Importance of Implantable Cardioverter-Defibrillator Back-Up in Cardiac Resynchronization Therapy Recipients: A Systematic Review and Meta-Analysis

Sérgio Barra, MD; Rui Providência, MD, MSc; Anthony Tang, MD; Patrick Heck, BM, BCh; Munmohan Virdee, MBBS, FRCP; Sharad Agarwal, MD

Background—It remains to be determined whether patients receiving cardiac resynchronization therapy (CRT) benefit from the addition of an implantable cardioverter-defibrillator (ICD).

Methods and Results—We performed a literature search looking for studies of patients implanted with CRTs. Comparisons were performed between patients receiving CRT-defibrillator (CRT-D) versus CRT-pacemaker (CRT-P). The primary outcome was all-cause mortality. Data were pooled using a random-effects model. The relative risk (RR) and hazard ratio (HR, when available) were used as measurements of treatment effect. Nineteen entries were entitled for inclusion, comprising 12 378 patients (7030 receiving CRT-D and 5348 receiving CRT-P) and 29 799 patient-years of follow-up. Those receiving CRT-D were younger, were more often males, had lower NYHA class, lower prevalence of atrial fibrillation, higher prevalence of ischemic heart disease, and were more often on beta-blockers. Ten studies showed significantly lower mortality rates with the CRT-D device, while the remaining 9 were neutral. The pooled data of studies revealed that CRT-D patients had significantly lower mortality rates compared with CRT-P patients (mortality rates: CRT-D 16.6% versus CRT-P 27.1%; RR=0.69, 95% CI 0.62–0.76; *P*<0.00001). The number needed to treat to prevent one death was 10. The observed I^2 values showed moderate heterogeneity among studies (I^2=48%). The benefit of CRT-D was more pronounced in ischemic cardiomyopathy (HR=0.70, 95% CI 0.59–0.83, *P*<0.001, I^2=0%), but a trend for benefit, albeit of lower magnitude, could also be seen in non-ischemic dilated cardiomyopathy (HR=0.79, 95% CI 0.61–1.02, *P*=0.07, I^2=36%).

Conclusions—The addition of the ICD associates with a reduction in the risk of all-cause mortality in CRT patients. This seems to be more pronounced in patients with ischemic cardiomyopathy. (***J Am Heart Assoc***. 2015;4:e002539 doi: 10.1161/JAHA.115.002539)

Key Words: cardiac resynchronization therapy • heart failure • implantable cardioverter-defibrillator • mortality • sudden death

C ardiac resynchronization therapy (CRT) is a widely used treatment for patients with heart failure, interventricular conduction delay, and optimized medical therapy.[1–5] With or without a defibrillator, CRT has been shown to decrease both morbidity and mortality in selected patients with heart failure and severe left ventricular (LV) systolic dysfunction.[1,2] The implantable cardioverter-defibrillator (ICD) has also been shown to decrease the risk of sudden cardiac death (SCD) in both ischemic or non-ischemic dilated cardiomyopathy.[6–8] Patients with indication for CRT typically also fulfill the *Sudden Cardiac Death in Heart Failure Trial* (SCD-HeFT) inclusion criteria[6] and are therefore candidates for an ICD. Although, we would expect CRT-Ds to be advantageous because SCD is frequently a cause of death in patients with heart failure,[9] data from randomized controlled trials, observational studies, and registries have not provided a clear support towards the advantage of CRT-Ds over CRT-Ps in that setting.[1,3,10–19] Among other possible issues, lack of statistical power may be one of the possible causes of this uncertain benefit.

An adequately powered randomized controlled trial on CRT-D versus CRT-P is very unlikely to be performed in the near future and therefore a meta-analysis is the most adequate method to address this subject. The meta-analysis by Jiang et al[20] provided valuable insight, but several studies

comparing CRT-D with CRT-P have been published since its publication.[3,12–14,16,18,19,21–23]

We aim to perform a systematic review with meta-analysis of the current literature regarding the potential applicability and effectiveness of the ICD in patients receiving CRT.

Methods

Study Selection

We performed searches on MEDLINE (via PubMED), EMBASE, clinicaltrials.gov, and COCHRANE databases (from inception to May 31, 2015) using the following search string: "cardiac resynchronization therapy" AND "implantable cardioverter-defibrillator"; "CRT" AND "ICD"; "CRT-D" AND "CRT-P"; "CRT" AND "CRT-D"; "biventricular pacemaker" AND "defibrillator." Reference lists of all accessed full-text articles were searched for sources of potentially relevant information and experts in the field were contacted about further potentially eligible studies. Authors of full-text papers and congress abstract authors were also contacted by email to retrieve additional information.

Only longitudinal studies performed in humans and written in English were considered for inclusion. The population, intervention, comparison, and outcome (PICO) approach was used.[24] The population of interest included patients with guideline indication for CRT and the intervention was CRT implant with or without a defibrillator. Comparisons were performed between patients receiving CRT-D versus CRT-P. The primary outcome was total all-cause mortality, evaluated at the longest follow-up available. In studies with significantly different follow-up durations between device groups, the primary outcome was assessed at the longest follow-up available for both groups simultaneously.

In order to be eligible, studies should present a minimum follow-up duration of 6 months. Registries, observational studies, and randomized trials were considered eligible for analysis. The methods sections of evaluated studies were reviewed to confirm the suitability and composition of the reported endpoint. Studies reporting only combined endpoints (eg, mortality and heart failure hospitalizations) were excluded from analysis.

Two independent reviewers (S.B., R.P.) screened all abstracts and titles to identify potentially eligible studies. The full text of these potentially eligible studies was then evaluated to determine the eligibility of the study for the review and meta-analysis. Agreement of both reviewers was required for decisions regarding inclusion or exclusion of studies. Study quality was formally evaluated using the Delphi Consensus criteria for randomized controlled trials[25] and a modified Newcastle–Ottawa Quality Assessment Scale for Cohort Studies[26] by both reviewers (S.B. and R.P.). An agreement was mandatory for the final classification of studies.

Data extraction and presentation for the preparation of this manuscript followed the recommendations of the PRISMA group.[27] The following data were extracted for characterizing each patient sample in the selected studies, whenever available: demographics and sample characterization, LV ejection fraction (EF), New York Heart Association (NYHA) class, QRS duration, etiology (ischemic or non-ischemic dilated cardiomyopathy), history of atrial fibrillation, treatment with beta-blockers and angiotensin-converting-enzyme inhibitors or angiotensin type-2 receptor blockers and follow-up duration.

Statistical Analysis

Data were pooled using random-effects, according to the Mantel–Haenszel model, through Review Manager (RevMan), Version 5.1. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Both the relative risk (RR) and the odds ratio (OR) with respective 95% confidence intervals (95% CI) were used as a measurement of treatment effect as these data were available in all studies. However, adjusted hazard ratios (HR) were also pooled as a separate analysis whenever available. Pairwise comparisons were performed for the endpoint total all-cause mortality.

Several sensitivity analyses were performed to assess potential differences in clinical effectiveness between CRT-D and CRT-P depending on study design (randomized versus non-randomized; single versus multicenter) and in specific scenarios: ischemic versus non-ischemic cardiomyopathy; studies in which mean age between groups differed > or <2 years; studies in which percentage of patients in class >2 NYHA differed ≥5% or <5% between groups.

Statistical heterogeneity on each outcome of interest was quantified using the I^2 statistic, which describes the percentage of total variation across studies due to heterogeneity rather than chance. Values of <25%, 25% to 50%, and >50% are by convention classified as low, moderate, and high degrees of heterogeneity, respectively.

Funnel plots and meta-regression analyses were obtained using Comprehensive Meta-Analysis software (Version 2). Funnel plots were used for evaluating the presence of publication bias and traced for comparisons including >10 studies (minimum number for assuring the appropriateness of the method) (Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from: www.cochrane-handbook.org). A meta-regression (using the Unrestricted ML method) was performed for comparisons involving >8 studies for assessing the possible association of moderator variables with the primary

endpoint. Meta-regressions are similar in essence to simple regressions, in which an outcome variable is predicted according to the values of one of more moderator variables. However, in a meta-regression the outcome variable is the effect estimate (for example, a log odds ratio, which is the natural logarithm of the odds ratio, that is, its logarithm to the base *e*, where *e* is a constant equivalent to 2, 718 281 828 459) and the moderator variables are characteristics of studies that might influence the effect estimate. The regression coefficient obtained from a meta-regression analysis describes how the effect estimate changes with a unit increase in the moderator variable.

Results

Search Results and Study Characteristics

A total of 272 entries were retrieved for analysis of titles and abstracts. Of these, 259 were excluded as they were either duplicates or deemed unsuitable for the purpose of our meta-analysis—case reports, editorials, letters, reviews, meta-analyses, or original papers with no comparison between CRT-D and CRT-P. The remaining 13 entries were considered adequate for inclusion in our meta-analysis.* A careful review of their reference list provided 2 more entries that were selected after revision of the full text,[11,17] and 1 additional entry was retrieved after reviewing the reference lists of these 2 studies.[15] Manual searches also provided 2 entries: 2 abstracts.[30,31] Experts in the field suggested the inclusion of a further article.[23] There was complete agreement between investigators on the inclusion of the selected studies.

The design of selected trials and baseline data are summarized in Tables 1 and 2. The final population for this meta-analysis included 12 378 patients (7030 receiving CRT-D and 5348 receiving CRT-P) and 29 799 patient-years of follow-up. One study was a randomized controlled trial,[1] while 2 were sub-analyses of randomized controlled trials.[3,18] The remaining studies were observational and/or registries. Eight studies were multi-center.[1,3,10,13,14,18,29,30] Quality assessment of the included studies is shown in Table 3. All randomized controlled studies had <6 Delphi criteria and only 2 cohort studies had a Newcastle-Ottawa score of ≥7. Important patient selection biases were seen in most observational studies, with CRT-D being preferentially offered to younger patients with less advanced heart failure.

Studies and treatment groups were not balanced at baseline (Tables 1 and 2). Patients receiving CRT-D had a mean age in their 60s in all studies, while the mean age of CRT-P patients was in their 70s in 7 studies.[13,14,16,19,22,30,31] In both groups,

mean LV ejection fraction and QRS duration were ≤30% and >150 ms, respectively, in all studies. Table 4 illustrates and compares overall baseline characteristics of CRT-D and CRT-P patients included in this meta-analysis. Those receiving CRT-D were younger, more often males, had lower NYHA class, lower prevalence of atrial fibrillation, higher prevalence of ischemic heart disease and were on beta-blockers more often than those receiving CRT-P. Except for the study by Gaita et al,[15] mean follow-up duration was longer than 12 months in all studies, ranging from 8.5[15] to 58 months.[29] Follow-up duration was similar between device groups in all studies, except for the one by Reitan et al, in which median follow-up was significantly longer in CRT-P patients.[22]

Role of the ICD in CRT Patients and Outcomes

The pooled data of studies revealed that CRT-D patients had significantly lower mortality rates compared with those receiving CRT-P (Figure 1): 31% relative risk reduction in all-cause mortality with CRT-D compared with CRT-P (mortality rates: CRT-D 16.6% versus CRT-P 27.1%; RR=0.69, 95% CI 0.62–0.76; *P*<0.00001). The number needed to treat (NNT) was 10. Ten studies showed significantly lower mortality rates with the CRT-D device,[10–14,21–23,28,30] while the remaining 9 were neutral.[1,3,15–19,29,31] The observed I^2 values showed moderate heterogeneity within this analysis (I^2=48%). Funnel plots for the primary endpoint suggested the presence of a small publication bias (Figure 2).

Repeated analyses using the OR and the HR (when available) provided similar results: OR=0.60, 95% CI 0.53 to 0.69, *P*<0.00001; and HR=0.73, 95% CI 0.63 to 0.85, *P*<0.0001 (Figures S1 and S2).

Sensitivity Analyses

Several scenarios were assessed in order to determine whether study design influenced the overall results and to find whether specific subsets of patients were more or less likely to benefit from the addition of the ICD (Table 5).

When separately pooling data on randomized versus non-randomized studies, a significant benefit was consistently found in favor of CRT-D, with the magnitude of such benefit more pronounced in non-randomized studies, albeit with much higher degree of heterogeneity: RR=0.80, 95% CI 0.66 to 0.98, *P*=0.03, I^2=0% for randomized studies and RR=0.68, 95% CI 0.60 to 0.77, *P*<0.001, I^2=55% for non-randomized studies. Likewise, a significantly lower relative risk of mortality in CRT-D patients was seen in both single- and multi-center studies.

To explore the impact of age difference on the overall results, a sensitivity analysis was performed for studies where difference in mean age between CRT-D and CRT-P groups was

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*References 1, 3, 10, 12–14, 16, 18, 19, 21, 22, 28, 29.

Table 1. Selected Studies for the Systematic Review

Author, Reference	Study Design	Sample Size (Pts)			Mean Follow-Up	Age, y	Male Gender (%)
		Total	CRT-D	CRT-P			
Gaita et al, 2000[15]	Double-center, Observational	96	29	67	283±170 days	*	*
Pappone et al, 2003[17]	Single-center, Observational	135	88	47	840±257 days	CRT-D- 64 CRT-P- 63	CRT-D- 79.2 CRT-P- 69.9
Bristow et al, 2004[1]	Multi-center, RCT	1212	595	617	CRT-D- 16 months CRT-P- 16.5 months	CRT-D- 67 CRT-P- 66	CRT-D- 67 CRT-P- 67
Ermis et al, 2004[11]	Single-center, Observational	126	62	64	13.5±12.0 months	CRT-D- 67.3 CRT-P- 69.5	CRT-D- 79 CRT-P- 73
Auricchio et al, 2007[10]	Multi-center, Observational	1298	726	572	34 months	CRT-D- 64 CRT-P- 64	CRT-D- 83 CRT-P- 66
Bai et al, 2008[28]	Single-center, Observational	542	395	147	811.6±536.7 in surviving patients	CRT-D- 66.1 CRT-P- 67	CRT-D- 79.7 CRT-P- 70.1
Stabile et al, 2009[29]	Multi-center, Observational	233	116	117	58 months	CRT-D- 68.2 CRT-P- 69.3	CRT-D- 81 CRT-P- 73.5
Bogale et al, 2012[14]	Multi-center, Registry	2092	1494	598	12 months	CRT-D- 68 CRT-P- 75	CRT-D- 79 CRT-P- 70
Gold et al, 2013[3]	Sub-study of a multi-center RCT	419	345	74	5 years	CRT-D- 62.7 CRT-P- 63.6	CRT-D- 79.4 CRT-P- 71.6
Morani et al, 2013[13]	Multi-center, Registry	374	266	108	CRT-D- 55 months CRT-P- 53 months	CRT-D- 67 CRT-P- 74	CRT-D- 85 CRT-P- 68
Santos, 2013[31]	Single-center, Observational	184	87	97	43 months	CRT-D- 63.8 CRT-P- 71.6	*
Schuchert et al, 2013[18]	Sub-study of a multi-center RCT	402	228	174	12 months	CRT-D- 68 CRT-P- 68	CRT-D- 86 CRT-P- 70
Verbrugge et al, 2013[19]	Single-center, Observational	172	74	98	18±9 months	CRT-D- 68 CRT-P- 74	CRT-D- 84 CRT-P- 56
Gillebert et al, 2014[21]	Single-center, Observational	144	98	46	57.4±32.4 months	CRT-D- 64.1 CRT-P- 69.1	CRT-D- 85.7 CRT-P- 78.3
Kutyifa et al, 2014[12]	Single-center, Observational	1122	429	693	28 months	CRT-D- 63.9 CRT-P- 66.3	CRT-D- 84 CRT-P- 71
Looi et al, 2014[16]	Single-center, Observational	500	146	354	29±14 months	CRT-D- 67 CRT-P- 70	CRT-D- 91.1 CRT-P- 72.6
Marijon, 2014[30]	Multi-center, Observational	1705	1170	535	24 months	CRT-D- 65.6 CRT-P- 75.9	CRT-D- 80 CRT-P- 69.5
Reitan et al, 2015[22]	Single-center, Observational	705	257	448	CRT-D- 26.7 months CRT-P-79.1 months	CRT-D- 65.3 CRT-P- 72.1	CRT-D- 84.4 CRT-P- 83
Witt et al, 2015[23]	Single-center, Observational	917	428	489	Median 4.0 years	CRT-D- 67.3 CRT-P- 68.9	CRT-D- 86 CRT-P- 75.1

CRT-D indicates cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; RCT, randomized controlled trial.
*Not provided.

<2 years versus those in which the difference was >2 years. Results were practically identical: RR=0.69, 95% CI 0.58 to 0.81, $P<0.001$, I^2=55% and RR=0.69, 95% CI 0.59 to 0.81, $P<0.001$, I^2=52%, respectively. Similar results were seen when performing a sensitivity analysis for studies in which difference in percentage of patients in class >2 NYHA between device groups was <5% versus ≥5% (identical RR).

Further sensitivity analysis involving 919 CRT-D and 893 CRT-P patients with ischemic cardiomyopathy confirmed a presumed benefit of CRT-D (HR=0.70, 95% CI 0.59–0.83, $P<0.001$, I^2=0%). However, in an analysis including 607 CRT-D and 1199 CRT-P patients with non-ischemic dilated cardiomyopathy, the potential benefit of CRT-D was of lower magnitude and borderline non-significant (HR=0.79, 95% CI

Table 2. Characteristics of Study Patients

Author, Reference	NYHA Class >2 (%)	NYHA Class 4 (%)	Ejection Fraction (%)	QRS Duration (ms)	Ischemic Aetiology (%)	Atrial Fibrillation (%)	On ACEi or ARA (%)	On Beta-Blockers (%)	Aldosterone Antagonists
Gaita et al, 2000[15]									
CRT-D	*	*	*	*	*	*	*	*	*
CRT-P	*	*	*	*	*	*	*	*	*
Pappone et al, 2003[17]									
CRT-D	*	*	28	153	43	4	70	61	*
CRT-P	*	*	29	152	42	3	68	60	*
Bristow et al, 2004[1]									
CRT-D	86	*	22	160	55	0	89	68	55
CRT-P	87	*	20	160	54	0	89	68	53
Ermis et al, 2004[11]									
CRT-D	87	*	21.9	*	56	*	*	63	*
CRT-P	86	*	22.8	*	56	*	*	45	*
Auricchio et al, 2007[10]									
CRT-D	93	15	25	169	55	17	90	84	47
CRT-P	95	11	25	168	27	18	93	76	60
Bai et al, 2008[28]									
CRT-D	100	18.7	19.9	160	68.6	53.2	80.5	70.1	*
CRT-P	100	21.1	20	164	61.2	39.5	85	64.6	*
Stabile et al, 2009[29]									
CRT-D	88	16	25	*	56	18	*	*	*
CRT-P	89	24	28.2	*	41	26	*	*	*
Bogale et al, 2012[14]									
CRT-D	*	*	*	*	56.3	22.6	*	*	*
CRT-P	*	*	*	*	41.9	34.6	*	*	*
Gold et al, 2013[3]									
CRT-D	0	0	26.1	152	58.6	0	95.9	96.5	*
CRT-P	0	0	30	157	45.9	0	98.6	91.9	*
Morani et al, 2013[13]									
CRT-D	75	14	27	165	62	0	88	75	77
CRT-P	80	16	27	175	41	0	79	70	23
Santos, 2013[31]									
CRT-D	*	*	*	*	56	*	*	*	*
CRT-P	*	*	*	*	29	*	*	*	*
Schuchert et al, 2013[18]									
CRT-D	100	13	25	159	*	22	83	73	17
CRT-P	100	17	25	169	*	16	86	71	34
Verbrugge et al, 2013[19]									
CRT-D	65	11	26	152	64	11	86	88	68
CRT-P	70	8	32	157	37	41	73	76	43
Gillebert et al, 2014[21]									
CRT-D	37.8	*	25.9	162.6	59.2	6.1	93.9	82.7	55
CRT-P	91.3	*	26.2	171.4	34.8	6.5	91.3	78.3	63

Table 2. Continued

Author, Reference	NYHA Class >2 (%)	NYHA Class 4 (%)	Ejection Fraction (%)	QRS Duration (ms)	Ischemic Aetiology (%)	Atrial Fibrillation (%)	On ACEi or ARA (%)	On Beta-Blockers (%)	Aldosterone Antagonists
Kutyifa et al, 2014[12]									
CRT-D	*	*	27.6	158	51	38	86	88	61
CRT-P	*	*	28.2	165.5	34	42	84	84	53
Looi et al, 2014[16]									
CRT-D	87.7	*	23.9	161	65.8	14.4	91.2	76.9	56
CRT-P	94.1	*	25.3	159	48.3	20	90.1	69.5	63
Marijon, 2014[30]									
CRT-D	82	*	28	154.9	*	22.1	*	*	*
CRT-P	88.3	*	29	160.8	*	38.7	*	*	*
Reitan et al, 2015[22]									
CRT-D	65	6.4	25	164	51.6	42.2	93.1	89.1	*
CRT-P	85.5	9	25	170	60	50	89.9	78.7	*
Witt et al, 2015[23]									
CRT-D	67.8	4.7	25	162.3	71.5	36.4	89.2	77.8	52
CRT-P	84.5	8.2	25	168.4	37.6	43.1	90.2	75.2	65

ACEi indicates angiotensin converting enzyme inhibitor; ARA, angiotensin receptor antagonists; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; NYHA, New York Heart Association Class.
*Not provided.

0.61–1.02, P=0.07, I^2=36%) (Figure 3). The NNT over >3 years in ischemic and non- ischemic cardiomyopathies was 9 and 15, respectively (based on data available in 4 studies[12,16,22,23]).

Meta-Regression: Assessment of Moderator Variables

The assessment of potential moderator variables through meta-regression revealed significant associations between male gender or ischemic cardiomyopathy and a stronger benefit of CRT-D. No other associations were seen (Table S2). These findings suggest that part of the heterogeneity in study outcomes may be explained by these 2 moderator variables. In studies with higher prevalence of male patients and/or patients with ischemic cardiomyopathy, the benefit of CRT-D compared with CRT-P was more pronounced (Figures S3 and S4). For example:

- 65% of male patients: OR=0.82 (equivalent to log OR= −0.20)
- 75% of male patients: OR=0.64 (equivalent to log OR= −0.45)
- 40% of patients with ischemic cardiomyopathy: OR=0.72 (log OR=−0.34)
- 65% of patients with ischemic cardiomyopathy: OR=0.50 (log OR=−0.70)

Discussion

Rationale for the Use of the ICD in CRT Patients

Before the current era of HF management, patients more often died of SCD at an earlier phase of their disease.[32–36] Current state-of-the-art treatments have led to delayed HF progression and a reduced risk of death from both progressive pump dysfunction and SCD. However, although the proportion of sudden death relative to the overall mortality decreases with increasing HF severity,[36] the risk of SCD in HF patients remains significant.[9] The prophylactic implantation of the ICD seems the logical step to further reduce all-cause mortality through a reduction in arrhythmic mortality. It is noteworthy though that sudden death may still account for 7% to 20% of all deaths among ICD and CRT-D patients.[6,37] Some cases are the result of nonarrhythmic causes such as cerebrovascular event, pulmonary embolism or an occlusive coronary thrombus, but others may result from postshock pulseless electrical activity, incessant or refractory ventricular arrhythmias, and shock failure. In SCD-HeFT, 20% of total deaths in the ICD group were classified as sudden deaths presumed to be ventricular tachyarrhythmias, but the ICD was still able to prevent ≈60% of all sudden deaths compared with placebo,[38] a similar reduction to that achieved in the *Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure* (COMPANION) trial.[1]

Table 3. Assessment of Studies According to Delphi or Newcastle–Ottawa Scale Criteria Included in the Meta-Analysis

Author, Reference	Study Classification	
	Delphi Criteria	Newcastle–Ottawa Scale
Gaita et al, 2000[15]		5
Pappone et al, 2003[17]		8
Bristow et al, 2004[1]	5	
Ermis et al, 2004[11]		9
Auricchio et al, 2007[10]		5
Bai et al, 2008[28]		5
Stabile et al, 2009[29]		5
Bogale et al, 2012[14]		6
Gold et al, 2013[3]	3	
Morani et al, 2013[13]		5
Santos, 2013[31]		5
Schuchert et al, 2013[18]	2	
Verbrugge et al, 2013[19]		6
Gillebert et al, 2014[21]		5
Kutyifa et al, 2014[12]		5
Looi et al, 2014[16]		5
Marijon, 2014[30]		6
Reitan et al, 2015[22]		6
Witt et al, 2015[23]		5

High-quality studies were defined as those with a Delphi score of ≥6 (for randomized studies) or a Newcastle-Ottawa score of ≥7 (for observational studies).

Table 4. Overall Baseline Characteristics of CRT-D and CRT-P Patients

	Baseline Characteristics	
	CRT-D	CRT-P
Age	65.8	70
Male gender	79.8%	71.6%
NYHA class >2	76.8%	85.6%
NYHA class 4	10.9%	11.8%
Left ventricular ejection fraction, %	24.4	25.3
QRS duration, ms	158.7	166.1
Ischemic cardiomyopathy	57.6%	42.6%
History of atrial fibrillation	17.5%	25%
Beta-blockers	78.6%	75.3%
ACEI or ARA-II	87.4%	88.9%
Aldosterone antagonists	52.9%	53.5%

ACEI indicates angiotensin converting enzyme inhibitor; ARA-II, type 2 angiotensin receptor antagonists; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; NYHA, New York Heart Association Class.

With or without a defibrillator, treatment with a CRT device has been shown to decrease both morbidity and mortality risk in patients with NYHA class II–IV heart failure, ischemic or non- ischemic cardiomyopathy, severe LV systolic dysfunction and cardiac dyssynchrony.[2,39] Compared with medical treatment alone, CRT treatment associated with a significant 10% decrease in the absolute risk of death in the CARE-HF trial[2] and a marginally significant 4% decrease in the absolute risk of death in the COMPANION trial.[1] A previous meta-analysis suggested that CRT alone compared with optimal medical therapy could reduce all-cause mortality by lowering heart failure mortality but not SCD.[40] However, data from the 8-month extension phase of the *Cardiac Resynchronization in Heart Failure Study* (CARE-HF) trial showed that reduction in mortality achieved with CRT treatment is due to fewer deaths both from worsening heart failure and from sudden death.[41]

The usual enrollment criteria for CRT trials have been (1) NYHA functional class II–IV despite optimal drug treatment, (2) LVEF <35%, (3) QRS duration >120 or >150 ms and (4) sinus rhythm (although CRT may also be effective in patients in atrial fibrillation, particularly when combined with AV node ablation to help achieve 100% effective biventricular pacing[42]). These criteria will include most patients with indication for ICD treatment according to SCD-HeFT.[6] A question arises as to whether the effect of the ICD is additive to that of CRT, considering that CRT treatment alone will already decrease all-cause mortality risk and the risk of ventricular arrhythmias.[43] Approximately one-third of all deaths in the group randomly assigned to CRT-P in CARE-HF were sudden,[2] a rate similar to that observed among patients assigned to CRT-P in the COMPANION trial.[1] Seven per cent of patients in the CRT arm of CARE-HF died suddenly, compared with only 2.9% in the CRT-D arm of COMPANION. It is then reasonable to speculate that the ICD may be able to further reduce the risk of all-cause death by decreasing the number of sudden deaths. However, it is debatable whether the ICD is of benefit in super-responders to CRT and those who do not respond to this therapy. While the former may have significantly lower mortality rates[44,45] and lower risk of ventricular arrhythmias,[45–50] the latter will have high mortality rates, mostly due to heart failure, and previous studies suggested the ICD has no effect on any mode of death in patients in NYHA class III.[6,38]

In the MADIT-CRT trial, 7.3% of patients achieved LV systolic function normalization (LVEF >50%) and these patients had very low absolute and relative risk of ventricular arrhythmias and a very favorable clinical course within 2.2 years of follow-up: only 1 patient had a ventricular arrhythmia faster than 200 bpm, none had ICD shocks and 2 died of non-arrhythmic causes.[48] Different studies revealed a consistently low risk of ICD therapies or

Study or Subgroup	CRT-D Events	CRT-D Total	CRT-P Events	CRT-P Total	Weight	Risk Ratio M-H, Random, 95% CI
Gaita 2000	5	29	8	67	0.9%	1.44 [0.52, 4.04]
Pappone 2003	7	88	9	47	1.2%	0.42 [0.17, 1.04]
Bristow 2004	105	595	131	617	8.0%	0.83 [0.66, 1.05]
Ermis 2004	8	62	26	64	1.8%	0.32 [0.16, 0.65]
Auricchio 2007	91	726	119	572	7.4%	0.60 [0.47, 0.77]
Bai 2008	73	395	57	147	6.5%	0.48 [0.36, 0.64]
Stabile 2009	49	116	53	117	6.4%	0.93 [0.70, 1.25]
Bogale 2012	129	1494	77	598	7.0%	0.67 [0.51, 0.87]
Gold 2013	40	345	13	74	2.6%	0.66 [0.37, 1.17]
Morani 2013	73	266	44	108	6.3%	0.67 [0.50, 0.91]
Santos 2013	27	87	35	97	4.3%	0.86 [0.57, 1.30]
Schuchert 2013	20	228	19	174	2.5%	0.80 [0.44, 1.46]
Verbrugge 2013	9	74	12	98	1.5%	0.99 [0.44, 2.23]
Gillebert 2014	39	98	26	46	5.2%	0.70 [0.50, 1.00]
Looi 2014	28	146	88	354	4.8%	0.77 [0.53, 1.13]
Kutyifa 2014	129	429	250	693	9.6%	0.83 [0.70, 0.99]
Marijon 2014	144	1170	123	535	8.3%	0.54 [0.43, 0.67]
Reitan 2015	38	254	109	451	5.5%	0.62 [0.44, 0.87]
Witt 2015	154	428	252	489	10.2%	0.70 [0.60, 0.81]
Total (95% CI)		**7030**		**5348**	**100.0%**	**0.69 [0.62, 0.76]**
Total events	1168		1451			

Heterogeneity: Tau² = 0.02; Chi² = 34.36, df = 18 (P = 0.01); I² = 48%
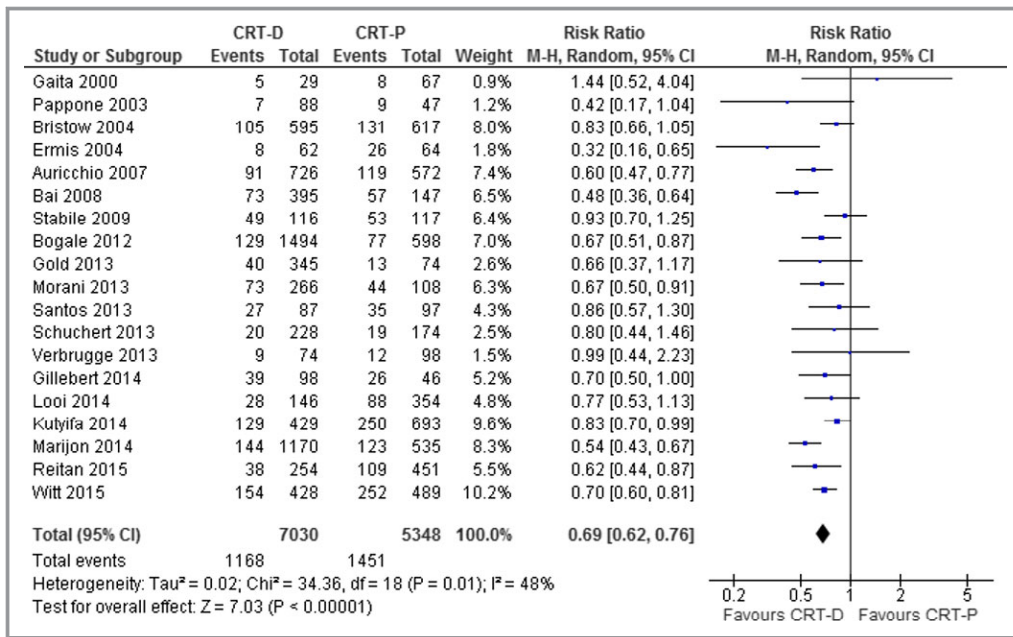Test for overall effect: Z = 7.03 (P < 0.00001)

Figure 1. Forest plots comparing CRT-D vs CRT-P regarding all-cause mortality. CRT-D indicates cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker.

sustained ventricular arrhythmias in responders and super-responders to CRT treatment (Table 6), ranging from 0.5% to 5.4% risk/year, with most studies reporting <2.5% risk/year. These results are consistent with those of Kini et al involving primary prevention ICD patients—at the time of elective generator replacement, those with improved LV function and no previous appropriate ICD therapies receive subsequent ICD therapies at a significantly lower rate (2.8%/year).[55]

Although these studies show that even super-responders to CRT remain at risk of appropriate ICD therapies, the risk is reassuringly low, especially considering that only a small percentage of ventricular arrhythmias are actually life threat-

Figure 2. Funnel plots for the primary endpoint revealing a small publication bias.

ening. An ICD therapy is not an accurate surrogate marker for mortality, as many therapies are unnecessary.[56,57] The number of appropriate ICD shocks in primary and secondary prevention trials have consistently outnumbered the rate of SCDs in control groups by a factor of 2 to 3.[58] Unfortunately, making the distinction between necessary and unnecessary therapies is very difficult if not impossible. Furthermore, although super-response is more likely in women, non-ischemic cardiomyopathy, normal renal function, lower pulmonary artery systolic pressure, left bundle branch block, QRS duration >150 ms, and smaller baseline left atrial volume index,[47,59] currently it is still not possible to predict super-response to CRT with such certainty that we could safely leave the ICD out of consideration at initial implant. However, this may be less of an issue at the time of elective CRT generator replacement.

In summary, despite the unequivocal benefit of CRT alone compared with medical treatment in reducing morbidity as well as mortality through reduction in both heart failure death and SCD, a percentage of deaths in CRT-P patients are sudden. The addition of the ICD may constitute an appropriate complement to CRT therapy in patients in NYHA class II and III, but probably not those in ambulatory NYHA class IV, very elderly patients, and those with advanced comorbidities. The decision to implant a CRT-D versus CRT-P also requires an exact understanding of the long-term risk of complications (higher in those with CRT-D[16,18,60,61]), the preference and expectations of the patients and the 3-fold higher cost of CRT-D compared with CRT-P.
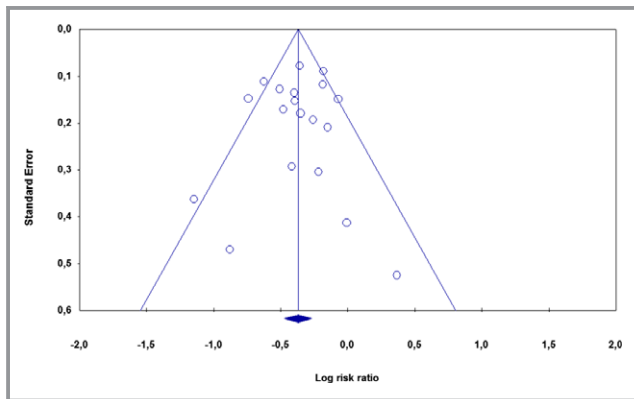
Table 5. Sensitivity Analyses

Sensitivity Analyses	OR (95% CI)	P Value	I²	RR (95% CI)	P Value	I²
RCTs	0.77 (0.60–0.98)	0.03	0%	0.80 (0.66–0.98)	0.03	0%
Non-RCTs	0.58 (0.50–0.68)	<0.001	47%	0.68 (0.60–0.77)	<0.001	55%
Multicenter	0.63 (0.53–0.75)	<0.001	36%	0.70 (0.61–0.82)	<0.001	48%
Single-center	0.56 (0.43–0.72)	<0.001	57%	0.68 (0.57–0.81)	<0.001	57%
Difference in mean age >2 years	0.61 (0.50–0.74)	<0.001	45%	0.69 (0.59–0.81)	<0.001	52%
Difference in mean age <2 years	0.59 (0.48–0.74)	<0.001	52%	0.69 (0.58–0.81)	<0.001	55%
Difference in % of patients in class >2 NYHA ≥5%	0.54 (0.46–0.62)	<0.001	0%	0.66 (0.60–0.73)	<0.001	0%
Difference in % of patients in class >2 NYHA <5%	0.58 (0.42–0.78)	<0.001	66%	0.66 (0.52–0.83)	<0.001	68%
Studies published ≥2012	0.61 (0.54–0.68)	<0.001	2%	0.70 (0.64–0.77)	<0.001	12%
Studies published <2012	0.56 (0.39–0.80)	0.002	70%	0.65 (0.49–0.85)	0.001	72%
Sensitivity Analysis	HR (95% CI)	P Value	I²			
DCM	0.79 (0.61–1.02)	0.07	36%			
Ischaemic CM	0.70 (0.59–0.83)	<0.001	0%			

CM indicates cardiomyopathy; DCM, (non-ischaemic) dilated cardiomyopathy; HR, hazard ratio; NYHA, New York Heart Association class; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

Cardiac Resynchronization Therapy: With or Without a Defibrillator?

Several observations can be made from the results of this meta-analysis. First, CRT-D patients as currently selected in daily clinical practice have significantly lower all-cause mortality rates compared with those who receive CRT without a defibrillator. There was one fewer death in every 10 CRT-D patients compared with the same number of CRT-P patients. Secondly, the lower mortality rate in CRT-D patients with
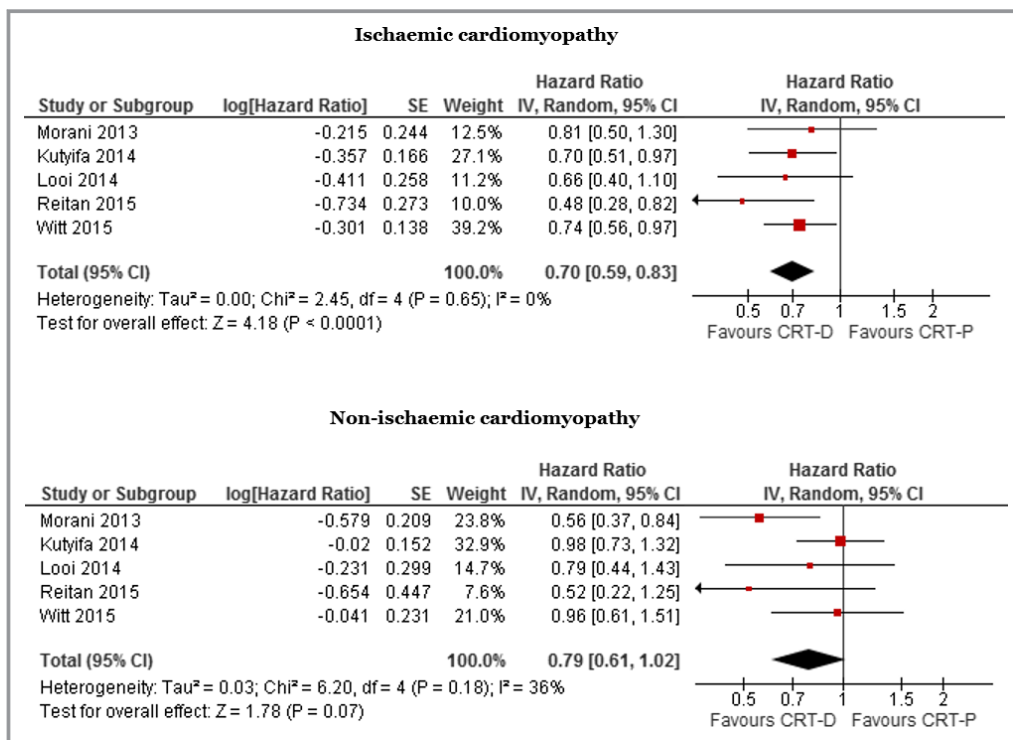

Figure 3. Forest plots comparing CRT-D vs CRT-P in ischaemic and non-ischemic dilated cardiomyopathy regarding all-cause mortality. CRT-D indicates cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker.

Table 6. Risk of ICD Therapies or Ventricular Arrhythmias in Specific Groups of Cardiac Resynchronization Therapy Patients

Author, Reference	Group Assessed	Definition	Mean Follow-Up	Risk of ICD Therapies or Ventricular Arrhythmias
Schaer et al, 2010[49]	Responders, primary prevention	LVEF improved to >35%	40 months	6% risk of ICD therapy (1.8%/year)
Thijssen et al, 2011[50]	Patients upgraded from ICD to CRT-D who respond to CRT	≥15% reduction of LVESV	37 months	0.30±0.59 risk of ICD therapy per patient per year
Hsu et al, 2012[47]	Super-responders	Highest quartile of LVEF change	2 years	3.6% risk of ICD therapy (1.8%/year)
Garcia-Quintana et al, 2013[51]	CRT-D patients with LV function improvement and absence of ICD therapies downgraded to CRT-P	LFEF >35%	5.1 years	Only 2 non-sustained episodes of VT in 14 patients
Zecchin et al, 2014[45]	Super-responders	LVEF >50% 1 to 2 years after implantation	68 months	9.7% risk of ICD therapy (1.7%/year)
García-Lunar et al, 2014[46]	Super-responders	LVEF at least twice of that measured before implantation, or above 45% at 12 months post-implantation	30 months	5.9% risk of ventricular arrhythmias (2.4%/year)
van der Heijden et al, 2014[52]	Super-responders	Decreased LVESV ≥30%	60 months	27% risk of ICD therapy (5.4%/year)
Bortnik et al, 2014[53]	CRT-P patients regardless of CRT responsiveness	-	29 months	1.2% risk of sustained ventricular arrhythmias, no sudden cardiac deaths (0.5%/year)
Sebag et al, 2014[54]	CRT-D patients due for elective generator replacement but without theoretical ongoing ICD indication	LVEF ≥40% and no prior appropriate ICD therapies	26.4 months	2.2% risk of ICD therapy per year
Ruwald et al, 2014[48]	CRT-D patients achieving LV systolic function normalization	LVEF >50%	2.2 years	Only 1 patient had a fast ventricular arrhythmia

CRT-D indicates cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; VT, ventricular tachycardia.

ischemic cardiomyopathy is clear but seems of lower magnitude in the context of non-ischemic cardiomyopathy. A higher number of CRT-D devices needs to be implanted in patients with non-ischemic cardiomyopathy for one fewer death to be reported compared with CRT-P patients. Thirdly, current CRT-P recipients are often older and have more advanced heart failure and higher comorbidity burden than those receiving CRT-D. Finally, the fact that most studies comparing CRT-D versus CRT-P were cohort studies with significant differences between device groups emphasizes the need for a randomized trial on this subject or eventually prospective cohort studies with a higher degree of matching between groups.

These observations are not disputed by the inherent limitations of this meta-analysis. However, the conclusion that the addition of the defibrillator to CRT reduces mortality risk should be taken cautiously. In fact, our main findings are not entirely unexpected when one considers the significant baseline differences between patients currently receiving CRT-D versus CRT-P (highlighted in Table 4). In the CERTI-TUDE cohort study, the higher all-cause mortality rate in CRT-P patients was almost entirely due to a much higher number

of heart failure-related or non-cardiac deaths, while SCD was only slightly more frequent. By cause-of-death analysis, 95% of the excess mortality among CRT-P subjects was related to an increase in non-sudden death.[30,62] This surprising finding is easily explained by the fact that CRT-P patients were older, had more advanced heart failure, and a higher number of comorbidities. In fact, those findings suggest that, in the context of primary prevention, the addition of the ICD to CRT-P patients as currently selected in daily clinical practice may be futile in some cases, as SCD only represents a minority of the additional number of deaths in CRT-P patients. On the other hand, a very recent study by Gold et al extrapolated lifelong treatment-specific all-cause mortality rates of CRT patients with mild heart failure enrolled in the REVERSE trial and concluded that, compared with CRT-P, CRT-D offered 2.77 additional life-years.[63] Given the high degree of matching between CRT-D and CRT-P patients in the REVERSE trial, this provided support towards the benefit of CRT-D, at least in those with mild heart failure.

Data on age-specific mortality rates in the United States in 2010 revealed that individuals aged 70 to 74 had a 53.2% higher relative risk of all-cause death than those aged 65 to 69, while

the latter had a 50.3% higher relative risk compared with individuals aged 60 to 64 (source: Centers for Disease Control and Prevention, http://www.cdc.gov). Patients included in this meta-analysis who received CRT-P had a 64% higher relative risk of all-cause death compared with a population of CRT-D patients who were 4 years younger on average (65.8 versus 70 years). We could speculate that age alone could explain most of the difference found in mortality rates between CRT-D and CRT-P patients. However, a sensitivity analysis of studies in which difference in mean age between CRT-D and CRT-P groups was less than 2 years revealed almost identical results to the main analysis. This suggests that age alone cannot explain the differences seen in mortality rates and therefore should not, only by itself, be used for device selection. However, through this meta-analysis we cannot exclude the possibility that comorbidities associated with age, rather than age itself, explained the differences in mortality rates. A similar sensitivity analysis of studies in which difference in percentage of patients in NYHA class >2 between CRT-P and CRT-D patients was ≥5% versus <5% revealed identical relative risk reduction. Again, this suggests that differences in NYHA class between study groups did not by itself mediate the differences in mortality rates. Differences in baseline characteristics between device groups were much less pronounced in the 3 randomized studies included in this meta-analysis and the advantage of CRT-D in these 3 studies, albeit of lower magnitude, was still present (RR 0.80 versus 0.68). These findings suggest that, although the lower mortality of CRT-D patients may be partly explained by their more favorable profile (especially in observational studies), the addition of the ICD plays an independent role in the reduction of all-cause mortality. The RR seen in the 3 randomized trials may more closely represent the true benefit of the ICD in CRT patients.

We have also shown that the potential benefit of the ICD in CRT patients is not homogeneously seen across different etiologies. Although ischemic cardiomyopathy CRT patients seemed to benefit from the addition of the ICD, such benefit was less clear in those with non-ischemic cardiomyopathy. Also, our meta-regression confirmed an association between ischemic cardiomyopathy and a stronger benefit of the CRT-D. This is a relevant finding, as in our meta-analysis patients with non-ischemic cardiomyopathy receiving CRT-P were in general older and had more advanced heart failure and higher number of comorbidities than non-ischemic CRT-D patients (Table S1). We would therefore expect a higher mortality in CRT-P patients in both etiologies. It is known that patients with non-ischemic dilated cardiomyopathy tend to respond better to CRT. As previously discussed, response to CRT predicts a lower risk of all-cause mortality,[44,45] ventricular arrhythmias,[45–50] and by inference a lower risk of SCD. The same rationale may help explain the association seen in our meta-regression between male gender and a larger benefit of CRT-D compared with CRT-P. Women are known to respond better to CRT than men and therefore their arrhythmic risk may be lower. This corroborates the results of a previous meta-analysis, which has shown that the benefit of ICD on mortality is significantly higher in men but does not reach statistical significance in women.[64]

Limitations

Several limitations are commonly linked to the methodology of meta-analyses and cross-comparisons, in particular heterogeneity between studies analyzed. In the present meta-analysis, heterogeneity, assessed through the I^2 test, was moderate for the pooled analysis of all-cause mortality. This was expected given the methodological differences between studies. However, the reported heterogeneity was mostly due to the different magnitude of benefit seen in the different studies, or underpowered studies that resulted in no benefit in favor of any of the 2 treatment groups, rather than opposing results. In fact, the lower mortality rates among CRT-D patients were seen consistently across studies. To address this limitation, we assessed the modulating effect of baseline differences in the different study populations through meta-regression, which has shown that only male gender and ischemic cardiomyopathy associated with a stronger benefit of CRT-D.

Furthermore, only a minority of studies presented data (in the form of hazard ratios) allowing sensitivity analysis of patients with ischemic versus non-ischemic dilated cardiomyopathy. As such, we were not able to provide conclusive evidence of the benefit, or lack thereof, of the CRT-D in the context of non-ischemic cardiomyopathy.

Patients receiving CRT-P were older and had higher NYHA class and comorbidity. A meta-analysis does not allow appropriate adjustment for the differences in patient characteristics between groups. As such, it is likely that the benefit conferred by CRT-D, compared with CRT-P, is less pronounced than what the overall results may suggest. However, the advantage of CRT-D, albeit of lower magnitude (RR 0.80, 95% CI 0.66–0.98, *P*=0.03), was still seen in a sensitivity analysis of the 3 randomized studies included in this meta-analysis, where differences in baseline characteristics between groups were much less pronounced. This supports the benefit of the ICD.

It should also be noted that the percentage of patients on beta-blockers may seem relatively low. However, this was seen throughout studies and represents real-life data.

Finally, overall study quality can be considered low, as only one randomized controlled trial was identified and included for analysis (although there were 2 sub-analyses of randomized controlled trials), and only 2 of the observational studies had a Newcastle–Ottawa score of ≥7. Bias is much more likely to be introduced in cohort studies and study groups among cohort

studies are more likely to be heterogeneous, as demonstrated in this meta-analysis. The reduction in the relative risk of death with CRT-D was less pronounced in randomized versus non-randomized studies, suggesting a bias towards CRT-D benefit in the latter.

Conclusion

Current CRT-P recipients are older and have more advanced heart failure and comorbidity than those receiving CRT-D. These differences notwithstanding, the addition of the ICD associates with a relative reduction in the risk of all-cause mortality in CRT patients, especially in the context of ischemic cardiomyopathy. The benefit of CRT-D compared with CRT-P in those with non-ischemic cardiomyopathy is less clear.

Disclosures

None.

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