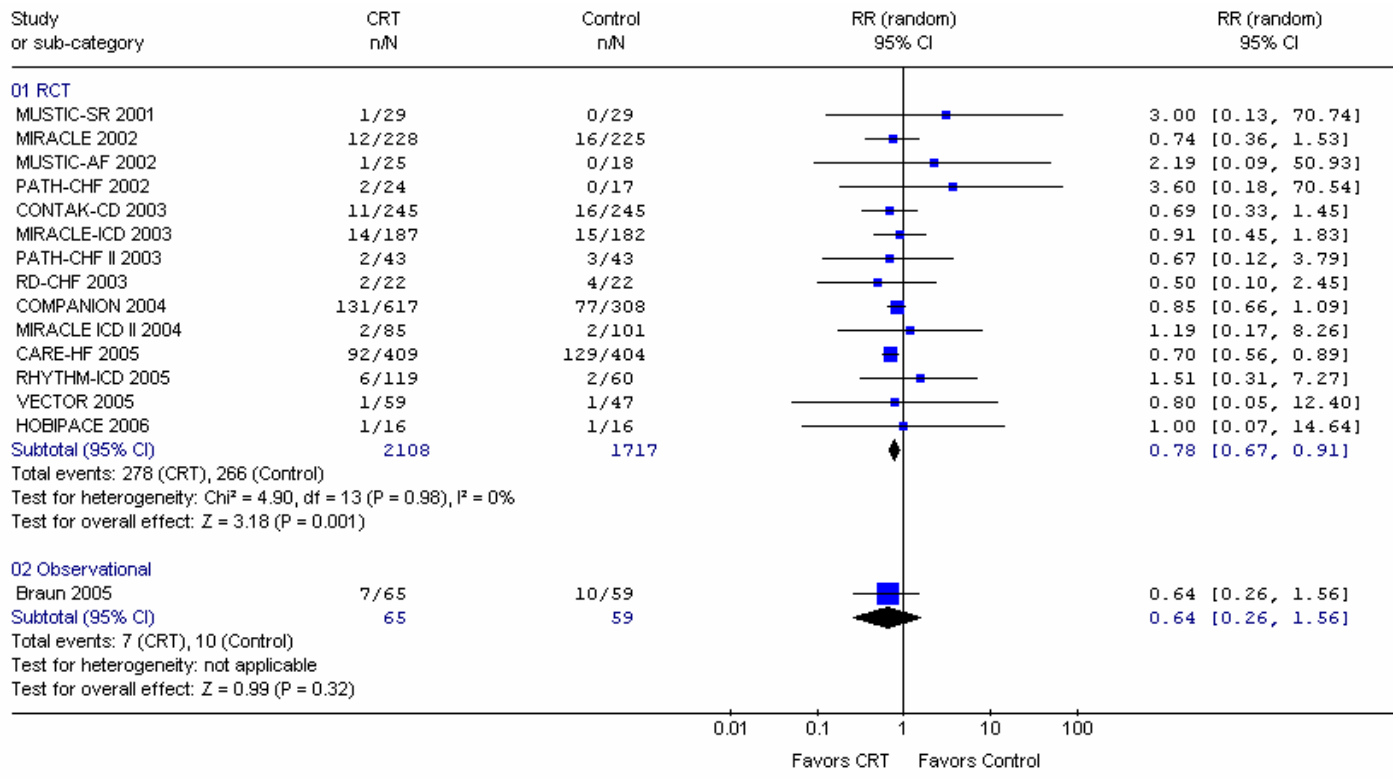


Figure 5. Metagraph of mortality due to progressive heart failure: CRT alone

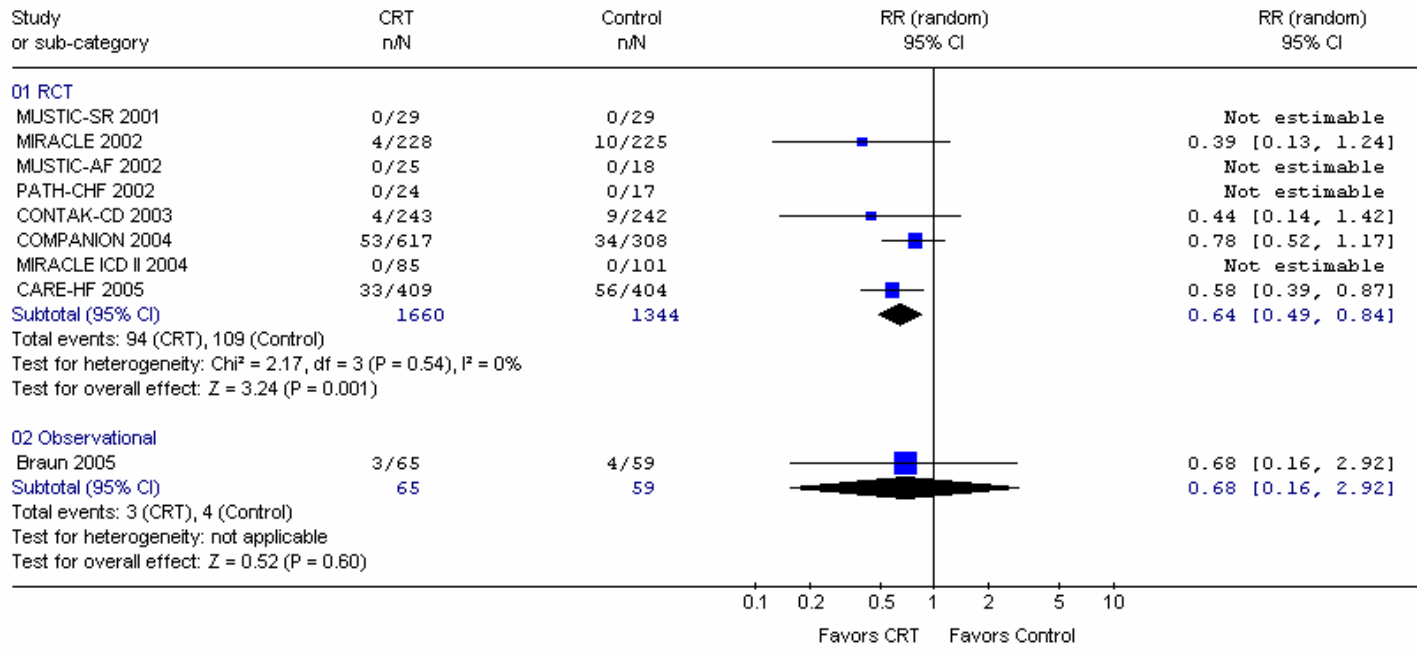


Figure 6. Metagraph of mortality due to sudden cardiac death: CRT alone

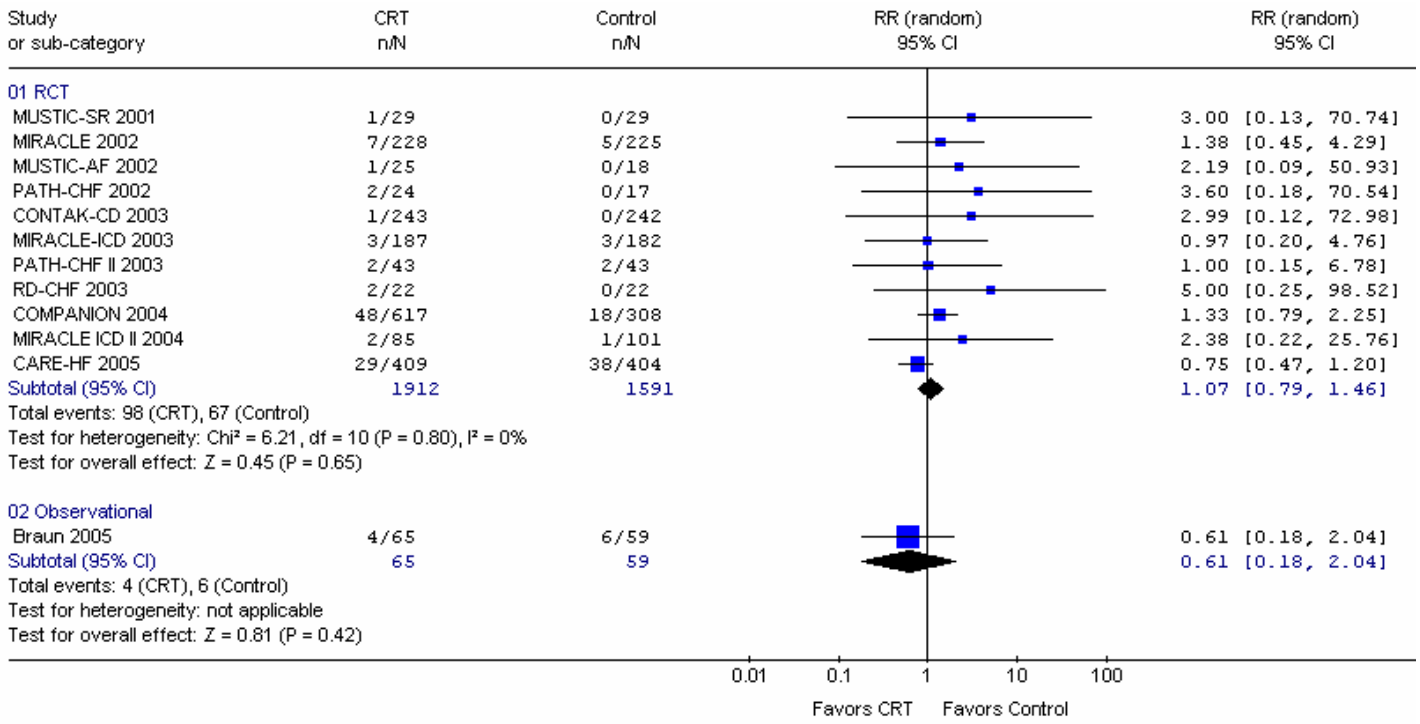


Figure 7. Metagraph of mortality due to noncardiac death: CRT alone

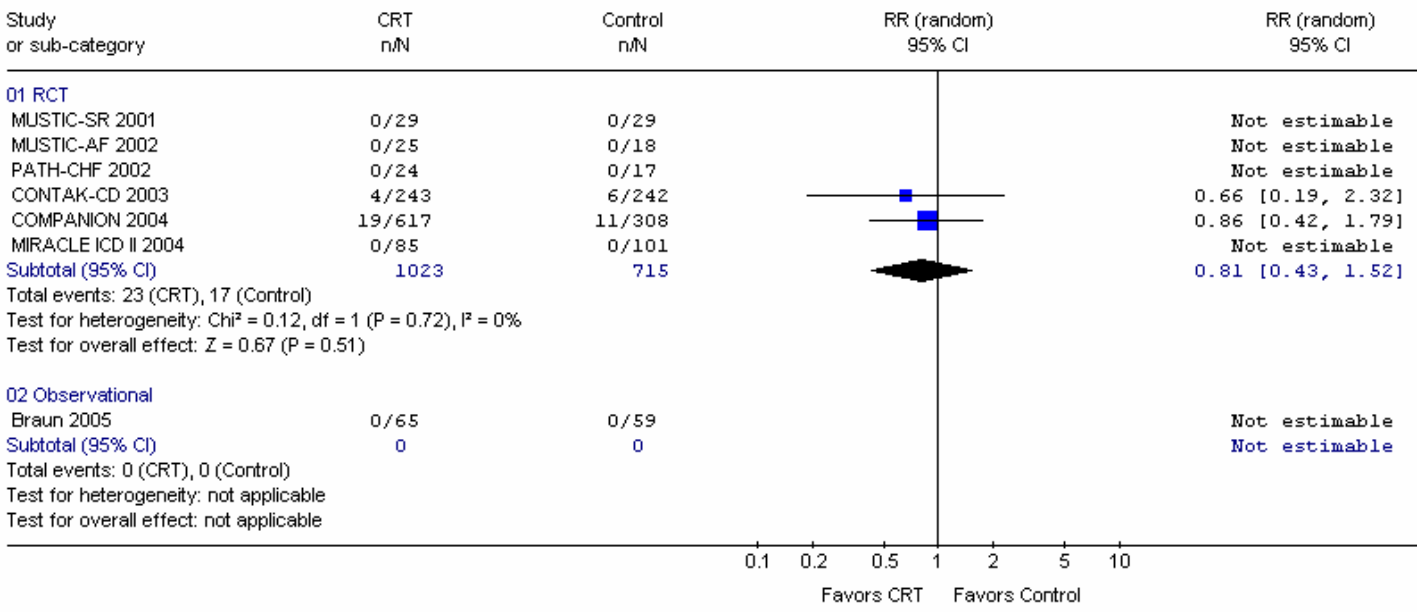


Figure 8. Metagraph of heart failure hospitalizations: CRT alone

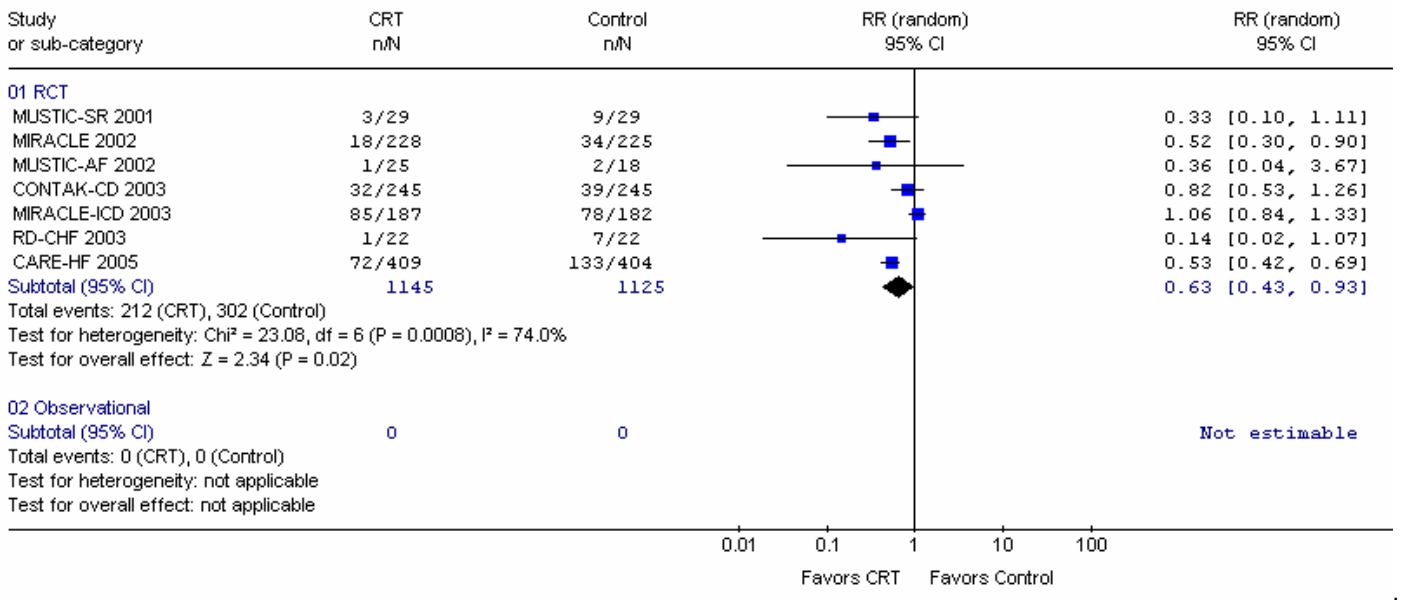


Figure 9. Metagraph of 6-minute walk test: CRT alone

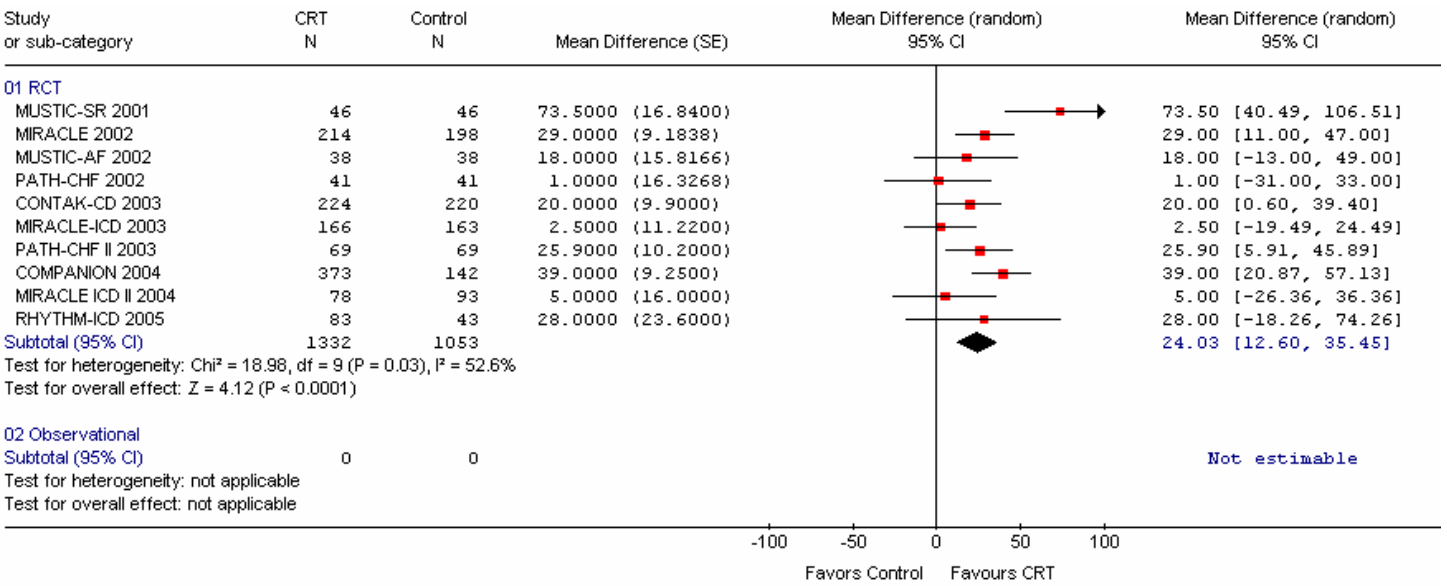


Figure 10. Metagraph of improvement in NYHA functional class: CRT alone

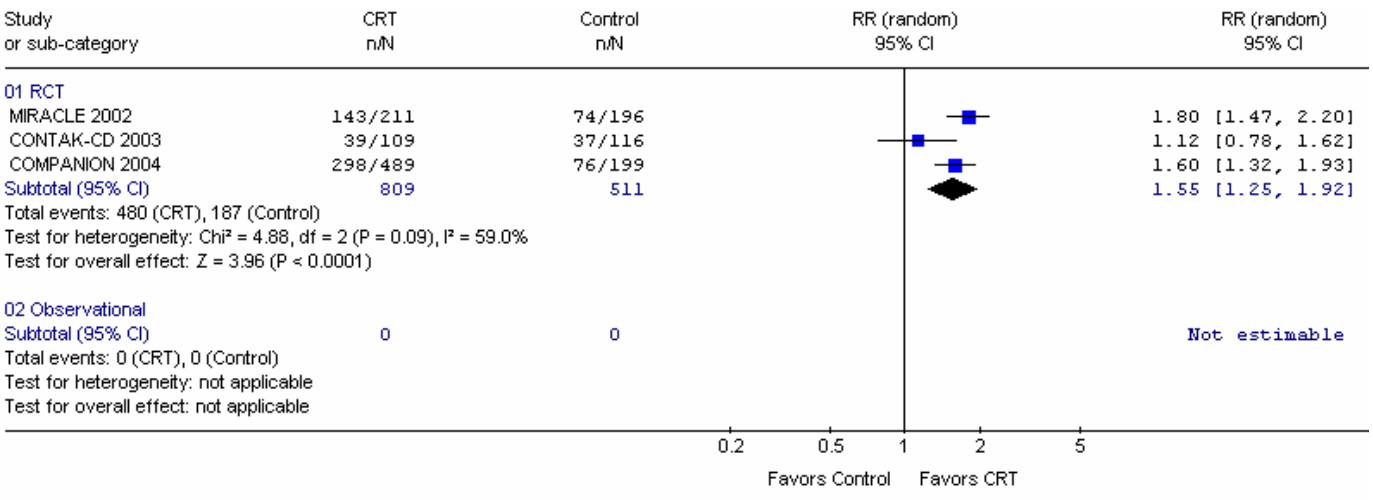
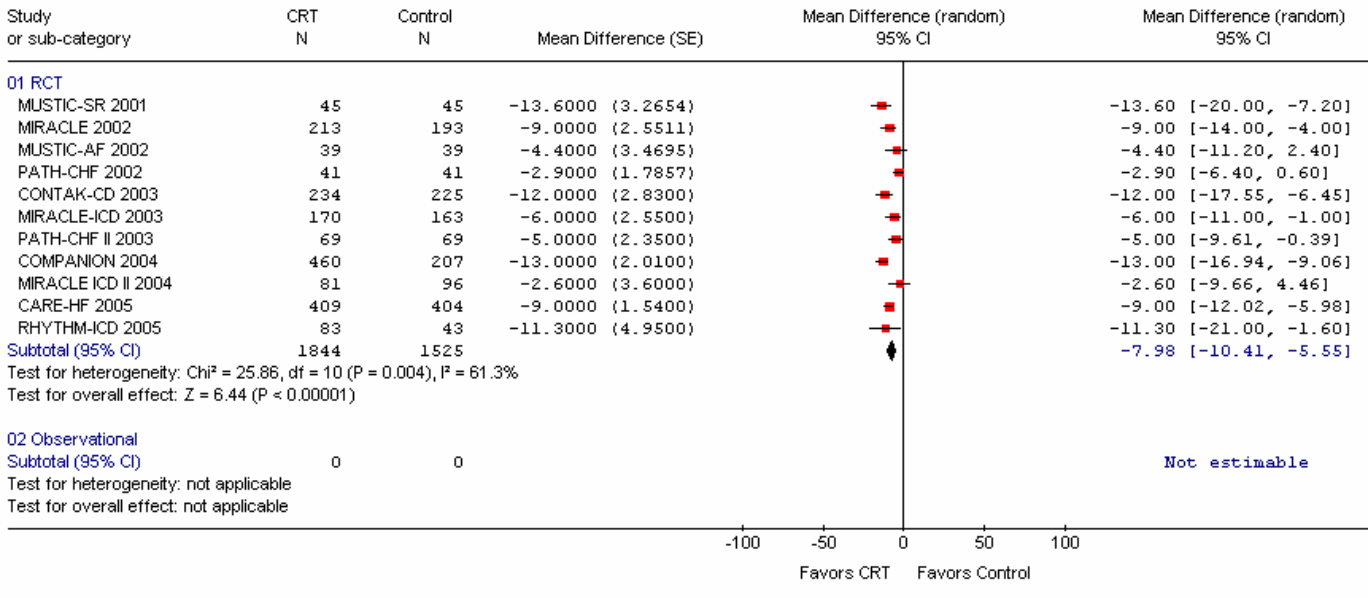


Figure 11. Metagraph of quality of life (MLHFI): CRT alone



MLHFI = Minnesota Living with Heart Failure Instrument

Figure 12. Metagraph of left ventricular ejection fraction: CRT alone

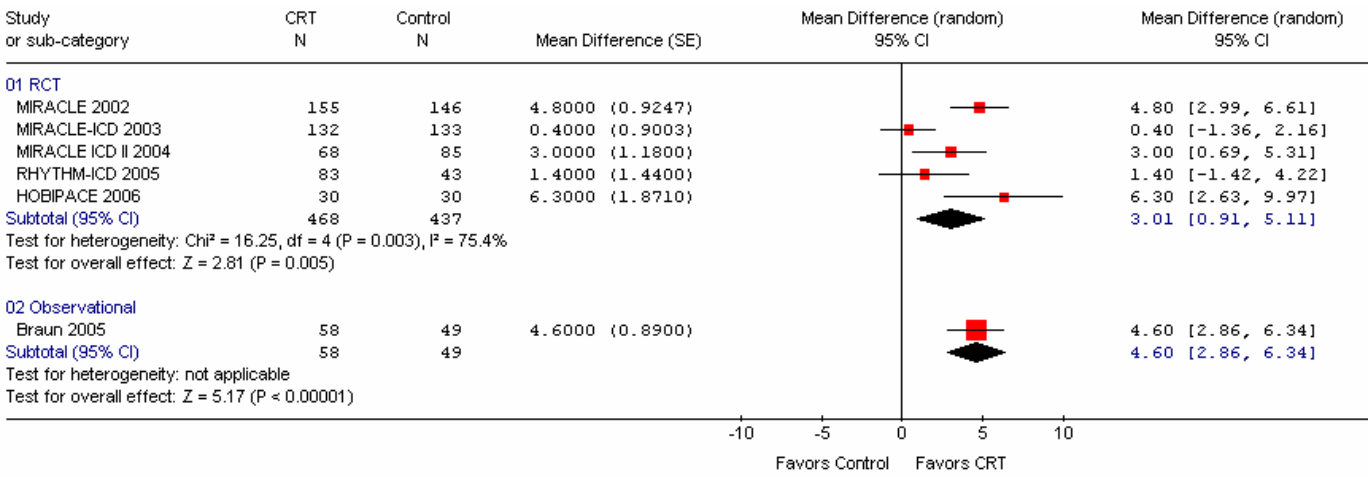


Figure 13. Metagraph of all-cause mortality: CRT alone or combined CRT-ICD devices

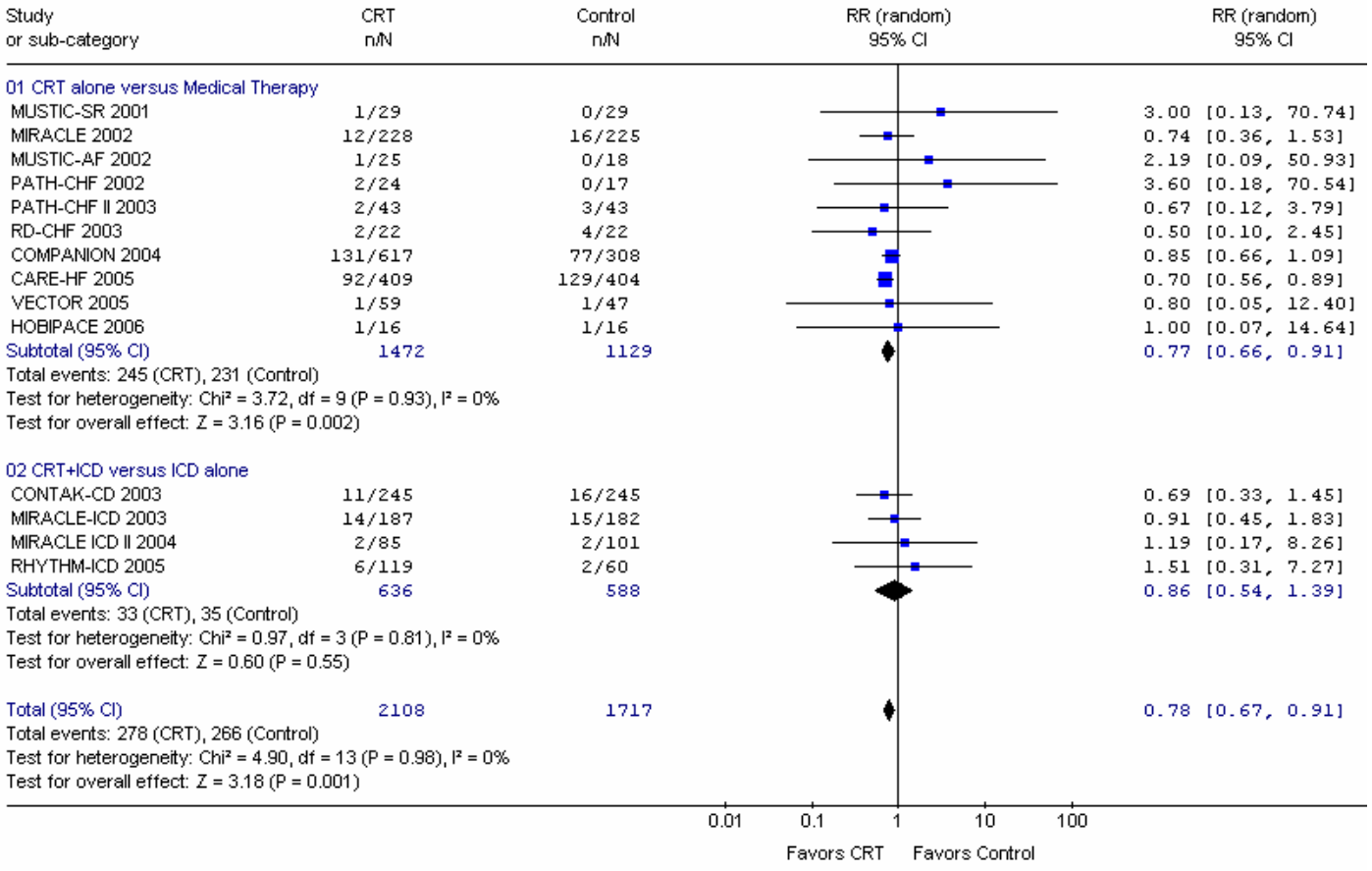


Figure 14. Funnel plot for all-cause mortality: CRT alone

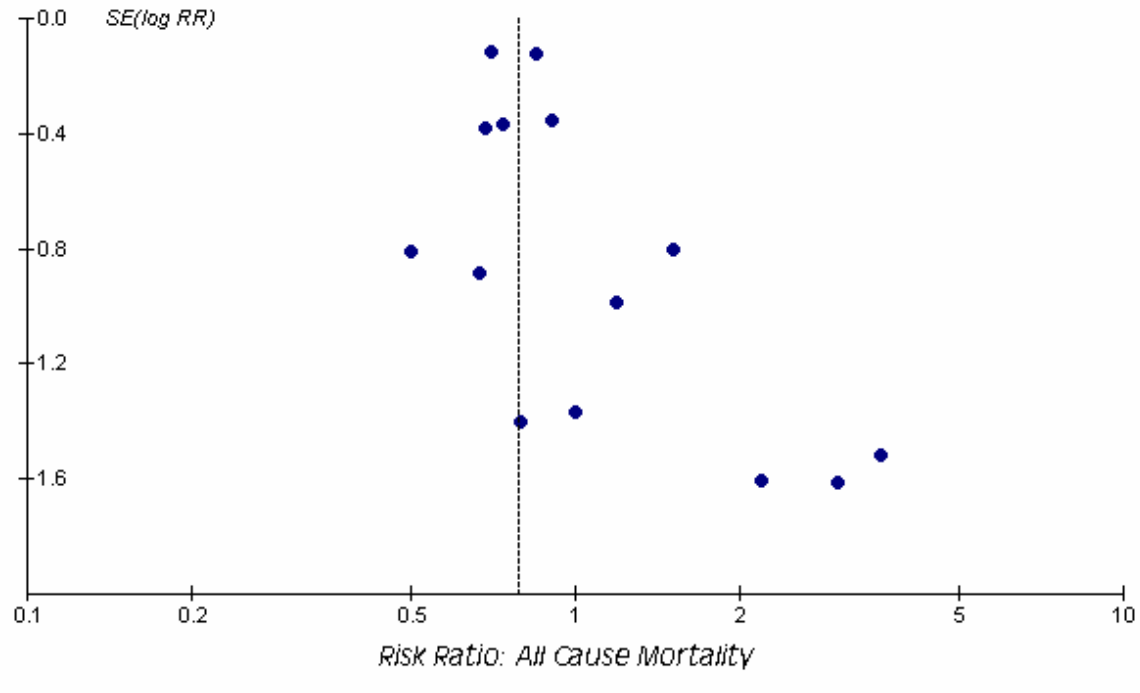


Figure 15. Metagraph of all-cause mortality: ICD alone

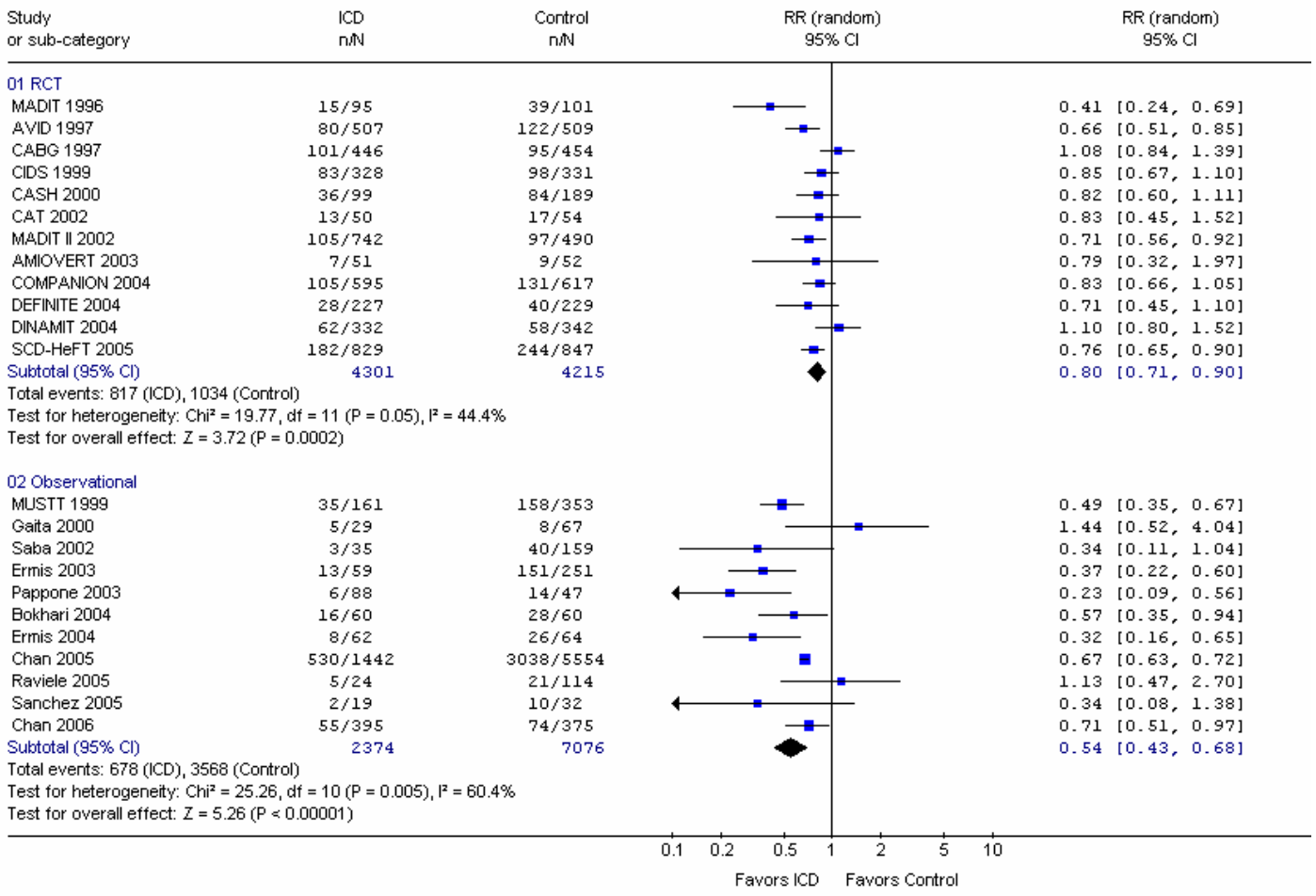


Figure 16. Metagraph of death due to progressive heart failure: ICD alone

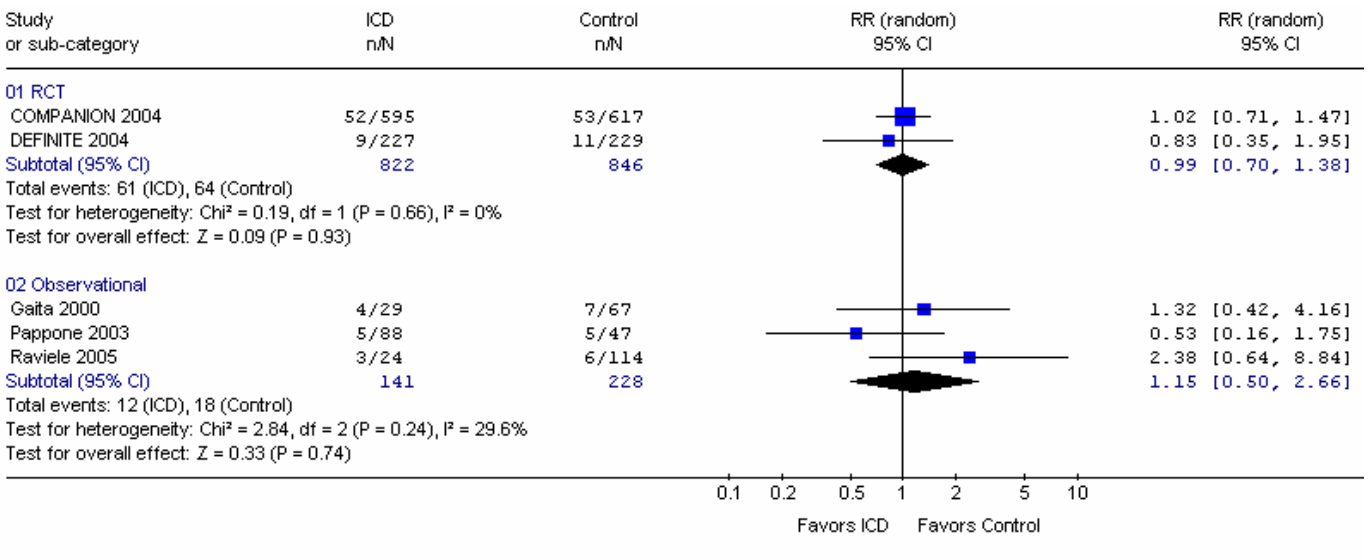


Figure 17. Metagraph of mortality due to sudden cardiac death: ICD alone

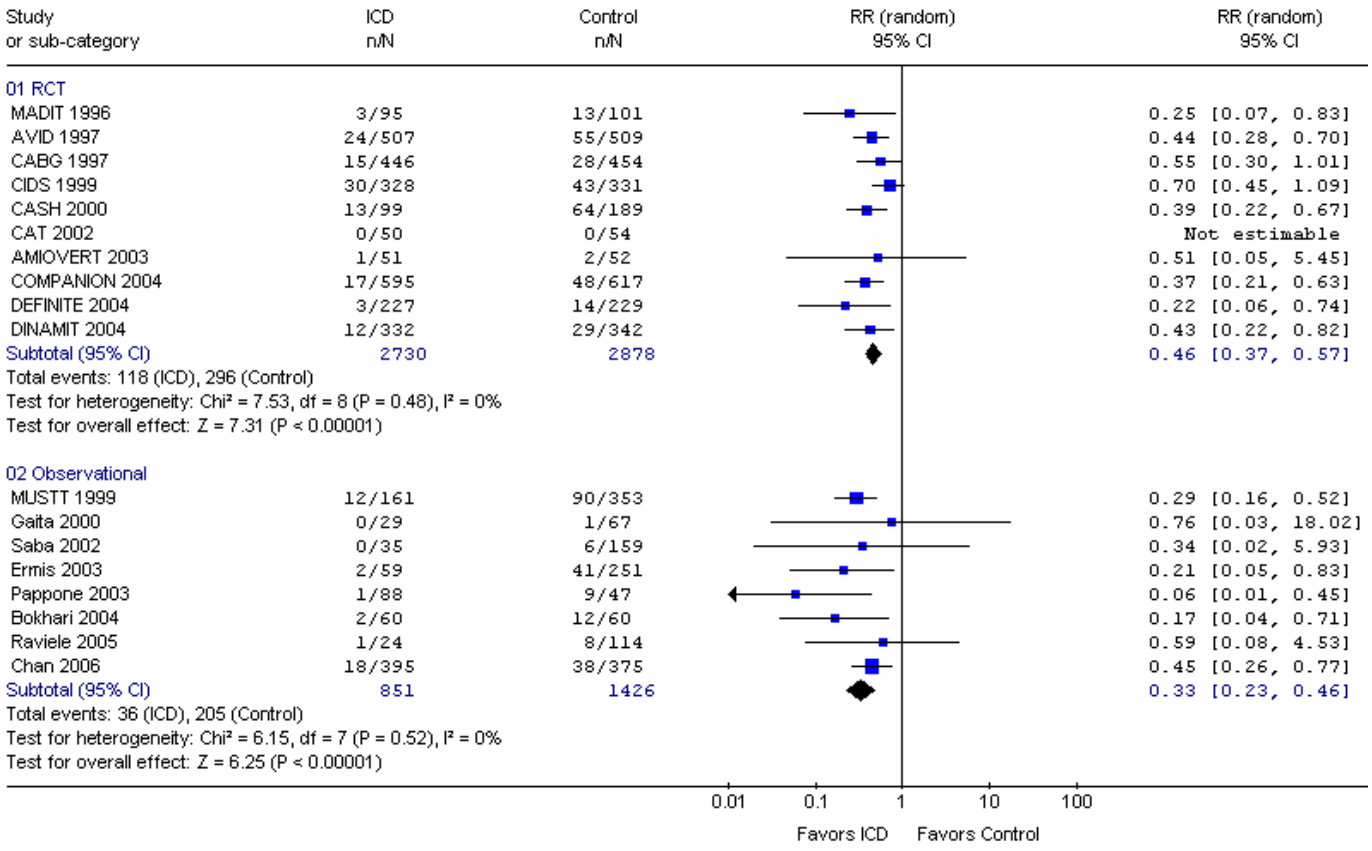


Figure 18. Metagraph of mortality due to non-cardiac death: ICD alone

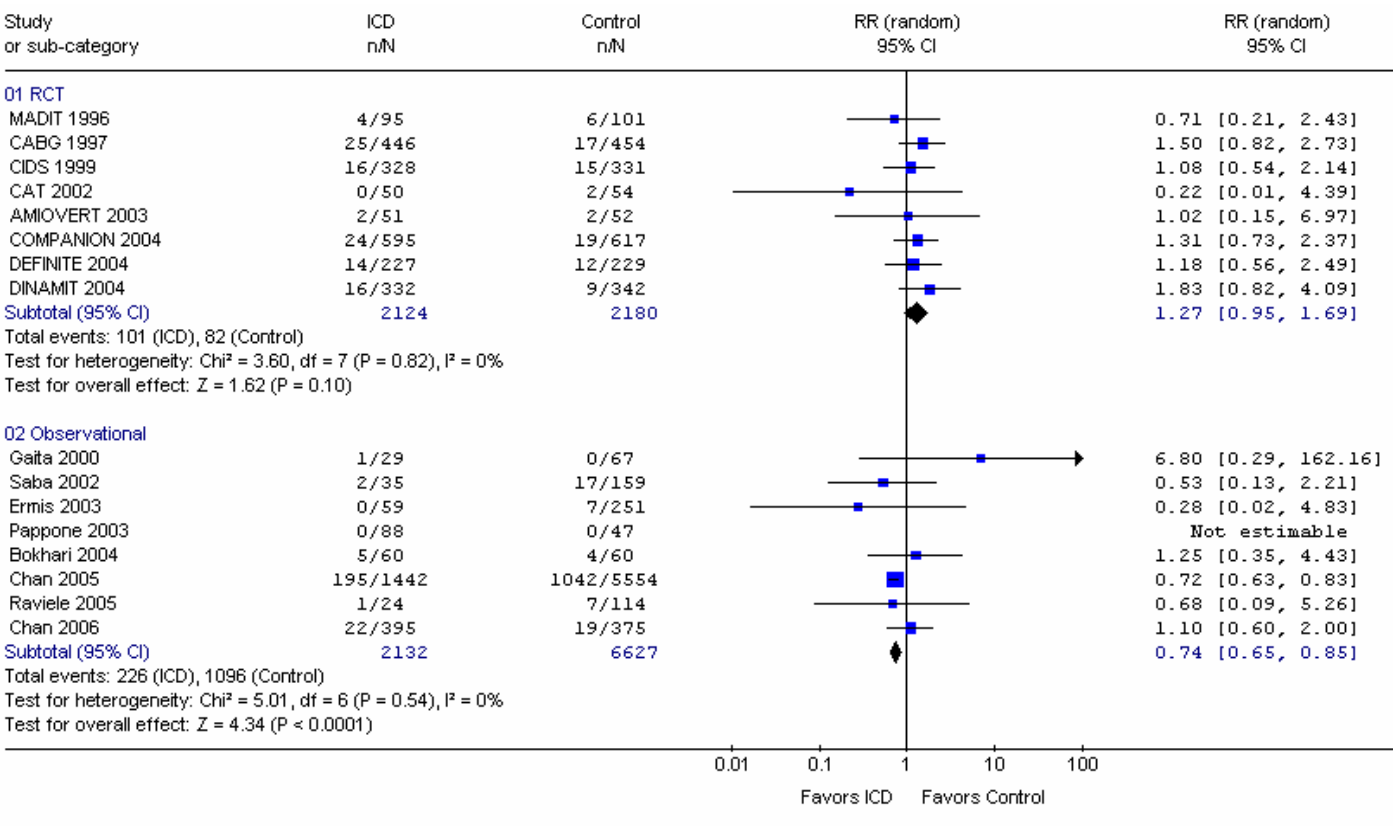


Figure 19. Metagraph of heart failure hospitalizations: ICD alone

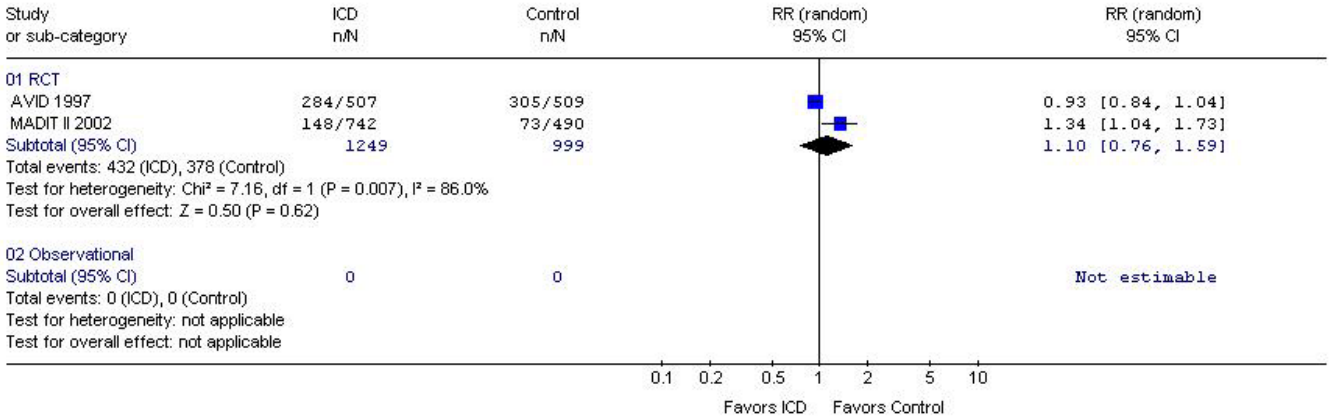


Figure 20. Summary results for all-cause mortality: ICD alone, stratified by primary or secondary prevention

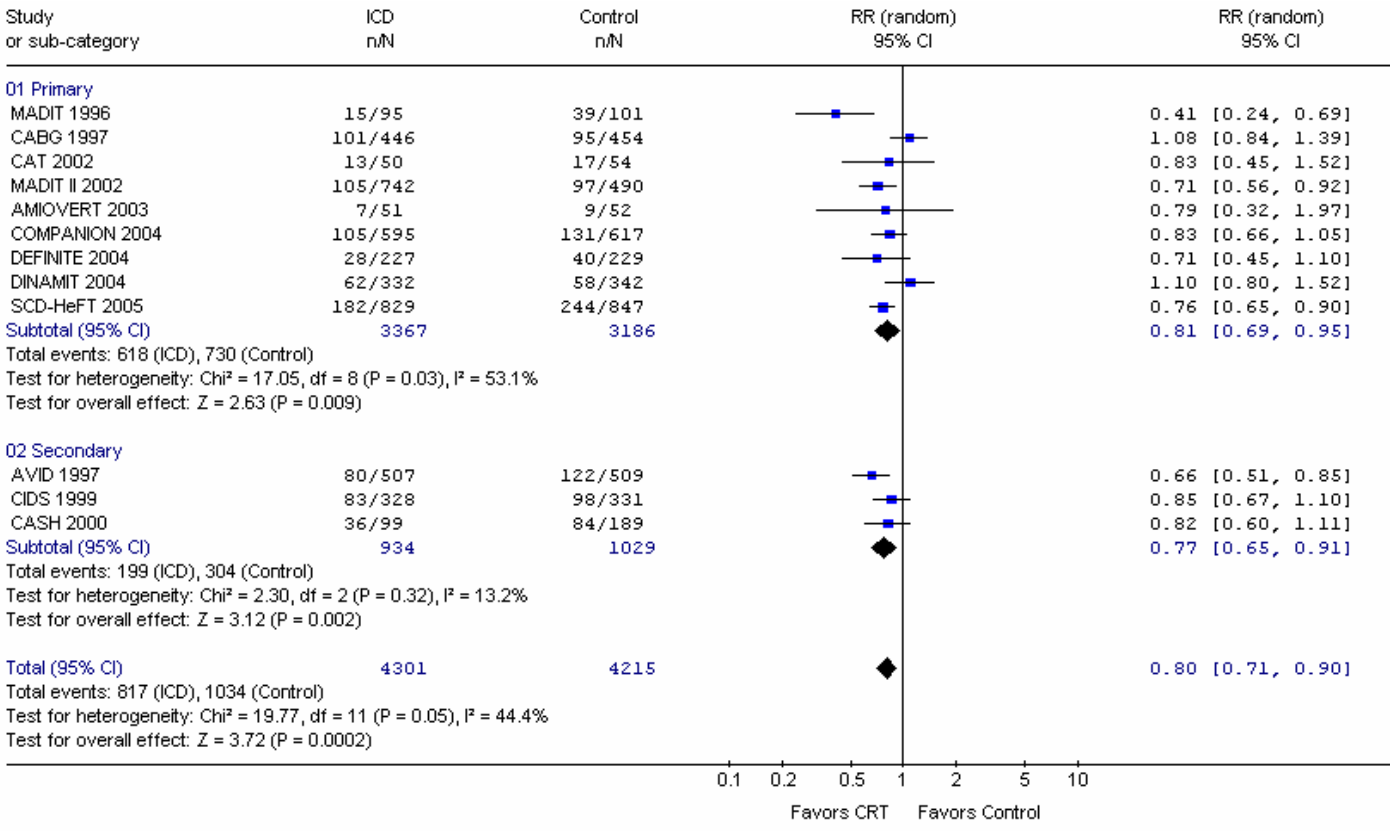


Figure 21. Funnel plot for all-cause mortality: ICD alone

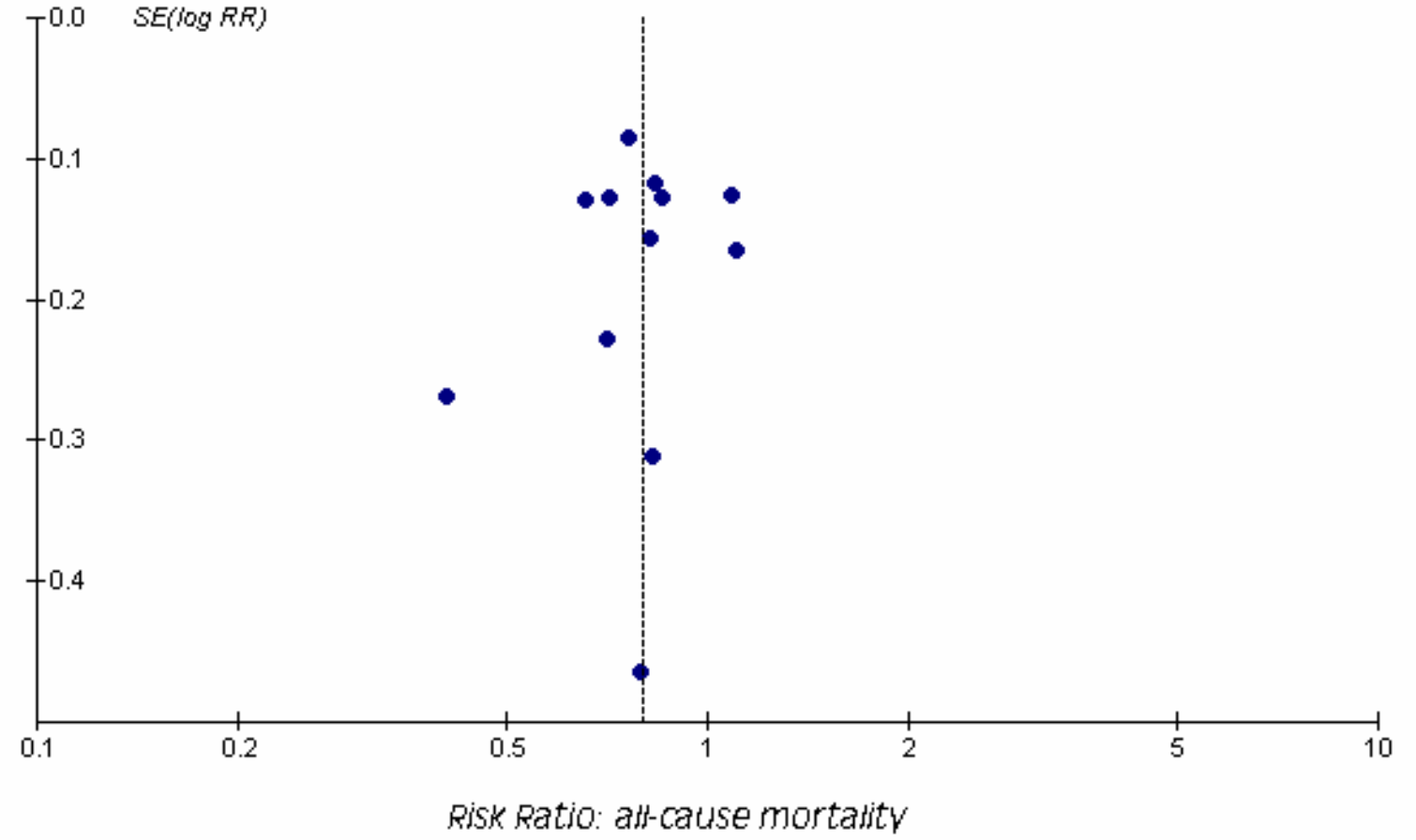
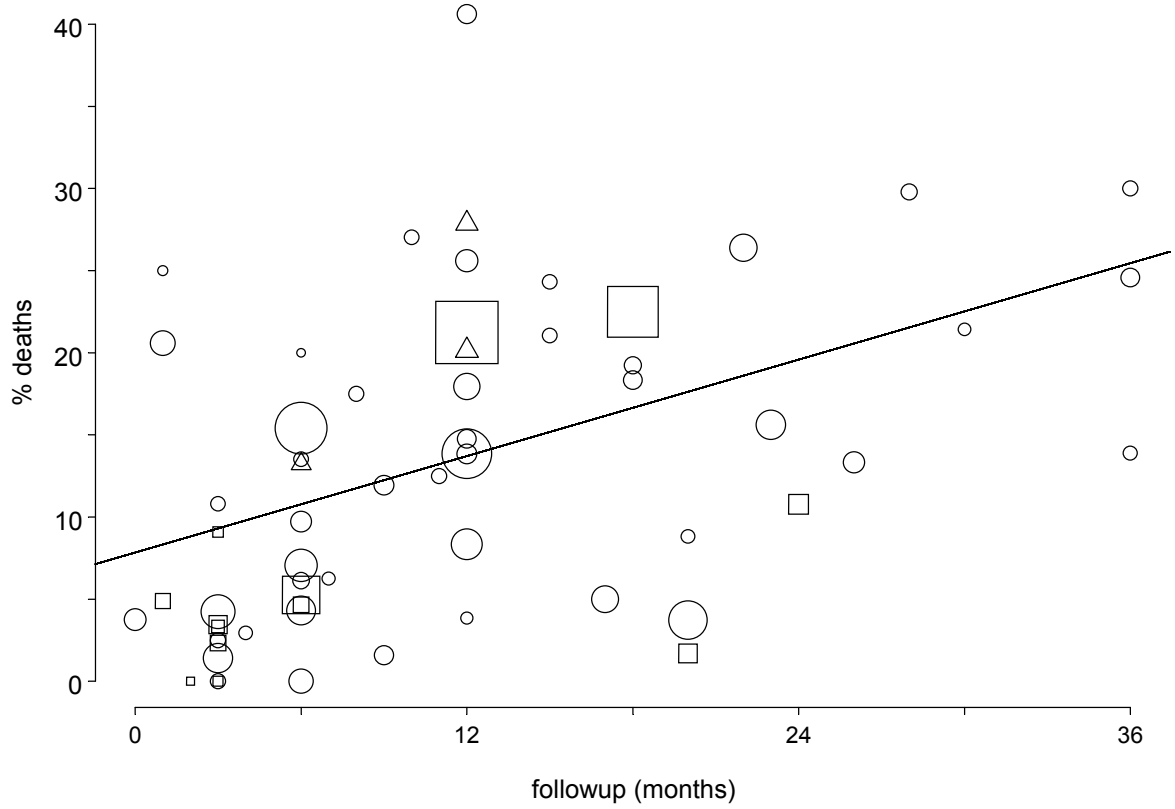
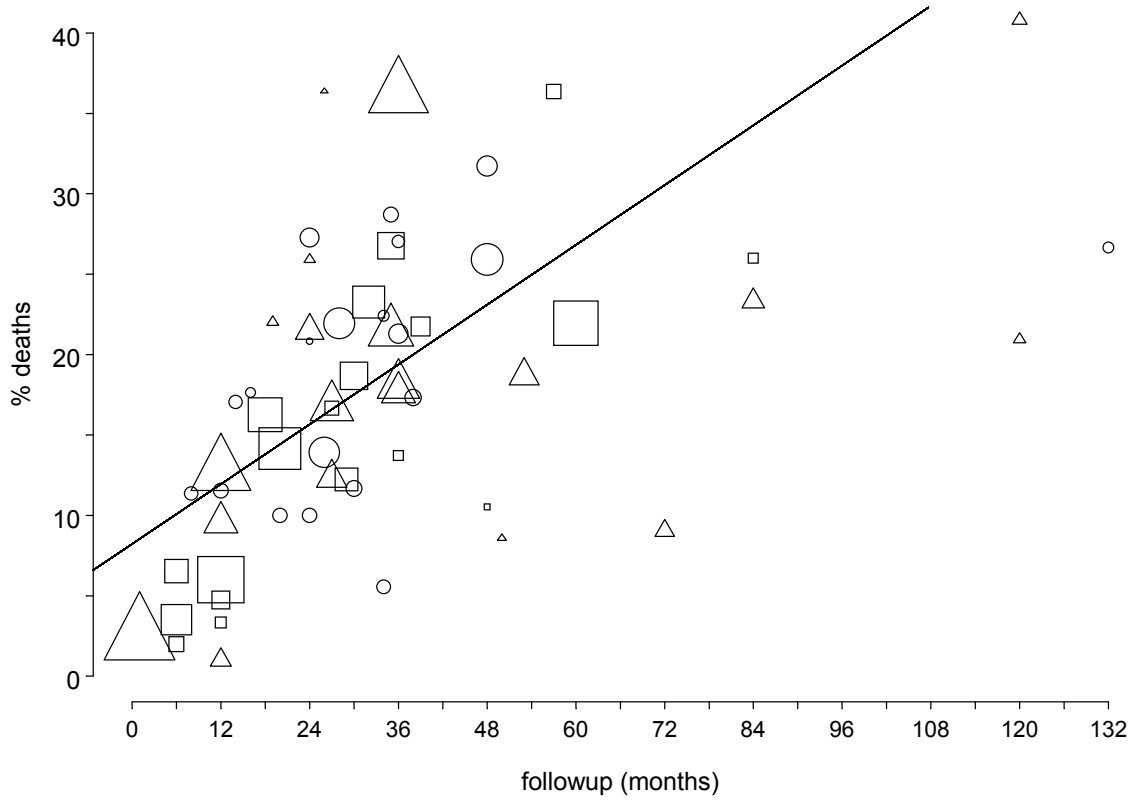


Figure 22. Scatter plot of all-cause mortality vs. length of followup: CRT alone



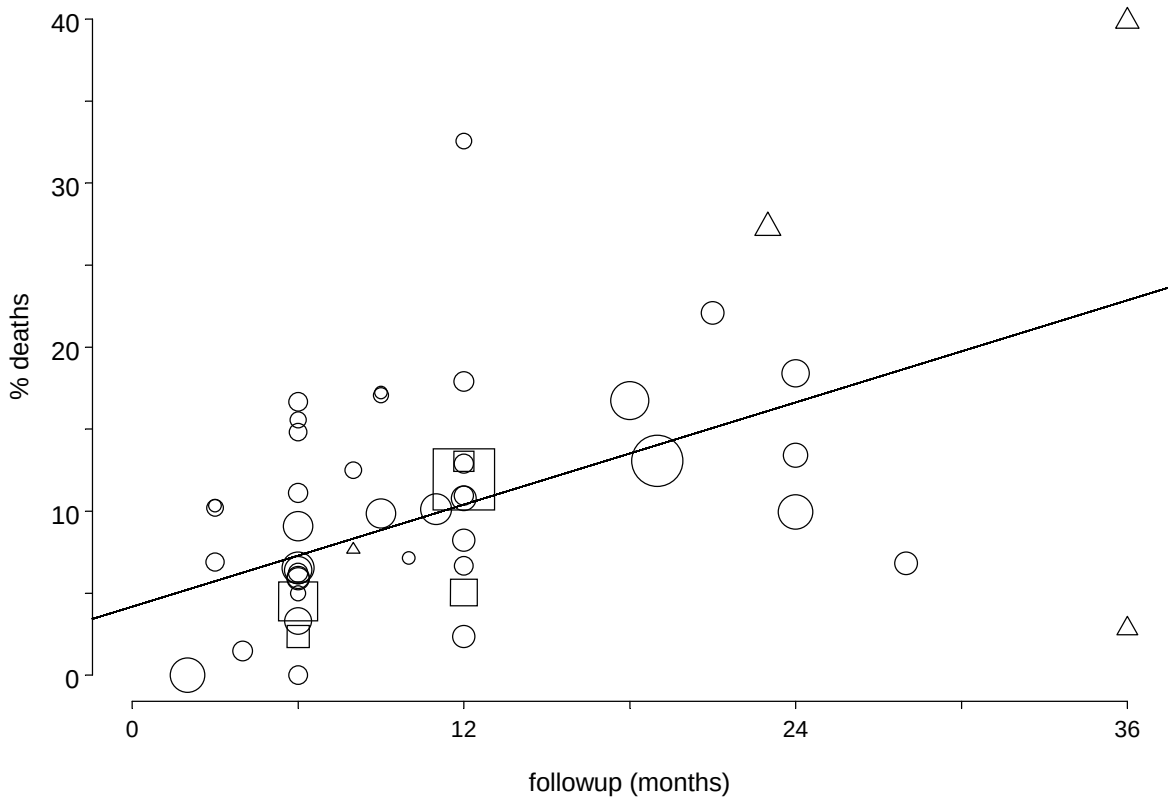
Legend: Square = RCT; Circle = prospective cohort; Triangle = retrospective cohort
Size of plotting character is proportional to square root of sample size of study

Figure 23. Scatter plot of all-cause mortality vs. length of followup: ICD alone



Legend: Square = RCT; Circle = prospective cohort; Triangle = retrospective cohort
Size of plotting character is proportional to square root of sample size of study

Figure 24. Scatter plot of all-cause mortality vs. length of followup: combined CRT-ICD devices



Legend: Square = RCT; Circle = prospective cohort; Triangle = retrospective cohort
Size of plotting character is proportional to square root of sample size of study

Chapter 4. Discussion

Benefits of CRT (CRT Efficacy/Effectiveness)

Using a comprehensive search strategy and concerted efforts to avoid publication and selection bias, this systematic review identified all of the available efficacy and effectiveness evidence on CRT therapy. Overall, our review reveals that CRT is both efficacious and effective when added to optimal medical therapy in certain HF patients. That is, in patients with LVEF ≤ 35 percent, prolonged QRS duration, and symptomatic HF despite optimal medical therapy, CRT reduced all-cause mortality by 22 percent (largely driven by a 36 percent reduction in progressive heart failure deaths) and HF hospitalizations by 37 percent while significantly improving LVEF (an absolute improvement of 3 percent), quality of life (by almost 8 points on the MLWHF score), and functional status (CRT recipients were 55 percent more likely to improve by at least one NYHA symptom class than non-recipients and were able to walk over 24 meters longer on the 6-minute walk test) in RCTs. As expected, the benefits of CRT were even more marked in patients with more severe HF (NYHA class III or IV): relative risk reductions were 22 percent for all-cause mortality, 44 percent for progressive heart failure deaths, and 49 percent for HF hospitalizations. While there was far less effectiveness data than efficacy data for CRT, those observational studies with contemporaneous controls that we identified reported reductions in all-cause mortality and improvements in 6-minute walk tests and LVEF with CRT which are consistent with the results of the RCTs.

The magnitude of these benefits are similar to those reported for angiotensin converting enzyme inhibitors, beta-blockers, and aldosterone antagonists in recent trials[219-223] and translate into a NNT of 31 patients with symptomatic HF (or 14 with NYHA class III or IV symptoms) to prevent one death over 6 months. Balanced against these benefits, the immediate risks of CRT appear modest: peri-implantation mortality rates were less than 1 percent (similar to rates reported for patients undergoing implantation of conventional dual-chamber pacemakers).[224] Although earlier reports raised concerns about a potentially higher risk of non-HF outcomes in patients with CRT (particularly an excess of ventricular arrythmias or sudden deaths),[225] pooling the data from all of the RCTs currently available did not reveal any excess risk of sudden death (RR = 1.07; 95% CI, 0.79 to 1.46) or noncardiac death (RR = 0.81; 95% CI, 0.43 to 1.52) in recipients of a CRT device. Moreover, an analysis of ventricular arrhythmia frequency in patients with ICD who were randomized to CRT "on" or "off" in the MIRACLE-ICD Trial did not reveal any significant differences (26 percent vs. 22 percent, $p>0.2$).[6]

However, implantation of a biventricular CRT pacemaker (in particular the left ventricular lead) is technically challenging, even in experienced hands (our systematic review identified an implantation failure rate of 7 percent, even under the optimal conditions inherent in RCTs and early cohort studies which tend to be reported by acknowledged experts in the field). Furthermore, even in the "ideal patient" (i.e., trial participants), nearly 10 percent of devices malfunctioned and 7 percent of patients had post-implant lead problems (most frequently with the left-ventricular lead) over a median followup of 11 months. While we found that implantation success rates and the frequency of peri-implantation adverse events were no different in the CRT RCTs as in the observational studies conducted in non-trial settings, and in patients implanted with combined CRT-ICD devices as CRT alone devices, these conclusions are based on studies reporting data from less than 7,000 patients and thus should not be

considered definitive. Further, it should be noted that the implant success rates and frequency of complications we found in the published literature may not reflect current rates in clinical practice since the experience of device implanters, the tools for implantation, and the sophistication of these devices change over time. This emphasizes the importance of ongoing surveillance programs for these devices, and as discussed under "The Challenge for Health Care Administrators and Funders" on page 177 of the Evidence Report, we believe there is a need to expand the recently established American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR) to collect comprehensive data on CRT devices as well as ICD devices, and to include implants in all patients, not just Medicare beneficiaries. Given the recent experiences with ICD recalls and FDA advisories, it seems prudent to recommend that all patients with left ventricular systolic dysfunction who have either a CRT or an ICD device implanted be entered into a registry and followed for long-term risks and benefits.

The degree of heterogeneity within and between trials in the proportion of patients exhibiting functional improvements with CRT highlights an important issue with CRT. Although these trials enrolled similar patient populations and implanted similar (and in many cases identical) devices, 59 percent of CRT recipients improved by at least one NYHA class while 41 percent did not. Clearly, CRT does not always restore mechanical synchrony, even when lead placement is felt to be successful.[226] While studies to define which patients are most likely to benefit from CRT and which positions in the ventricular wall are most appropriate for implantation of the pacing leads are clear research priorities,[226,229,229] our examination of subgroup analyses in these trials was unable to identify any particular subgroups who are more (or less) likely to derive benefit from CRT. In nontrial participants, the rates of nonresponse to CRT have varied even more widely. Determining the true rate of nonresponse in clinical practice is hampered by the lack of a universally accepted definition for "response." The most frequently cited definitions either rely on functional status (an improvement of at least one in NYHA class) or echocardiographic assessments of remodelling (most commonly a decrease of at least 15 percent in left ventricular end-systolic volume).[227] Complicating matters is the fact that patients may demonstrate a response clinically but not echocardiographically, or vice versa (for example, there was only 76 percent agreement in one study which conducted both assessments as to whether patients were classified as responders/nonresponders under both definitions).[271] Examining only those studies employing either of these definitions reveals that CRT non-response rates (after successful device implantation) range from 20 to 28 percent in those studies using a functional status definition but in studies employing the more objective echocardiographic remodelling definition CRT nonresponse rates range from 32 to 45 percent.

A variety of reasons have been advanced for the relatively high rates of nonresponse with CRT therapy.[227] For one, the optimal pacing site in the left ventricle (i.e., the most delayed site on the left ventricular free wall) is not consistent between patients and thus it is not surprising that inserting leads in the same place in all individuals will have varying impacts.[272] Second, it has been suggested that the etiology of HF is an important predictor of CRT responsiveness: however, although some studies have suggested that patients with ischemic cardiomyopathy exhibit less echocardiographic benefit from CRT than patients with idiopathic dilated cardiomyopathy,[4,273] this has not translated into appreciable differences between the two groups in clinical outcomes in the RCTs conducted to date.[11,15] Third, the most frequently cited reason for the relatively high rates of nonresponse with CRT therapy is that electrical dyssynchrony on the electrocardiogram does not always translate into mechanical dyssynchrony—a fact proven in several studies.[227,274,275] Indeed, some authors have estimated that up to a quarter of all HF

patients with QRS width < 120 msec may have sufficient mechanical dyssynchrony to potentially benefit from CRT.[276-278] As a result, attention has focused on improving the assessment of mechanical dyssynchrony in HF patients with new echocardiographic techniques (such as Tissue Doppler Imaging) and the ongoing Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) Study is an attempt to prospectively test and validate which of the various echocardiographic indices will best identify those patients most likely to respond to CRT.[228]

An important question about CRT, as with any new therapy, is whether efficacy proven in trials translates into effectiveness when applied in clinical practice. This is of particular concern for novel therapies which either (1) have been tested in a selected spectrum of patients or (2) depend on specialized technical expertise. Both caveats apply to CRT. Thus, while the trials proving the efficacy of CRT enrolled relatively young subjects (mean age 65 years), 72 percent of whom were male, population-based cohort data[279-282] demonstrate that HF patients in clinical practice are almost a decade older than trial participants and have a substantially greater burden of comorbid illnesses. The impact of CRT in these patients (particularly given the higher peri-implantation risks) is unknown. In addition, it bears emphasizing that only selected cases and experienced providers participated in these trials. Consequently, it is plausible that the efficacy and safety rates observed in these trials may not be applicable in usual clinical practice. In particular, recent analyses of Medicare files have confirmed that in the United States these devices are being implanted in older patients with more comorbidities[203] than the participants in the RCTs reviewed in this report; in addition, CRT devices are being implanted by less experienced providers working in institutions with lower implant volumes[204] than those centers that participated in the trials we have reviewed herein. This again emphasizes the importance of the prospective national device registry which the Centers for Medicare and Medicaid Services has established (https://www.accncdr.com/webncdr/ICD/Default_ssl.aspx) since any nonselective uptake of CRT beyond the highly specialized settings in which it was shown to be beneficial in these trials would be expected to attenuate its risk/benefit ratio and undermine its cost-effectiveness ratios.

In addition to providing "real world" estimates of complication rates, ongoing surveillance is required to assess (1) the effects of CRT on mortality and morbidity (including functional status and 6-minute walk distances) over longer timeframes than these RCTs have reported, (2) the effects of CRT in patient subgroups excluded from the trials conducted to date (such as those with atrial fibrillation, chronic kidney disease, or less symptomatic HF), (3) to what extent the reductions in HF hospitalizations seen in these trials with CRT may be offset by increased admissions for pacemaker revisions, and (4) to track changes in complication rates as device implanters, the tools for implantation, and the sophistication of the devices change over time.

Caveats for CRT Efficacy/Effectiveness Data

It should be recognized that few participants in these trials had bradyarrhythmias or atrial fibrillation. As such, the role of CRT in such patients is unknown (despite promising reports from the small HOBIPACE trial[13] and registry data[283]) and is an important area for further study, particularly since almost one-third of patients with HF have atrial fibrillation or indications for conventional pacemakers.[279] Similarly, since less than one-tenth of CRT trial participants had a right bundle branch block pattern on their enrolment electrocardiograms, it remains a subject of debate whether to extrapolate the CRT trial findings published thus far to HF patients with right

bundle branch block patterns (although a recent study suggested that the degree of left ventricular activation delay and the pattern of activation was similar in patients with right or left bundle branch blocks).[280,284] In a similar vein, the benefits of CRT in patients with less symptomatic HF (NYHA class I or II symptoms) are uncertain due to a relative paucity of trial data and awaits further study, despite promising data in subgroup analyses from the CRT trials and observational studies.[32]

While none of the trials that examined subgroup effects reported differences in the efficacy of CRT across subgroups, and our meta-regression was unable to detect any statistically significant differences in the subgroups we examined (ischemic vs. nonischemic etiology, age strata, duration of followup), our meta-regression did reveal that studies with a higher proportion of NYHA class II patients and higher mean LVEF at baseline, and studies with ICD in both the control and CRT arms, found less beneficial effects of CRT on heart failure hospitalizations (but no differences in the survival benefits apparent with CRT). However, it should be emphasized that these subgroup analyses were underpowered (both within trials and between trials). Thus, individual patient data is essential to appropriately examine this issue. We have been involved in discussions with all manufacturers of CRT devices to provide individual patient data for this review; however, no individual patient data was available by January 9, 2007. Examination of the trial data for differential subgroup effects should be an urgent research priority in this field, particularly since, in the words of one editorialist, "it is the entry criterion and not the group actually studied that has driven practice guidelines."[235] For example, there are no data on the impact of CRT (with or without ICD) in different strata of baseline LVEF (for example, 10 to 20 percent vs. 20 to 30 percent vs. 31 to 35 percent) and thus CRT is currently advocated for patients who would have met trial eligibility criteria, even though the mean LVEF in the randomized trials proving the efficacy of these devices was substantially lower than the LVEF required for trial entry. In the same vein, the degree of heterogeneity within and between trials in the proportion of patients exhibiting functional improvements with CRT highlights the need for detailed subgroup analyses. Although these trials enrolled similar patient populations and implanted similar (and in many cases identical) devices, 59 percent of CRT recipients improved by at least one NYHA class while 41 percent did not. Clearly, CRT does not always restore mechanical synchrony, even when lead placement is felt to be successful.[226] Moreover, studies to define which patients are most likely to benefit from CRT and which positions in the ventricular wall are most appropriate for implantation of the pacing leads are clear research priorities.[226,235]

Another limitation of these RCTs is that randomization occurred after implantation of the device in all but three trials. This design, similar to the run-in period used in some pharmaceutical trials, does not affect the internal validity of the trials since the randomly assigned groups should still be balanced for unmeasured confounders. However, it does affect the tests of statistical significance (as it causes narrower confidence intervals and increases the chance of type 1 errors) and does impact the generalizability of the results as patients who could not tolerate the procedure or in whom implantation was unsuccessful would not have been included in the final trial data. As a result, these trials likely overestimate the potential benefits and underestimate adverse events from cardiac resynchronization—although the univariate meta-regression did not demonstrate statistical significance on this factor ($p = 0.18$), this analysis was underpowered due to the small number of studies. This further emphasizes the importance of ongoing surveillance registries to track device effectiveness and complication rates (particularly given the marked paucity of data on the efficacy or complication rates with cardiac resynchronization therapy beyond one year).[285]

Mode of death analyses should always be viewed as hypothesis generating exercises given the well-documented uncertainties around the sub-classification of deaths, particularly in classifying cardiac deaths as being due to sudden arrhythmic events versus progressive HF.[286]

Finally, it is uncertain whether, and to what extent, the use of newer techniques to detect electro-mechanical dyssynchrony, such as Tissue Doppler Imaging rather than the current criteria based on QRS and LVEF, to select patients for CRT in the future will impact on the effectiveness and safety of these devices.[226]

Safety of CRT

It is well known that trials under-estimate complication rates from both medical and surgical interventions due to their selection criteria, relatively short followup time-frames, and close monitoring of patients (and providers).[251] Although our analysis of peri- and post-implantation risks revealed similar frequencies in the RCT data and the observational data at this point in time, it should be recognized that this is based on sample sizes of only a few thousand patients and reports of device implantations appearing early in the literature are most likely to come from larger institutions/more experienced investigators with early experience and competence with these devices. Regardless, our analysis demonstrated that CRT implantation was successful approximately 93 percent of the time and the peri-implantation risks included a 0.3 percent chance of peri-implantation death and a 4 to 5 percent chance of mechanical complication at the time of implantation—these rates were almost identical for CRT alone or combined CRT-ICD devices. Both types of devices exhibited a 7 percent frequency of post-implant lead problems, a 5 percent frequency of device malfunction, and a 1 to 2 percent frequency of post-implant infections) over a median followup of 6 months. However, it should be recognized that all of the published evidence thus far is relatively short-term and based on relatively few patients. This further emphasizes the importance of ongoing surveillance registries to track complication rates and costs (including costs and complications of failed implantation attempts) over the long-term.

Cost-Effectiveness of CRT

Numerous decision analytic studies have explored the cost-effectiveness of CRT therapy. In an earlier AHRQ report (a Markov Model with a lifetime horizon, but based on data from the relatively short-term trials published to that point in time—most of which reported outcome data only within the first 3 months after CRT activation), a median incremental cost of US$107,800 per QALY with CRT vs. medical therapy was reported.[287] However, three subsequent cost-utility analyses which have incorporated more recently published trials with substantially longer followup durations have reported markedly lower incremental costs per QALY gained for CRT devices: US$19,600 in an analysis of the COMPANION trial data,[288] £19,319 in an analysis employing the CARE-HF trial data,[289] and £16,598 in a Markov decision analytic model with a lifetime horizon developed for the NHS Research and Development Health Technology Assessment Programme from a meta-analysis of the five longest CRT trials.[290] However, even these analyses found that the incremental cost-effectiveness of CRT-ICD over CRT alone was markedly higher ($171,538 per QALY in the United States and £34,664 in the United Kingdom) since the benefit of CRT-ICD over CRT is marginal, but at a much higher cost (for example, initial implant costs are $20,500 in the United States for CRT devices, but $29,500 in the United

States for CRT-ICD devices and followup costs over 7 years are $39,400 vs. $52,700).[288] In the words of one editorialist, although CRT alone devices are clearly cost-effective in patients similar to those enrolled in the trials, pending further trial data comparing CRT-ICD devices with CRT alone devices (see "Implications of our findings" section below), "the question of which device is most cost effective for patients with heart failure remains open."[291]

Proportion of HF Patients Likely To Be Eligible for CRT

Approximately 1 to 3 percent of all patients discharged alive after their index hospitalization for HF[280,292] and 15 to 20 percent of patients seen in specialized heart failure clinics[280,293,294] meet CRT trial eligibility criteria (LVEF ≤ 35 percent, QRS ≥ 120 msec, sinus rhythm, and NYHA class III or IV symptoms despite treatment with ACE inhibitor/angiotensin receptor blocker and beta-blocker). Of these patients, approximately one half also meet trial eligibility criteria for an ICD.[295] Since clinicians tend to overestimate the severity of functional impairment in heart failure,[226] and the NYHA classification system demonstrates substantial inter-rater variability,[296] it is possible that even fewer patients would require CRT if an objective functional assessment (such as 6 minute walk test distance < 450 m) were included in the evaluation.

Benefits of ICD (ICD Efficacy/Effectiveness)

Using a comprehensive search strategy and concerted efforts to avoid publication and selection bias, this systematic review identified all of the available efficacy and effectiveness evidence on ICD therapy in patients with left ventricular systolic dysfunction. Overall, our review reveals that ICD is both efficacious and effective when added to optimal medical therapy in patients with LVEF ≤ 35 percent, regardless of whether they have HF symptoms or not. In the randomized trials, ICD reduced all-cause mortality by 20 percent (largely driven by a 54 percent reduction in sudden cardiac deaths) and, given the control mortality rate of 24 percent, this relative risk reduction translates into a NNT of 20 to prevent one death over 35 months. The relative benefits were similar in the primary prevention and secondary prevention trials (19 percent relative risk reduction vs. 23 percent relative risk reduction, respectively), although given the differences in absolute risk (23 percent all-cause mortality in the primary prevention trials vs. 30 percent all-cause mortality in the secondary prevention trials) the NNTs to prevent one death were different: 23 in the primary prevention trials vs. 15 in the secondary prevention trials. The benefits of ICD outside of the trial setting were confirmed in our analyses of observational studies with contemporaneous control groups.

Although ICD did not appear to be associated with an increase in HF symptoms or deteriorations in functional status or quality of life in trial participants, these analyses are certainly not definitive given the lack of reporting of these endpoints in most of the trials published to date. For example, HF events were reported in just two trials (one of which[135] did report a statistically significant excess risk of HF hospitalizations in ICD recipients: RR = 1.34; 95% CI, 1.04 to 1.73). A secondary analysis of data from the same trial has confirmed that it was those ICD recipients who were saved from sudden death by ICD shocks (as compared to those patients who had an ICD implanted but never received any shocks) who were most likely to subsequently be hospitalized for HF (hazard ratio 1.90 for first HF hospitalization and 1.74 for recurrent HF hospitalizations) and a factor predicting increased risk of subsequent HF was a

QRS interval ≥ 120 msec.[297] This finding may reflect the fact that sicker patients are those most likely to have ventricular arrythmias; however, it serves to highlight a subgroup of ICD eligible patients (those with symptomatic HF and QRS interval ≥ 120 msec, as well as the LVEF ≤ 35 percent currently advocated in the ACC/AHA/ESC guidelines)[298] who should be considered for a combined CRT-ICD device rather than an ICD alone.

Another factor which clinicians and their patients must weigh in the decision about ICD implantation is their quality of life. Due to a paucity of data in the trials conducted thus far, this did not feature in our systematic review; however, there is some evidence that while quality of life improves in some patients after ICD implantation, it declines in others, especially those who experience frequent ICD firings.[299] Indeed, it has been reported that ICD recipients not infrequently demonstrate substantial anxiety and can develop a psychological dependence on their device.[300] Not unexpectedly, patient anxiety and psychologic distress scores are significantly and substantially higher after an ICD shock.[301] Further, it has been shown that device recalls also substantially increase psychological distress in patients and their families,[302] an increasingly relevant factor given analyses of FDA Enforcement Reports demonstrating marked increases in device advisories and recall rates over time (as devices get smaller and more complicated).[303] Indeed, there have been 29 FDA advisories affecting nearly 337,000 ICDs since 1990—a figure which does not include the 62,000 Guidant ICDs recalled voluntarily by the company in June 2005.[304]

Akin to the situation with CRT (in which between one-quarter and one-half of patients may not respond to the device), three-quarters to two-thirds of ICD recipients never received any therapeutic ICD discharges in these trials (therapeutic ICD discharges ranged from 5 percent to 12 percent of patients per year in the trials included in this review).[217] In fact, based on analyses from MADIT-II demonstrating 50 percent mortality rates within 2 years of an appropriate ICD firing,[230] it has been estimated that 10 percent of those who receive an ICD for primary prevention will receive an appropriate shock and survive at least 1 year.[217] Moreover, registry data has demonstrated that less than one-quarter of cardiac arrest victims have a LVEF < 30 percent prior to their event.[233] While this clearly has implications for the cost-effectiveness of this therapy (see "Cost-Effectiveness of ICD" below) and resource distribution, it also serves to highlight the urgent research need to develop and validate tools which will permit adequate risk stratification to distinguish those patients who are at increased risk for sudden cardiac death and likely to benefit from an ICD from those patients unlikely to benefit.

Thus, while the MADIT-II and SCD-HeFT trial eligibility criteria are commonly cited as a means by which to identify patients who would potentially benefit from an ICD, the identification of particular patient groups who are more or less likely to benefit from an ICD is vitally important.[230,231] Although our meta-regression analyses did not reveal any statistically significant differences in the sub-groups we examined (ischemic vs. non-ischemic etiology, patient age, duration of followup, presence of CRT or not, the use of concomitant medications, QRS width, or mean LVEF in the randomized trials—recognizing that since these trials enrolled patients within a narrow LVEF range its potential predictive ability would have been markedly reduced), it should be emphasized that these analyses were underpowered due to the small number of trials and a meta-analysis of individual patient data would be necessary to appropriately examine this issue. Indeed, the establishment of the ICD Registry by the ACC-NCDR in collaboration with the Heart Rhythm Society is an important initiative which will permit the collection of comprehensive data on ICD implants and long-term patient outcomes. This should help to identify whether particular patient subgroups derive more or less benefit than

the averages reported in this report and whether specific devices or programming parameters are associated with better or worse outcomes.[234]

Regardless, the current evidence base does provide some guidance in the selection of candidates for a primary prevention ICD. For example, as ICD was not associated with a mortality benefit in the DINAMIT trial (in which ICD implants were performed within 40 days of an acute myocardial infarction)[139] or in MADIT-II patients enrolled within 6 months of coronary revascularization (HR = 1.19; p = 0.76),[305] it seems reasonable to infer that ICD implantation should be delayed for a period of time after acute coronary events (and the 40 day window specified in the ACC/AHA/ESC 2006 guidelines[298] is supported by the literature). Other risk stratification tools, such as microvolt T-wave alternans, have been suggested as potential means to identify high and low risk groups and have now been formally tested in prospective observational cohorts[306] and modelling suggests use of this test to identify those most likely to benefit from ICD may enhance the cost-effectiveness of ICD therapy.[307] Indeed, CMS approved reimbursement for this test in 2006 to identify patients at increased risk who may derive most benefit from an ICD within the existing guidelines.

Although the effectiveness analyses suggest that the benefits of ICD demonstrated in the RCTs are achievable in clinical practice, the same cautions raised about the CRT randomized trial data apply to the ICD randomized trial data, namely that (1) the trials proving the efficacy of ICD enrolled relatively young and comparatively healthy subjects (while recent analyses in the United States suggest that ICD recipients in clinical practice are older and have a higher co-morbidity burden),[203] and (2) only experienced ICD implanters from high volume institutions participated in these trials (while recent analyses in the United States suggest that ICD implants are most commonly performed by less experienced providers working in institutions with lower implant volumes).[204] This again emphasizes the importance of the ACC-NCDR registry for surveillance of outcomes with ICD implantation over time since any nonselective uptake of ICD beyond the highly specialized settings in which it was shown to be beneficial in these trials may well attenuate its risk/benefit ratio and undermine its cost-effectiveness ratios.

Caveats for ICD Efficacy/Effectiveness Data

In addition to the caveats listed above with respect to our inability to identify patient groups most likely to benefit from ICD with aggregate trial data, our analysis is also limited by a paucity of data on more complex dual-chamber ICD devices capable of antitachycardia pacing. Antitachycardia pacing offers another method by which ICD could prevent sudden cardiac death, conserve battery life, prevent a reduction in quality of life, and limit the number of inappropriate shocks patients receive.[308] This device is not without risk, however, since antitachycardia pacing can accelerate ventricular tachycardia into ventricular fibrillation requiring a shock.[308]

While early reports suggested that dual-chamber (i.e., right atrium and right ventricle) pacing could improve symptoms in patients with advanced heart failure,[309] theoretically at least there is a risk of inducing ventricular dyssynchrony with right ventricular pacing. Although three studies[194,310,311] have failed to demonstrate a significant benefit with the addition of an additional atrial lead to the right ventricular ICD lead, and one study suggested that dual-chamber ICD may exacerbate heart failure in patients without an indication for dual-chamber pacing,[312] one study[201] did report a 47 percent improvement in the odds of detecting supraventricular tachycardias, thus averting potentially inappropriate shocks. Adding to the confusion, while one trial suggested potential harm with an increase in the composite endpoint of mortality and HF hospitalization

with dual-chamber pacing compared to backup ventricular pacing in ICD patients with left ventricular dysfunction and without an indication for dual-chamber pacing,[313] the Dual Chamber and Atrial Tachyarrhythmias Adverse Events (DATAS) Study[314] reported fewer inappropriate shocks with dual-chamber ICD than with standard single right ventricular lead ICD. Importantly, the DATAS Trial used different settings with a longer AV delay in order to minimize pacing, and indeed the rate at which the right ventricular lead had to pace was halved, highlighting the need for clarity about both the device to be tested and the settings in a larger randomized trial to settle this issue. A secondary post hoc analysis of the MADIT-II Trial comparing the 404 patients who received a single-chamber ICD with the 313 patients who received a dual-chamber ICD demonstrated a higher risk of death or heart failure hospitalization with dual-chamber ICD.[263] However, the choice of single vs. dual-chamber was not randomized in this trial but left to the discretion of the attending physician and those patients who received dual-chamber ICD were older, had more advanced heart failure symptoms, and more comorbidities. As a result, after adjustment the Cox proportional hazards regression revealed that dual-chamber ICD were associated with trends to higher rates of death (hazard ratio 1.27, 95% CI 0.76-2.12) or HF hospitalization (hazard ratio 1.27, 95% CI 0.87-1.86) which were not statistically significant. Thus, although dual-chamber ICD therapy is promising, it must be tested against single-chamber ICD in appropriately powered RCTs before definitive conclusions can be drawn. In the meantime, although the most recent guidelines for ICD and the prevention of sudden cardiac death are silent on the indications for dual-chamber devices,[298] we believe it prudent to restrict the use of dual-chamber ICD to those patients who require an ICD and have conventional indications for dual-chamber pacing (such as chronotropic incompetence, sick sinus syndrome, or AV conduction abnormalities).[315]

Safety of ICD

Although ICD alone devices are clearly easier to implant than CRT capable devices (implant success rates of 99 percent vs. 93 percent), rates of peri-implant deaths and/or mechanical complications did not differ appreciably between the CRT or ICD devices. As outlined earlier in our report, implantation success rates were significantly lower (98 percent vs. 100 percent), peri-implantation death rates were significantly higher (1.7 percent vs. 0.8 percent), and inappropriate ICD discharge rates were substantially higher (39 percent vs. 16 percent over 24 months) in the ICD RCTs compared to the observational studies, likely reflecting closer scrutiny in the randomized trial setting or publication bias in the observational data.

In addition to the data we report from our systematic review of randomized trials and observational studies, it is important to acknowledge that it is difficult to estimate the true incidence of ICD (or indeed CRT) device failures since the observed failure rates are likely to be an underestimate due to under-reporting and the tendency to attribute patient deaths to the underlying disease process rather than unrecognized device malfunction. While there have already been 29 FDA advisories affecting nearly 337,000 ICDs since 1990 (and that doesn't include lead advisories, which are more frequent, or the 62,000 ICDs Guidant recalled voluntarily in June 2005),[304] analyses of FDA Enforcement Reports over the past decade demonstrated marked increases in device recall rates over time (as devices get smaller and more complicated). Currently, ICD recall rates are as high as 16.4 per 100 person years—54 percent for hardware malfunctions (electrical/circuitry malfunctions, battery/capacitor malfunctions, problems with hermetic seals, defective crystals, defective headers) and 41 percent for firmware

malfunctions (integral device computer programming).[303] It has been estimated that almost three-quarters of all ICD advisories result in device replacements and the resultant increases in monitoring, outpatient visits, hospitalizations, and use of hospital resources to replace recalled devices cost over US$90 million per year.[303]

Although there is inadequate long-term data to reliably define battery lifetime and the costs/risks of ICD replacement in patients with reduced LV systolic function, cost-effectiveness analyses commonly use a 5-year period as the average anticipated interval when ICD generators would need to be replaced in their models (based on observational data).[316] However, this is clearly an over-simplification since the generator life of an ICD will depend on whether it is single or dual chamber, the various parameters it is set to, and the frequency of discharges.

Cost-Effectiveness of ICD

The cost-effectiveness of ICD in patients with left ventricular dysfunction has recently been analyzed in four decision analyses. In an analysis incorporating data from eight of the trials included in our analysis, the incremental cost-effectiveness of ICD compared to medical therapy alone ranged between US$34,000 to US$70,200 per QALY gained over a lifetime horizon as long as the ICD was assumed to retain its effectiveness for at least 7 years.[317] Using data from the SCD-HeFT trial the incremental cost-effectiveness ratio for ICD was estimated to be US$41,530 per QALY, but was also sensitive to long-term survival and only remained attractive if the ICD prolonged life for at least 8 years.[318] On the other hand, an analysis using data from the MADIT-II Trial demonstrated a far less favourable incremental cost-effectiveness ratio for ICD of US$235,000 per life-year saved during the 3.5 years of the trial.[319] Modelling the benefits and costs over a longer time frame (12 years) yielded lower incremental cost-effectiveness ratios of US$78,600 to US$114,000 per life-year saved. Finally, a modelling study based on up to 15 years of cost and survival data from the Duke University Medical Center revealed cost-effectiveness ratios ranging from US$367,200 per life-year gained when a 3-year time horizon was examined to US$67,800 per life-year gained over a 15-year time horizon for patients within the Duke databases who would have been eligible for the MADIT-II study.[320] Thus, as the costs of ICD implantation are high initially but lower during followup, the results of ICD cost-effectiveness analyses are very sensitive to the time horizon used. Regardless, none of these analyses have taken into account the cost of device recalls to the healthcare system —whilst the device and replacement costs may be covered, the number of days lost from work, lower work productivity for spouses and family members and the delay for other patients waiting for appropriate and cost-effective therapy (e.g., a regular pacemaker) is sure to increase these estimates. As pointed out by the editorialist for one of these cost-effectiveness analyses, we need to strive "to identify the right patients at the right time for ICD implantation to deliver enough bangs for the bucks."[217]

Implications of Our Findings

Over the past decade, device therapy options have emerged as promising adjuncts to optimal medical therapy for patients with heart failure—CRT and ICD are the two that hold the most promise for the greatest proportion of heart failure patients. Although the evidence base

underpinning these therapies has evolved rapidly and fulfilled much of this promise, there remain some areas of uncertainty.

Our findings allow us to summarize the areas of certainty as follows. CRT is a proven efficacious (and cost effective) therapy for patients with (1) NYHA class III or IV symptomatic HF despite optimal medical management, (2) LVEF ≤ 35 percent, (3) sinus rhythm, and (4) ventricular dyssynchrony (i.e., prolonged QRS duration) which improves ventricular function and remodelling, symptoms, and exercise capacity, while also reducing HF hospitalizations and death. ICD is also a proven efficacious (and cost effective) therapy for patients with LVEF ≤ 35 percent and predominantly NYHA class II and III symptoms which reduces sudden cardiac deaths (and all-cause mortality) without appreciably impacting on functional status or morbidity outcomes.

However, despite this apparent clarity, a number of areas of uncertainty surround CRT and/or ICD therapy in patients with left ventricular systolic dysfunction. This report will end with 3 challenges to address the key grey areas in the current evidence base—one for health outcome investigators, one for administrators and health care funders, and one for trialists and device manufacturers.

The Challenge for Health Outcome Investigators

While the expected benefits with either CRT and/or ICD should be greater (and the cost-effectiveness ratios lower) in higher risk patients, a clear research need that this systematic review highlights is the current paucity of risk stratification tools to accurately identify those patients with left ventricular systolic dysfunction who are most likely to benefit from either (or both) of these devices.

The Challenge for Health Care Administrators and Funders

The recently established ACC-NCDR will permit the collection of comprehensive data on ICD and combined CRT-ICD implants and outcomes in Medicare beneficiaries. While this registry will help to define the long-term benefits, risks, and costs of these devices and help to clarify whether particular patient subgroups derive more or less benefit from these devices than the averages reported in this report, we believe there is a need for this registry to be expanded. For example, inclusion of data on all implants (i.e., in all patients, not just those in the over 65 year old age group that comprises Medicare beneficiaries) and collection of data on patients who receive CRT alone devices should be considered. Given the recent experiences with ICD recalls and FDA advisories, it seems prudent to recommend that all patients with left ventricular systolic dysfunction who have either a CRT or an ICD device implanted be entered into a registry and followed for long-term risks and benefits, particularly in light of the small sample sizes of current studies reporting on CRT safety. In addition, we believe that the impact of these devices on outcomes other than mortality or hospitalizations (such as functional status and 6-minute walk distances over longer timeframes than these RCTs have reported) would be important to collect as such information would usefully inform clinical and policy decision making.

The Challenge for Trialists and Device Manufacturers

Trialists and device manufacturers are to be congratulated for a plethora of ongoing studies designed to address a number of questions about CRT and/or ICD therapy which we raised earlier in our discussion under the "Caveats with efficacy/effectiveness data" for these devices. For example, the REVERSE (Resynchronization reverses Remodeling in Systolic left vEntricular dysfunction) Trial[321] is evaluating the efficacy of CRT alone in patients with NYHA class I or II symptoms while the MADIT CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) Trial[322] is comparing combined CRT-ICD to ICD alone in patients with NYHA class I or II symptoms—a subgroup of HF patients who have been under-represented in the trials thus far. Similarly, the Trip HF (Triple resynchronization in paced Heart Failure patients - NCT00187265 on clinicaltrials.gov) and APAF (Assessment of cardiac resynchronization therapy in patients undergoing "Ablate and Pace" therapy for permanent Atrial Fibrillation—NCT00111527 on clinicaltrials.gov) Trials will provide much needed data on the efficacy and safety of CRT in patients with atrial fibrillation—another patient subgroup under-represented in CRT trials thus far. Furthermore, the BLOCK HF (Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block– NCT00267098 on clinicaltrials.gov) Trial will to provide data necessary to determine the efficacy and safety of CRT in patients with atrioventricular block. Although our analyses suggest that the efficacy of CRT is not altered by the presence of an ICD, two ongoing trials (The Resynchronization/Defibrillation for Advanced Heart Failure [RAFT] Trial–NCT00251251 on clinicaltrials.gov - and The Device Evaluation of CONTAK RENEWAL 2 and EASYTRAK 2: Assessment of Safety and Effectiveness in Heart Failure [DECREASE-HF][236] Trials) will provide further detail to solidify the evidence base and resolve the question of the incremental benefits of combined CRT-ICD devices over ICD alone in patients with more symptomatic left ventricular dysfunction (i.e., NYHA class III and IV).

A key area of residual uncertainty regarding device therapy in left ventricular systolic dysfunction is the incremental benefit of combined CRT-ICD devices over CRT alone. As others have pointed out, "the effects of these devices may not be additive."[291] While trials are ongoing (as detailed above) to evaluate the incremental benefit of combined CRT-ICD devices over ICD alone devices, we challenge device manufacturers and trialists to also test the incremental benefits of combined CRT-ICD devices over CRT alone devices. Although some may argue that CRT alone devices have been superseded by combined CRT-ICD devices, we would argue that the incremental benefits of combined CRT-ICD devices over CRT alone devices are still unknown (due to a paucity of trial data comparing these two devices head-to-head in patients with left ventricular systolic dysfunction). The indirect comparisons we described (between two arms of the COMPANION trial and the meta-regression across trials as discussed on page 123 of this report) certainly cannot be considered definitive evidence. Indeed, given the changing epidemiology of HF mortality (i.e., HF patients who are living longer due to disease modifying agents such as ACE inhibitors, beta-blockers, and spironolactone and multidisciplinary HF management clinics are now far more likely to die of progressive HF than sudden death than they were even a decade ago),[323] we believe that the incremental benefits of ICD therapy in a patient who has a CRT device may well be substantially less than anticipated from the ICD trial data presented in this report. Clearly, any such trial would need to target those patients who currently fail to qualify for ICD therapy, for example, patients with LVEF in the range of 30 to 40 percent and/or patients with greater degrees of LV systolic dysfunction and more heart failure symptoms

(NYHA class IV). It has been estimated that such a trial would require over 1,300 patients per arm followed for 3 years. To quote Dr. Daubert, "who will undertake such a study?"[324] Given the markedly higher costs for combined CRT-ICD devices than CRT alone devices and the rapidly expanding population of HF patients eligible for such devices, perhaps this question is better framed "how can we not undertake such a study?

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APPENDIXES:

to

“Cardiac Resynchronization Therapy and Implantable Cardiac Defibrillators in Left Ventricular Systolic Dysfunction”

Prepared by the University of Alberta
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APPENDIX A: Exact String Searches

Electronic Databases Searched	Search Strategies and Results
MEDLINE® Ovid Version: rel10.3.2 2005 to November Week 1 2006 Searched November 14, 2006	CRT – efficacy/effectiveness Results: 272 1. resynchroni?ation therapy.mp. 2. biv.mp. 3. ((biventricular or dual-chamber or single-chamber) adj1 (pacing or pacer or stimulat$)).mp. 4. ((cardiac or heart) adj resynchroni?ation$).mp. 5. medtronic.mp. 6. insync.mp. 7. "ela medical".mp. 8. exp cardiac pacing, artificial/ 9. or/1-8 10. exp heart failure, congestive/ 11. "congestive heart failure$".mp. 12. "congestive cardiac failure$".mp. 13. "chronic cardiac failure$".mp. 14. "chronic heart failure$".mp. 15. chf.mp. 16. exp heart diseases/ 17. or/10-16 18. RANDOMIZED CONTROLLED TRIAL.pt. 19. CONTROLLED CLINICAL TRIAL.pt. 20. RANDOMIZED CONTROLLED TRIALS/ 21. RANDOM ALLOCATION/ 22. DOUBLE BLIND METHOD/ 23. SINGLE-BLIND METHOD/ 24. or/18-23 25. ANIMAL/ not HUMAN/ 26. 24 not 25 27. CLINICAL TRIAL.pt. 28. exp CLINICAL TRIALS/ 29. (clin$ adj25 trial$).ti,ab. 30. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 31. PLACEBOS/ 32. placebo$.ti,ab. 33. random$.ti,ab. 34. RESEARCH DESIGN/ 35. or/27-34

	36. 35 not 25 37. 36 not 26 38. COMPARATIVE STUDY/ 39. exp EVALUATION STUDIES/ 40. FOLLOW UP STUDIES/ 41. PROSPECTIVE STUDIES/ 42. (control$ or prospectiv$ or volunteer$).ti,ab. 43. or/38-42 44. 43 not 25 45. 44 not (26 or 37) 46. 26 or 37 or 45 47. "Case series".mp. 48. "time series".mp. 49. (efficacy or effectiveness).ti,ab. 50. meta-analysis.pt. 51. multicenter study.pt. 52. or/47-51 53. 52 not 25 54. or/46,53 55. and/9,17,54 CRT Safety Results: 90 1. ((biventricular or dual-chamber or single-chamber) adj1 (pacing or pacer or stimulat$)).mp. 2. resynchroni?ation therapy.mp. 3. biv.mp. 4. ((cardiac or heart) adj resynchroni?ation$).mp. 5. medtronic.mp. 6. insync.mp. 7. "ela medical".mp. 8. exp cardiac pacing, artificial/ 9. or/1-8 10. exp heart failure, congestive/ 11. exp heart diseases/ 12. "congestive cardiac failure$".mp. 13. "congestive heart failure$".mp. 14. "chronic cardiac failure$".mp. 15. "chronic heart failure$".mp. 16. chf.mp. 17. or/10-16 18. (safe or safety).mp. 19. risk$.mp. 20. exp risk/ 21. (adverse adj1 (effect$ or symptom$)).mp.

	22. side effect$.mp. 23. harm.mp. 24. etiology.mp. 25. aetiology.mp. 26. contraindicat$.mp. 27. (cause or causation or causing or causal$).mp. 28. exp causality/ 29. predict$.mp. 30. or/18-29 31. and/9,17,30 32. limit 31 to yr="2005 - 2006" ICD efficacy/effectiveness Results: 194 1. exp Defibrillators, Implantable/ 2. icd.ti,ab. 3. aicd.ti,ab. 4. (implant$ adj2 (defibrillat$ or defibrilat$)).mp. 5. or/1-4 6. exp heart failure, congestive/ 7. "congestive heart failure$".mp. 8. "congestive cardiac failure$".mp. 9. "chronic cardiac failure$".mp. 10. "chronic heart failure$".mp. 11. chf.mp. 12. exp heart diseases/ 13. or/6-12 14. RANDOMIZED CONTROLLED TRIAL.pt. 15. CONTROLLED CLINICAL TRIAL.pt. 16. RANDOMIZED CONTROLLED TRIALS/ 17. RANDOM ALLOCATION/ 18. DOUBLE BLIND METHOD/ 19. SINGLE-BLIND METHOD/ 20. or/14-19 21. ANIMAL/ not HUMAN/ 22. 20 not 21 23. CLINICAL TRIAL.pt. 24. exp CLINICAL TRIALS/ 25. (clin$ adj25 trial$).ti,ab. 26. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 27. PLACEBOS/ 28. placebo$.ti,ab. 29. random$.ti,ab. 30. RESEARCH DESIGN/

	31. or/23-30 32. 31 not 21 33. 32 not 22 34. COMPARATIVE STUDY/ 35. exp EVALUATION STUDIES/ 36. FOLLOW UP STUDIES/ 37. PROSPECTIVE STUDIES/ 38. (control$ or prospectiv$ or volunteer$).ti,ab. 39. or/34-38 40. 39 not 21 41. 40 not (22 or 33) 42. 22 or 33 or 41 43. "Case series".mp. 44. "time series".mp. 45. (efficacy or effectiveness).ti,ab. 46. meta-analysis.pt. 47. multicenter study.pt. 48. or/43-47 49. 48 not 21 50. or/42,49 51. and/5,13,50 ICD safety Results: 127 1. exp Defibrillators, Implantable/ 2. icd.ti,ab. 3. aicd.ti,ab. 4. (implant$ adj2 (defibrillat$ or defibrilat$)).mp. 5. or/1-4 6. exp heart failure, congestive/ 7. exp heart diseases/ 8. "congestive cardiac failure$".mp. 9. "congestive heart failure$".mp. 10. "chronic cardiac failure$".mp. 11. "chronic heart failure$".mp. 12. chf.mp. 13. or/6-12 14. (safe or safety).mp. 15. risk$.mp. 16. exp risk/ 17. (adverse adj1 (effect$ or symptom$)).mp. 18. side effect$.mp. 19. harm.mp. 20. etiology.mp. 21. aetiology.mp.

	22. contraindicat$.mp. 23. (cause or causation or causing or causal$).mp. 24. exp causality/ 25. predict$.mp. 26. complicat$.mp. 27. shock$.mp. 28. bleeding.mp. 29. exp HEMORRHAGE/ 30. exp INFECTION/ 31. infect$.mp. 32. (inappropriate adj2 pacing).mp. 33. or/14-32 34. and/5,13,33
Ovid MEDLINE® In-Process & Other Non-Indexed Citations Ovid Version: rel10.3.2 Searched November 14, 2006	CRT Results: 0 1. ((biventricular or dual-chamber or single-chamber) adj1 (pacing or pacer or stimulat$)).mp. 2. resynchroni?ation therapy.mp. 3. biv.mp. 4. ((cardiac or heart) adj resynchroni?ation$).mp. 5. medtronic.mp. 6. insync.mp. 7. "ela medical".mp. 8. or/1-7 9. "congestive heart failure$".mp. 10. "congestive cardiac failure$".mp. 11. "chronic cardiac failure$".mp. 12. "chronic heart failure$".mp. 13. heart disease$.mp. 14. chf.mp. 15. or/9-14 16. 8 and 15 ICD Results: 1 1. icd.ti,ab. 2. aicd.ti,ab. 3. (implant$ adj2 (defibrillat$ or defibrilat$)).mp. 4. or/1-3 5. "congestive heart failure$".mp. 6. "congestive cardiac failure$".mp. 7. "chronic cardiac failure$".mp. 8. "chronic heart failure$".mp.

	9. heart disease$.mp. 10. chf.mp. 11. or/5-10 12. 4 and 11
Cochrane Central Register of Controlled Trials Ovid Version: rel10.3.2 2005 - 4th Quarter 2006 Searched November 14, 2006	CRT Results: 0 1. ((biventricular or dual-chamber or single-chamber) adj1 (pacing or pacer or stimulat$)).mp. 2. resynchroni?ation therapy.mp. 3. biv.mp. 4. ((cardiac or heart) adj resynchroni?ation$).mp. 5. medtronic.mp. 6. insync.mp. 7. "ela medical".mp. 8. or/1-7 9. "congestive heart failure$".mp. 10. "congestive cardiac failure$".mp. 11. "chronic cardiac failure$".mp. 12. "chronic heart failure$".mp. 13. heart disease$.mp. 14. chf.mp. 15. or/9-14 16. 8 and 15 ICD Results: 2 1. icd.ti,ab. 2. aicd.ti,ab. 3. (implant$ adj2 (defibrillat$ or defibrilat$)).mp. 4. or/1-3 5. "congestive heart failure$".mp. 6. "congestive cardiac failure$".mp. 7. "chronic cardiac failure$".mp. 8. "chronic heart failure$".mp. 9. heart disease$.mp. 10. chf.mp. 11. or/5-10 12. 4 and 11

Cochrane Database of Systematic Reviews (CDSR) Ovid Version: rel10.3.2 2005 - 4th Quarter 2006 Searched November 14, 2006	CRT Results: 2 1. ((biventricular or dual-chamber or single-chamber) adj1 (pacing or pacer or stimulat$)).mp. 2. resynchroni?ation therapy.mp. 3. biv.mp. 4. ((cardiac or heart) adj resynchroni?ation$).mp. 5. medtronic.mp. 6. insync.mp. 7. "ela medical".mp. 8. or/1-7 9. "congestive heart failure$".mp. 10. "congestive cardiac failure$".mp. 11. "chronic cardiac failure$".mp. 12. "chronic heart failure$".mp. 13. heart disease$.mp. 14. chf.mp. 15. or/9-14 16. 8 and 15 ICD Results: 5 1. icd.ti,ab. 2. aicd.ti,ab. 3. (implant$ adj2 (defibrillat$ or defibrilat$)).mp. 4. or/1-3 5. "congestive heart failure$".mp. 6. "congestive cardiac failure$".mp. 7. "chronic cardiac failure$".mp. 8. "chronic heart failure$".mp. 9. heart disease$.mp. 10. chf.mp. 11. or/5-10 12. 4 and 11
Database of Abstracts of Reviews of Effects (DARE) Ovid Version: rel10.3.2 2005 - 4th Quarter 2006 Searched November 14, 2006	CRT Results: 0 1. ((biventricular or dual-chamber or single-chamber) adj1 (pacing or pacer or stimulat$)).mp. 2. resynchroni?ation therapy.mp. 3. biv.mp. 4. ((cardiac or heart) adj resynchroni?ation$).mp. 5. medtronic.mp.

	6. insync.mp. 7. "ela medical".mp. 8. or/1-7 9. "congestive heart failure$".mp. 10. "congestive cardiac failure$".mp. 11. "chronic cardiac failure$".mp. 12. "chronic heart failure$".mp. 13. heart disease$.mp. 14. chf.mp. 15. or/9-14 16. 8 and 15 ICD Results: 1 1. icd.ti,ab. 2. aicd.ti,ab. 3. (implant$ adj2 (defibrillat$ or defibrilat$)).mp. 4. or/1-3 5. "congestive heart failure$".mp. 6. "congestive cardiac failure$".mp. 7. "chronic cardiac failure$".mp. 8. "chronic heart failure$".mp. 9. heart disease$.mp. 10. chf.mp. 11. or/5-10 12. 4 and 11
Health Technology Assessment Database (HTA) via The Cochrane Library Wiley InterScience® Searched November 14, 2006	CRT Results: 1 MeSH descriptor **Cardiac Pacing, Artificial** explode all trees ICD Results: 2 MeSH descriptor **Defibrillators, Implantable** explode all trees
EMBASE Ovid Version: rel10.3.2 2005 - 2006 Week 45 Searched November 14, 2006	CRT efficacy/effectiveness Results: 431 1. ((biventricular or dual-chamber or single-chamber) adj1 (pacing or pacer or stimulat$)).mp. 2. exp heart pacing/ 3. resynchroni?ation therapy.mp. 4. biv.mp.

	5. ((cardiac or heart) adj resynchroni?ation$).mp. 6. medtronic.mp. 7. insync.mp. 8. "ela medical".mp. 9. or/1-8 10. exp congestive heart failure/ 11. "congestive heart failure$".mp. 12. chf.mp. 13. exp heart disease/ 14. "congestive cardiac failure$".mp. 15. "chronic cardiac failure$".mp. 16. "chronic heart failure$".mp. 17. or/10-16 18. Randomized Controlled Trial/ 19. exp Randomization/ 20. Double Blind Procedure/ 21. Single Blind Procedure/ 22. or/18-21 23. Clinical Trial/ 24. (clin$ adj25 trial$).mp. 25. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp. 26. exp Placebo/ 27. (placebo$ or random$).mp. 28. exp Methodology/ 29. exp Comparative Study/ 30. exp Evaluation/ 31. exp Follow Up/ 32. exp Prospective Study/ 33. (control$ or prospectiv$ or volunteer$).mp. 34. or/23-33 35. 22 or 34 36. limit 35 to human 37. Nonhuman/ 38. 36 not 37 39. exp Controlled Study/ 40. "systematic review"/ 41. Meta Analysis/ 42. ((multi center or multi centre or multicenter or multicentre) adj1 trial$).mp. 43. exp Case Study/ 44. "Case series".mp. 45. "Time series".mp. 46. (efficacy or effectiveness).ti,ab. 47. or/39-46 48. limit 47 to human

	49. 48 not 37 50. 38 or 49 51. and/9,17,50 CRT safety Results: 91 1. ((biventricular or dual-chamber or single-chamber) adj1 (pacing or pacer or stimulat$)).mp. 2. exp heart pacing/ 3. resynchroni?ation therapy.mp. 4. biv.mp. 5. ((cardiac or heart) adj resynchroni?ation$).mp. 6. medtronic.mp. 7. insync.mp. 8. "ela medical".mp. 9. or/1-8 10. exp congestive heart failure/ 11. "congestive heart failure$".mp. 12. chf.mp. 13. exp heart disease/ 14. "congestive cardiac failure$".mp. 15. "chronic cardiac failure$".mp. 16. "chronic heart failure$".mp. 17. or/10-16 18. (safe or safety).mp. 19. exp risk/ 20. risk$.mp. 21. exp side effect/ 22. side effect$.mp. 23. (adverse adj1 (effect$ or symptom$)).mp. 24. harm.mp. 25. exp etiology/ 26. aetiology.mp. 27. treatment contraindication/ 28. contraindicat$.mp. 29. (cause or causation or causing or causal$).mp. 30. *epidemiology/ 31. exp prediction/ 32. or/18-31 33. and/9,17,32 34. limit 33 to yr="2005 - 2006" ICD efficacy/effectiveness Results: 350

	1. exp defibrillator/ 2. icd.ti,ab. 3. aicd.ti,ab. 4. exp DEFIBRILLATION/ 5. (implant$ adj2 (defibrillat$ or defibrilat$)).mp. 6. or/1-5 7. exp congestive heart failure/ 8. "congestive heart failure$".mp. 9. chf.mp. 10. exp heart disease/ 11. "congestive cardiac failure$".mp. 12. "chronic cardiac failure$".mp. 13. "chronic heart failure$".mp. 14. or/7-13 15. Randomized Controlled Trial/ 16. exp Randomization/ 17. Double Blind Procedure/ 18. Single Blind Procedure/ 19. or/15-18 20. Clinical Trial/ 21. (clin$ adj25 trial$).mp. 22. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp. 23. exp Placebo/ 24. (placebo$ or random$).mp. 25. exp Methodology/ 26. exp Comparative Study/ 27. exp Evaluation/ 28. exp Follow Up/ 29. exp Prospective Study/ 30. (control$ or prospectiv$ or volunteer$).mp. 31. or/20-30 32. 19 or 31 33. limit 32 to human 34. Nonhuman/ 35. 33 not 34 36. exp Controlled Study/ 37. "systematic review"/ 38. Meta Analysis/ 39. ((multi center or multi centre or multicenter or multicentre) adj1 trial$).mp. 40. exp Case Study/ 41. "case series".mp. 42. "time series".mp. 43. (efficacy or effectiveness).ti,ab. 44. or/36-43

	45. limit 44 to human 46. 45 not 34 47. or/35,46 48. and/6,14,47 ICD safety Results: 239 1. exp defibrillator/ 2. icd.ti,ab. 3. aicd.ti,ab. 4. exp DEFIBRILLATION/ 5. (implant$ adj2 (defibrillat$ or defibrilat$)).mp. 6. or/1-5 7. exp congestive heart failure/ 8. "congestive heart failure$".mp. 9. chf.mp. 10. exp heart disease/ 11. "congestive cardiac failure$".mp. 12. "chronic cardiac failure$".mp. 13. "chronic heart failure$".mp. 14. or/7-13 15. (safe or safety).mp. 16. exp risk/ 17. risk$.mp. 18. exp side effect/ 19. side effect$.mp. 20. (adverse adj1 (effect$ or symptom$)).mp. 21. harm.mp. 22. exp etiology/ 23. aetiology.mp. 24. treatment contraindication/ 25. contraindicat$.mp. 26. (cause or causation or causing or causal$).mp. 27. *epidemiology/ 28. exp prediction/ 29. complicat$.mp. 30. shock$.mp. 31. exp BLEEDING/ 32. bleeding.mp. 33. exp Infection/ 34. infect$.mp. 35. (inappropriate adj2 pacing).mp. 36. or/15-35 37. and/6,14,36 38. limit 37 to yr="2005 - 2006"

Science Citation Index Expanded (via Web of Science®),
2005 – 2006
Searched November 14, 2006

CRT, ICD efficacy/effectiveness
Results: 20

#10	#9 NOT #7
#9	#8 AND #6 AND #1
#8	TS=(implantable same defibrillat*) or TS=(implantable same defibrilat*)
#7	#6 AND #2 AND #1
#6	#5 OR #4 OR #3
#5	TS=(randomized controlled trial* or controlled clinical trial* or research design or comparative stud* or evaluation stud* or controlled trial* or follow-up stud* or prospective stud*)
#4	TS=(single blind* or double blind* or clinical trial* or placebo* or random*)
#3	TS=(case series or time series or efficacy or effectiveness or meta-analysis or multicenter study or multicentre study)
#2	TS=(biventricular pacing or biventricular pacer* or resynchronization therap* or resynchronisation therap* or biv or dual-chamber pacing or dual-chamber pacer* or dual-chamber stimulat* or single-chamber pacing or single-chamber pacer* or single-chamber stimulat* or cardiac resynchronization or cardiac resynchronisation or heart resynchronization or heart resynchronisation or cardiac pacing or medtronic or insync or ela medical)
#1	TS=(congestive heart failure* or chf or heart disease or congestive cardiac failure* or chronic cardiac failure* or chronic heart failure*)

CRT/ICD safety (Searched from 2005-2006)
Results: 20

#16	#15 NOT (#7 OR #10 OR #13)
#15	#14 AND #8 AND #1
#14	TS=(safe or safety or risk* or adverse effect* or adverse symptom* or side effect* or harm or etiology or aetiology or contraindicat* or cause or causation or causing or causal* or predict* or complicat* or shock* or bleeding or hemorrhag*

		or infect*) or TS=(inappropriate same pacing)
	#13	#12 NOT (#7 OR #10)
	#12	#11 AND #2 AND #1
	#11	TS=(safe or safety or risk* or adverse effect* or adverse symptom* or side effect* or harm or etiology or aetiology or contraindicat* or cause or causation or causing or causal* or predict*)
	#10	#9 NOT #7
	#9	#8 AND #6 AND #1
	#8	TS=(implantable same defibrillat*) or TS=(implantable same defibrilat*)
	#7	#6 AND #2 AND #1
	#6	#5 OR #4 OR #3
	#5	TS=(randomized controlled trial* or controlled clinical trial* or research design or comparative stud* or evaluation stud* or controlled trial* or follow-up stud* or prospective stud*)
	#4	TS=(single blind* or double blind* or clinical trial* or placebo* or random*)
	#3	TS=(case series or time series or efficacy or effectiveness or meta-analysis or multicenter study or multicentre study)
	#2	TS=(biventricular pacing or biventricular pacer* or resynchronization therap* or resynchronisation therap* or biv or dual-chamber pacing or dual-chamber pacer* or dual-chamber stimulat* or single-chamber pacing or single-chamber pacer* or single-chamber stimulat* or cardiac resynchronization or cardiac resynchronisation or heart resynchronization or heart resynchronisation or cardiac pacing or medtronic or insync or ela medical)
	#1	TS=(congestive heart failure* or chf or heart disease or congestive cardiac failure* or chronic cardiac failure* or chronic heart failure*)
International Pharmaceutical Abstracts Ovid Version: rel10.3.2 2005 to November 2006 Searched November 14, 2006	CRT Results: 0 1. ((biventricular or dual-chamber or single-chamber) adj1 (pacing or pacer or stimulat$)).mp. 2. resynchroni?ation therapy.mp. 3. biv.mp.	

	4. ((cardiac or heart) adj resynchroni?ation$).mp. 5. medtronic.mp. 6. insync.mp. 7. "ela medical".mp. 8. or/1-7 9. "congestive heart failure$".mp. 10. "congestive cardiac failure$".mp. 11. "chronic cardiac failure$".mp. 12. "chronic heart failure$".mp. 13. heart disease$.mp. 14. chf.mp. 15. or/9-14 16. 8 and 15
PubMed® U.S. National Library of Medicine Searched from June 2006 to November 2006	CRT/ICD efficacy/effectiveness and safety Results: 50 #16 Search #15 NOT (#6 OR #8 OR #13) #15 Search #3 AND #7 AND #14 #14 Search safe OR safety OR risk* OR risk[MeSH] OR (adverse AND (effect* OR symptom*)) OR side effect* OR harm OR etiology OR aetiology OR contraindicat* OR cause OR causation OR causing OR causal* OR causality[MeSH] OR predict* OR bleeding OR hemorrhage[MeSH] OR complicat* OR shock* OR (inappropriate AND pacing) #13 Search #12 NOT (#6 OR #8) #12 Search #3 AND #4 AND #11 #11 Search safe OR safety OR risk* OR risk[MeSH] OR (adverse AND (effect* OR symptom*)) OR side effect* OR harm OR etiology OR aetiology OR contraindicat* OR cause OR causation OR causing OR causal* OR causality[MeSH] OR predict* #10 Search #8 NOT #6 #8 Search #3 AND #5 AND #7 #7 Search "Defibrillators, Implantable"[MeSH] OR icd[tiab] OR aicd[tiab] OR (implant* AND (defibrillat* OR defibrilat*)) #6 Search #3 AND #4 AND #5 #5 Search #1 OR #2 #4 Search (resynchronization therapy OR

	resynchronisation therapy OR biv OR ((biventricular OR dual-chamber OR single-chamber) AND (pacing OR pacer OR stimulat*)) OR ((cardiac OR heart) AND (resynchronization* OR resynchronisation*)) OR medtronic OR insync OR ela medical OR cardiac pacing, artificial[MESH]) #3 Search "Heart Failure, Congestive"[MeSH] OR "Heart Diseases"[MeSH] OR congestive heart failure* OR congestive cardiac failure* OR chronic cardiac failure* OR chronic heart failure* OR chf #2 Search case series OR time series OR efficacy[tiab] OR effectiveness[tiab] OR meta-analysis[pt] OR multicenter study[pt] #1 Search ("Clinical Trial"[Publication Type] OR "Clinical Trials"[MeSH] OR "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials"[MeSH] OR "Random Allocation"[MeSH] OR "double-blind method" [MeSH] OR "single-blind method" [MeSH] OR placebos [MeSH] OR research design [MeSH] OR comparative study [MeSH] OR evaluation studies [MeSH] OR follow-up studies [MeSH] OR prospective studies [MeSH] OR (clinical[Title/Abstract] AND trial*[Title/Abstract]) OR control*[Title/Abstract] OR prospectiv* [Title/Abstract] OR volunteer*[Title/Abstract] OR random* [Title/Abstract] OR ((singl*[Title/Abstract] OR doubl* [Title/Abstract] OR trebl* [Title/Abstract]OR tripl* [Title/Abstract]) AND (blind* [Title/Abstract] OR mask*[Title/Abstract])))
OCLC Proceedings First and Papers First OCLC FirstSearch Searched 2005 – November 14, 2006	CRT Results: 4 biventricular pacing or biventricular pacer* or resynchronization therap* or resynchronisation therap* or biv or dual-chamber pacing or dual-chamber pacer* or dual-chamber stimulat* or single-chamber pacing or single-chamber pacer* or single-chamber stimulat* or cardiac resynchronization or cardiac resynchronisation or heart resynchronization or heart resynchronisation or cardiac pacing or medtronic or insync or ela medical

	AND congestive heart failure* or chf or heart disease or congestive cardiac failure* or chronic cardiac failure* or chronic heart failure* ICD Results: 0 (implantable and defibrillat*) or (implantable and defibrilat*) AND congestive heart failure* or chf or heart disease or congestive cardiac failure* or chronic cardiac failure* or chronic heart failure*

APPENDIX B: Sample Data Extraction Form

Study Characteristics

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

Design Characteristics

Study design:	If Crossover, was carryover effect mentioned?	Other
❑ RCT – Parallel ❑ RCT – Crossover ❑ Cohort ❑ Registry ❑ Case series ❑ Other	❑ Yes ❑ No	
Intent to treat analysis: □ Yes □ No □ N/A		
Patient or data source		
Intervention 1:		
Intervention 2 (if applicable):		

Participants

Number enrolled in study:	Number completed study:
Number excluded after meeting inclusion criteria:	Number lost to follow up:
Length of study	
Reasons for exclusion : [not the same as exclusion criteria on page 1; ones stated to explain why not included in analysis]	
Number Withdrawals/dropouts:	

If yes, reasons:	Intervention 1:
	Intervention 2 (if applicable):
	All participants:

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

	Intervention 1	Intervention 2	All participants
Males/females:			
Age:			
Race:			
Ischemic/non-ischemic:			
Diabetes Mellitus:			
Hypertension:			
Ejection Fraction (%)			
QRS duration			
previous MI			
previous PTCA			
CABG			
History of SCD:			
Atrial fibrillation:			
Other			

Baseline data on QOL; 6MWT; NYHA class; etc on same table as outcomes [to save space]

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

	Intervention 1	Intervention 2	All participants
Drug therapy:			
Angiotensin receptor blockers			
ACE inhibitors			
Antiarrhythmics			
Beta blockers			
digoxin			
diuretics			
furosemide			
lipid lowering agents			
antiplatelet agents			
Nitrates			
Spironolactone			
Warfarin			
Other			
Not reported			
Device:			
Method of implantation:			
Other co-interventions:			

Outcomes Timepoints indicate time since RANDOMIZATION in DAYS.

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

	Intervention 1			Intervention 2		
Time to death: ❑ **All-cause mortality or Transplant**	Number at risk	Number of events		Number at risk	Number of events	
Timepoint:						
Timepoint:						
Timepoint:						
Timepoint:						
	Intervention 1			Intervention 2		
Time to death: ❑ **Sudden cardiac death**	Number at risk	Number of events		Number at risk	Number of events	
Timepoint:						
Timepoint:						
Timepoint:						
Timepoint:						
	Intervention 1			Intervention 2		
Time to death: ❑ **CHF**	Number at risk	Number of events		Number at risk	Number of events	
Timepoint:						
Timepoint:						
Timepoint:						
Timepoint:						
	Intervention 1			Intervention 2		
Time to death: ❑ **Cardiac**	Number at risk	Number of events	Number censored	Number at risk	Number of events	Number censored
Timepoint:						
Timepoint:						
Timepoint:						

Outcomes Timepoints indicate time since RANDOMIZATION in DAYS.

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

	Intervention 1				Intervention 1			
Dichotomous outcomes: **n/N**	Baseline	Time-point	Time-point	Time-point	Baseline	Time-point	Time-point	Time-point
CHF hospitalizations								
ED visits								
Transplants								
Other								

	Intervention 1				Intervention 2			
Continuous outcomes: **n mean(sd)**	Baseline	Time-point	Time-point	Time-point	Baseline	Time-point	Time-point	Time-point
6 minute walk test								
QoL [name scale]								
LV ejection fraction (LVEF)								
Other								

Outcomes Timepoints indicate time since RANDOMIZATION in DAYS.

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

NYHA

	Intervention 1				Intervention 2			
n/N or %	Baseline	Time-point	Time-point	Or % who improved 1 class	Baseline	Time-point	Time-point	Or % who improved 1 class
class I								
class II								
class III								
class IV								

Safety:

n/N or %	Baseline	Timepoints (specify)
Implantation Risks: • Death • Lead misplacement • Device-related malfunction		
Post-Implantation Risks • Mechanical malfunction • Lead dislodgement • Infection		
ICD • Inappropriate delivery of therapy		
Successful implant rate		
Battery longevity		
Recall of devices		

APPENDIX C: Primary Publications and Associated Publications of Included Studies

Cardiac resynchronization therapy studies

CARE-HF

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

Other publications associated with CARE-HF

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Other publications associated with COMPANION

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CONTAK CD

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Other publications associated with Leclercq study

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

MIRACLE

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

Other publications associated with the MIRACLE study

Abraham WT. Rationale and design of a randomized clinical trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with advanced heart failure: The Multicenter InSync Randomized Clinical Evaluation (MIRACLE). J Card Fail 2000;6(4):369-80

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Auricchio A, Ding J, Spinelli JC, et al. Cardiac resynchronization therapy restores optimal atrioventricular mechanical timing in heart failure patients with ventricular conduction delay. J Am Coll Cardil 2002;39(7):1163-69

Baumann LS, Kadhiresan VA, Yu Y, et al. Optimization of cardiac resynchronization therapy in heart failure patients by measuring transient cycle length changes [abst]. Eur Heart J 2001;22:443

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Vogt J, Krahnefeld O, Lamp B, et al. Electrocardiographic remodeling in patients paced for heart failure. Am J Cardiol 2000;86(Supp 1):152-56K

PATH CHF II

Primary report: Auricchio A., Stellbrink C, Butter C, Sack S, et al. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay.[see comment]. J Am Coll Cardiol.;42(12):2109-16

Other publications associated with PATH-CHF II

Butter C, Auricchio A, Stellbrink C, et al. Clinical efficacy of one year cardiac resynchronization therapy in heart failure patients stratified by QRS duration: Results of the PATH-CHF II trial. Eur Heart J 2003;24:363

INSYNC (observational)

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

Other publications associated with InSync

Gasparini M, Lunati M, Bocchiardo M, et al. Cardiac resynchronization and implantable cardioverter defibrillator therapy: preliminary results from the InSync Implantable Cardioverter Defibrillator Italian Registry. Pacing Clin Electrophysiol 2003;26(1 Pt 2): 148-151

Gras D, Mabo P, Tang T, et al. Multisite pacing as a supplemental treatment of congestive heart failure: preliminary results of the Medtronic Inc. InSync Study. Pacing Clin Electrophysiol 1998;21(11 pt2):2249-55

Gras D, Cazeau S, Ritter P, et al. Long term results of cardiac resynchronization for heart failure patients: The InSync Clinical Trial [abst] Circulation 1999;100(18):2714

Gras D, Cazeau S, Mabo P, et al. Long-term benefit of cardiac resynchronization in heart failure patients: The 12 month results of the InSync trial. [abst] J Am Coll Cardiol 2000;35(2):230A.

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Implantable cardioverter defibrillator studies

AVID

Primary report: The Antiarrhythmics vs. Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients rescuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997; 337(22):1576-83

Other publications associated with AVID

Kron J. Clinical significance of device-related complications in clinical trials and implications for future trials: insights from the Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial. Card Electrophysiol Rev 2003; 7(4)473-8

Klein RC, Raitt MH, Wilkoff BL et al. Analysis of implantable cardioverter defibrillator therapy in the Antiarrhythmics Versus Implantable Cardioverter Defibrillators (AVID) Trial. J Cardiovasc Electrophysiol 2003; 14(9):940-8

AMIOVIRT

Primary report: Strickberger SA, Hummel JD, Bartlett TG et al. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and aymoptomatic nonsustained ventricular tachycardia—AMIOVIRT. J Am Coll Cardiol 2003; 41(10): 1707-12.

Other publications associated with AMIOVIRT

Wijetunga M, Strickberger SA, Amiodarone Versus Implantable Defibrillators Randomized Trial. Amiodarone versus Implantable Defibrillator(AMIOVIRT): background, rationale, design, methods, results and implications. Card Electrophysiol Rev 2003; 7(4):452-6.

APPENDIX D: List of Excluded Studies

Excluded Studies: CRT Alone and Combined CRT-ICD

The four main reasons for exclusion were based on the publication not having the right study design, population, intervention or outcomes.

Population

1. Becker R, Ruf-Richter J, Senges-Becker JC, et al. Patient alert in implantable cardioverter defibrillators: toy or tool? J Am Coll Cardiol 2004;44(1):95-8.

2. D'Andrea A, Ducceschi V, Caso P, et al. Usefulness of Doppler tissue imaging for the assessment of right and left ventricular myocardial function in patients with dual-chamber pacing. Int J Cardiol 2001;81(1):75-83.

3. Daoud EG, Kalbfleisch SJ, Hummel JD, et al. Implantation techniques and chronic lead parameters of biventricular pacing dual-chamber defibrillators. J Cardiovasc Electrophysiol 2002;13(10):964-70.

4. De Souza FSO, Mortati NL, Braile DM, et al. Technical aspects of coronary sinus catheterization based on the atrial component of the intracavitary electrogram and radiological anatomy during the implantation procedure of a biventricular pacemaker. Arq Bras Cardiol 2006;86(4):261-7.

5. Dorwarth U, Frey B, Dugas M, et al. Transvenous defibrillation leads: high incidence of failure during long-term follow-up. J Cardiovasc Electrophysiol 2003;14(1):38-43.

6. 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;16(11):1160-5.

7. Ferro A, Duilio C, Santomauro M, Cuocolo A. Walk test at increased levels of heart rate in patients with dual-chamber pacemaker and with normal or depressed left ventricular function. Eur Heart J 2003;24(23):2123-32.

8. Gould PA, Krahn AD. Complications associated with implantable cardioverter-defibrillator replacement in response to device advisories. JAMA 2006;295(16):1907-11.

9. Greenberg JM, Leon AR, Book WM, et al. Benefits of cardiac resynchronization therapy in outpatients with indicators for heart transplantation. J Heart Lung Transplant 2003;22(10): 1134-40.

10. Hansky B, Vogt J, Gueldner H, et al. Left heart pacing–experience with several types of coronary vein leads. J Interv Card Electrophysiol 2002;6(1):71-5.

11. Hauser RG, Hayes DL, Epstein AE, et al. Multicenter experience with failed and recalled implantable cardioverter-defibrillator pulse generators. Heart Rhythm 2006;3(6):640-4.

12. Hoffmeister P, Chaudhry GM, Orlov MV, Shukla G, Haffajee CI. Sheathless implantation of permanent coronary sinus-LV pacing leads. Pacing Clin Electrophysiol 2006;29(2):117-23.

13. James KB, Militello M, Barbara G, Wilkoff BL. Biventricular pacing for heart failure patients on inotropic support: a review of 38 consecutive cases. Tex Heart Inst J 2006;33(1):19-22.

14. Janousek J, Tomek V, Chaloupecky VA, et al. Cardiac resynchronization therapy: a novel adjunct to the treatment and prevention of systemic right ventricular failure. J Am Coll Cardiol 2004;44(9):1927-31.

15. Kolb C, Deisenhofer I, Schmieder S, et al. Long-term follow-up of patients supplied with single-chamber or dual-chamber cardioverter defibrillators. Pacing Clin Electrophysiol 2006;29(9):946-52.

16. Kuhlkamp V, Wilkoff BL, Brown AB, et al. Experience with a dual chamber implantable defibrillator. Pacing Clin Electrophysiol 2002;25(7):1041-8.

17. Porterfield JG, Porterfield LM, Smith BA, Bray L. Experience with three different third-generation cardioverter-defibrillators in patients with coronary artery disease or cardiomyopathy. Am J Cardiol 1993;72(3):301-4.

18. Proclemer A, Facchin D, Pagnutti C, Fioretti P, De Michele C. Safety of pacemaker implantation prior to radiofrequency ablation of atrioventricular junction in a single session procedure. Pacing Clin Electrophysiol 2000;23(6):998-1002.

19. Sadoul N, Jung W, Jordaens L, et al. Diagnostic performance of a dual-chamber cardioverter defibrillator programmed with nominal settings: a European prospective study. J Cardiovasc Electrophysiol 2002;13(1):25-32.

20. Seif M, Al-Ajmi T, Khokhar A, Idris M, Al-Khadra A. Doppler echocardiographic assessment of left ventricular diastolic function following biventricular pacing in patients with congestive heart failure. The XIIth World Congress on Cardiac Pacing & Electrophyiology. Tse HF, Lee KLF, Lau CPMonduzzi, 2003: 833-6.

21. Senges-Becker JC, Klostermann M, Becker R, et al. What is the 'optimal' follow-up schedule for ICD patients? Europace 2005;7(4):319-26.

22. Thackray SD, Witte KK, Nikitin NP, Clark AL, Kaye GC, Cleland JG. The prevalence of heart failure and asymptomatic left ventricular systolic dysfunction in a typical regional pacemaker population. Eur Heart J 2003;24(12):1143-52.

Intervention

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2. Blanc JJ, Bertault-Valls V, Fatemi M, Gilard M, Pennec PY, Etienne Y. Midterm benefits of left univentricular pacing in patients with congestive heart failure. Circulation 2004;109(14):1741-4.

3. Blanc JJ, Fatemi M, Bertault V, Baraket F, Etienne Y. Evaluation of left bundle branch block as a reversible cause of non-ischaemic dilated cardiomyopathy with severe heart failure. A new concept of left ventricular dyssynchrony-induced cardiomyopathy. Europace 2005;7(6):604-10.

4. Bongiorni MG, Soldati E, Arena G, et al. Multicenter clinical evaluation of a new SSIR pacemaker. Pacing Clin Electrophysiol 1992;15(11 Pt 2):1798-803.

5. Bordachar P, Garrigue S, Reuter S, et al. Hemodynamic assessment of right, left, and biventricular pacing by peak endocardial acceleration and echocardiography in patients with end-stage heart failure. Pacing Clin Electrophysiol 2000;23(11 Pt 2):1726-30.

6. Bracke FALE, Meijer A, van Gelder LM. Lead extraction for device related infections: a single-centre experience. Europace 2004;6(3):243-7.

7. Butter C, Gras D, Ritter P, et al. Comparative prospective randomized efficacy testing of different guiding catheters for coronary sinus cannulation in heart failure patients. J Interv Card Electrophysiol 2003;9(3):343-51.

8. Butter C, Meisel E, Tebbenjohanns J, et al. Transvenous biventricular defibrillation halves energy requirements in patients. Circulation 2001;104(21):2533-8.

9. Capucci A, Romano S, Puglisi A, et al. Dual chamber pacing with optimal AV delay in congestive heart failure: a randomized study. Europace 1999;1(3):174-8.

10. da Silva Menezes A. Outcome of right ventricular bifocal pacing in patients with permanent atrial fibrillation and severe dilated cardiomiopathy due to Chagas disease: three years of follow-up. J Interv Card Electrophysiol 2004;11(3):193-8.

11. Doll N, Opfermann UT, Rastan AJ, et al. Facilitated minimally invasive left ventricular epicardial lead placement. Ann Thorac Surg 2005;79(3):1023-5.

12. Ector B, Willems R, Heidbuchel H, et al. Epicardial pacing: a single-centre study on 321 leads in 138 patients. Acta Cardiol 2006;61(3):343-51.

13. Etienne Y, Mansourati J, Touiza A, et al. Evaluation of left ventricular function and mitral regurgitation during left ventricular-based pacing in patients with heart failure. Eur J Heart Fail 2001;3(4):441-7.

14. Fatemi M, Etienne Y, Gilard M, Mansourati J, Blanc JJ. Short and long-term single-centre experience with an S-shaped unipolar lead for left ventricular pacing. Europace 2003;5(2):207-11.

15. Feruglio GA, Petz E, Zanuttini D, Ragonese P. Un'esperienza regionale di elettrostimolazione cardiaca: nel Friuli-Venezia Giulia la maggior densita di portatori di pacemaker in Italia, oggi [A regional experience with permanent cardiac pacing: in Friuli-Venezia Giulia the highest density of pacemaker patients in Italy, to-day (author's transl)]. (Ita). G Ital Cardiol 1978;8 Suppl 1:159-65.

16. Fonarow GC, Feliciano Z, Boyle NG et al. Improved survival in patients with nonischemic advanced heart failure and syncope treated with an implantable cardioveter-defibrillator. Am J Cardiol 2000;85(8):981-5.

17. Galizio NO, Pesce R, Valero E, et al. Which patients with congestive heart failure may benefit from biventricular pacing? Pacing Clin Electrophysiol 2003;26(1 Pt 2):158-61.

18. Gasparini M, Bocchiardo M, Lunati M, et al. Comparison of 1-year effects of left ventricular and biventricular pacing in patients with heart failure who have ventricular arrhythmias and left bundle-branch block: the Bi vs Left Ventricular Pacing: an International Pilot Evaluation on Heart Failure Patients with Ventricular Arrhythmias (BELIEVE) multicenter prospective randomized pilot study . Am Heart J 2006;152(1):155.e1-7.

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20. Gold MR, Brockman R, Peters RW, et al. Acute hemodynamic effects of right ventricular pacing site and pacing mode in patients with congestive heart failure secondary to either ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 2000;85(9):1106-9.

21. Hayes DL, Graham KJ, Irwin M, et al. Multicenter experience with a bipolar tined polyurethane ventricular lead. Pacing Clin Electrophysiol 1995;18(5 Pt 1):999-1004.

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32. Nagele H, Schomburg R, Petersen B, Rodiger W. Dual chamber pacing in patients with severe heart failure on beta blocker and amiodarone treatment: preliminary results of a randomised study. Heart 2002;87(6):566-7.

33. Oldershaw PJ , Sutton MG, Ward D, Jones S, Miller GA. Ten-year experience of 359 epicardial pacemaker systems: complications and results. Clin Cardiol 1982;5(10):515-9.

34. Perrins EJ, Morely CA, Chan SL, Sutton R. Randomised controlled trial of physiological and ventricular pacing. Br Heart J 1983;50(2):112-7.

35. Pires LA, Hassan SA, Johnson KM. Coronary sinus lead placement via the internal jugular vein in patients with advanced heart failure: a simplified percutaneous approach. J Int Cardiac Electrophysiol 2005;12(2):157-62.

36. Schwaab B, Frohlig G, Berg M, Schwerdt H, Schieffer H. Five-year follow-up of a bipolar steroid-eluting ventricular pacing lead. Pacing Clin Electrophysiol 1999;22(8):1226-8.

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43. Valls-Bertault V, Mansourati J, Gilard M, Etienne Y, Munier S, Blanc JJ. Adverse events with transvenous left ventricular pacing in patients with severe heart failure: early experience from a single centre. Europace 2001;3(1):60-3.

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Outcomes

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3. Alonso C, Ritter P, Leclercq C, et al. Effects of cardiac resynchronization therapy on heart rate variability in patients with chronic systolic heart failure and intraventricular conduction delay. Am J Cardiol 2003;91(9):1144-7.

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