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ORIGINAL ARTICLE

Individual patient data network meta-analysis of mortality effects of implantable cardiac devices

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▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2015-307634).

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Received 6 February 2015
Revised 24 May 2015
Accepted 18 June 2015
Published Online First 12 August 2015

▸ http://dx.doi.org/10.1136/heartjnl-2015-308295

To cite: Woods B, Hawkins N, Mealing S, *et al*. *Heart* 2015;**101**: 1800–1806.

ABSTRACT

Objective Implantable cardioverter defibrillators (ICD), cardiac resynchronisation therapy pacemakers (CRT-P) and the combination therapy (CRT-D) have been shown to reduce all-cause mortality compared with medical therapy alone in patients with heart failure and reduced EF. Our aim was to synthesise data from major randomised controlled trials to estimate the comparative mortality effects of these devices and how these vary according to patients' characteristics.

Methods Data from 13 randomised trials (12 638 patients) were provided by medical technology companies. Individual patient data were synthesised using network meta-analysis.

Results Unadjusted analyses found CRT-D to be the most effective treatment (reduction in rate of death vs medical therapy: 42% (95% credible interval: 32–50%), followed by ICD (29% (20–37%)) and CRT-P (28% (15–40%)). CRT-D reduced mortality compared with CRT-P (19% (1–33%)) and ICD (18% (7–28%)). QRS duration, left bundle branch block (LBBB) morphology, age and gender were included as predictors of benefit in the final adjusted model. In this model, CRT-D reduced mortality in all subgroups (range: 53% (34–66%) to 28% (−1% to 49%)). Patients with QRS duration ≥150 ms, LBBB morphology and female gender benefited more from CRT-P and CRT-D. Men and those <60 years benefited more from ICD.

Conclusions These data provide estimates for the mortality benefits of device therapy conditional upon multiple patient characteristics. They can be used to estimate an individual patient's expected relative benefit and thus inform shared decision making. Clinical guidelines should discuss age and gender as predictors of device benefits.

INTRODUCTION

In addition to optimal medical therapy, implantable cardiac devices have an established role in the treatment of heart failure with reduced EF. International clinical guidelines[1 2] make recommendations for implantable cardioverter defibrillators (ICD), cardiac resynchronisation therapy pacemakers (CRT-P) and the combined device, CRT-D, based on the presence of specific patient characteristics, recognising that the clinical benefit associated with these devices varies across subgroups within the broader population of patients with heart failure and reduced EF. These differences arise due to difference in underlying prognosis as well as differences in the relative treatment effects of devices (ie, the HRs comparing alternative interventions). Estimates of relative treatment effects for patients with different characteristics are, therefore, required to assess the comparative clinical benefit and cost-effectiveness of these devices. With this objective, we pooled individual patient data from all major randomised controlled trials of the devices in a network meta-analysis. This work was developed to inform National Institute for Health and Care Excellence (NICE) guidance for the devices.[3]

Until now, meta-analyses of published randomised trials[4–8] have reported differences in treatment effects of CRT according to QRS duration and morphology and of ICD according to gender.[9] In addition, subgroup analyses of individual trials have reported statistically significant variation in all-cause mortality benefit (or composite endpoints, including all-cause mortality) by New York Heart Association (NYHA) class,[10] QRS duration;[11 12] QRS morphology[11] and gender.[12] An *individual* patient data meta-analysis is the ideal vehicle to explore the effect of these and other patient characteristics on relative treatment effects. This type of analysis avoids reliance on inconsistent individual trial subgroup results or restricting meta-analysis to published subgroup data. A *network* meta-analysis was necessary as patients with heart failure and reduced EF may benefit from ICD, CRT-D or CRT-P (ie, simple pairwise comparisons do not answer the clinical question of interest). Network meta-analysis (or mixed treatment comparison) allows the synthesis of individual trials that compare different sets of treatments.[13] For example, the treatment effect for CRT-D versus medical therapy will reflect the direct evidence from COMPANION[14–17] supplemented by the larger volume of indirect evidence from the CRT-D versus ICD and ICD versus medical therapy trials.

METHODS

Systematic review

A systematic review was conducted to identify randomised controlled trials comparing ICD, CRT-P and CRT-D with each other or with placebo or medical therapy in patients with heart failure and reduced EF (defined as LVEF ≤40%). All English language full publications from 1990 onwards were considered. Studies were excluded if: patients had experienced recent myocardial infarction or coronary revascularisation (≤45 days before enrolment); they compared device variants (eg, different pacing strategies); patients had familial cardiac conditions

with a high risk of sudden cardiac death or patients had a secondary prevention indication for ICD.

Twenty-two trials were identified, and individual patient-level data from 13 of these were provided by three device manufacturers (Boston Scientific, Medtronic and St. Jude Medical). This represents 95% (12,638/13,350) of patients randomised in the overall network of evidence, see figure 1. 'Optimal' and 'conventional' medical therapy was considered to be equivalent. REsynchonization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE)[18] was considered as four separate designs; Contak-CD[19] as two separate designs and Miracle ICD[20] and Miracle ICD II[21] as one trial in keeping with the underlying study designs. The two non-device arms of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (placebo and amiodarone)[10] were pooled. Further details of the systematic review are provided in the on-line supplementary appendix.

Network meta-analysis

A series of network meta-analyses was performed for all-cause mortality. As is standard in network meta-analyses of survival data,[22 23] we assume that HRs are multiplicative, that is, the HR for CRT-D versus medical therapy can be estimated as the product of the HRs for CRT-D versus ICD and ICD versus medical therapy. This assumption will be violated when differences exist between the trials comparing alternative sets of treatments, and these differences are expected to impact upon the trial HRs. Analyses adjusting for such differences were developed as previous meta-analyses and subgroup analyses support the presence of such differences.[4–8 10–12]

Unadjusted network meta-analyses were performed to establish the efficacy of the devices in the overall randomised populations, to determine the impact of excluding studies for which individual patient data were unavailable and to assess the appropriateness of fixed-effects and random-effects analyses. Adjusted network meta-analyses were performed in order to explore whether patients with different baseline characteristics (age, gender, country (USA vs outside-USA), NYHA class, ischaemic aetiology, LVEF, QRS duration and left bundle branch block (LBBB) morphology) experienced different effects of treatment. These variables were recorded across the trials and were selected following a review of risk scores, clinical guidelines, trial subgroup analyses and clinical advice. For the adjusted analyses, patients with QRS duration <120 ms in CRT trials were excluded as the very low number of deaths (five in total in the CRT arms) made modelling unstable and there is no evidence that CRT is effective in this group. This resulted in the exclusion of 149 patients. In patients with QRS duration <120 ms, the adjusted analysis only compares ICD with medical therapy. A sensitivity analysis was run restricted to patients with QRS≥120 ms and NYHA class II–IV as these were considered to be a more homogeneous group.

Data were included from each trial throughout the follow-up period prespecified in the trial protocols. Although longer term follow-up data are available for a number of trials, these were not included because of the high rates of cross-over observed during the additional follow-up periods.[24 25]

Statistical analysis

The studies for which individual patient data were unavailable reported summary data in binary form (number of deaths and number of participants by arm) rather than as HRs. The binary data were, therefore, combined with HRs obtained from the individual patient data studies using published statistical methods.[23] These analyses were repeated with and without the data from the studies for which individual patient data were unavailable. Fixed-effects and random-effects analyses were run.

In the analysis adjusting for patient characteristics, individual patient time-to-event data were synthesised across trials using a Cox proportional hazard model stratified by trial.[22 26] All *adjusted* models were fitted as fixed- effects analyses. In all analyses, the impact of baseline patient characteristics on the efficacy of the devices was assumed to be device specific, reflecting the potentially different mechanisms of action of the devices.

Selection of interaction effects for the adjusted model followed the model selection process described by Collett using a p value of 0.10.[27] All results were reviewed for biological plausibility. For the final adjusted model, multiple imputation was used to address missing baseline variables and continuous variables were dichotomised to facilitate presentation.

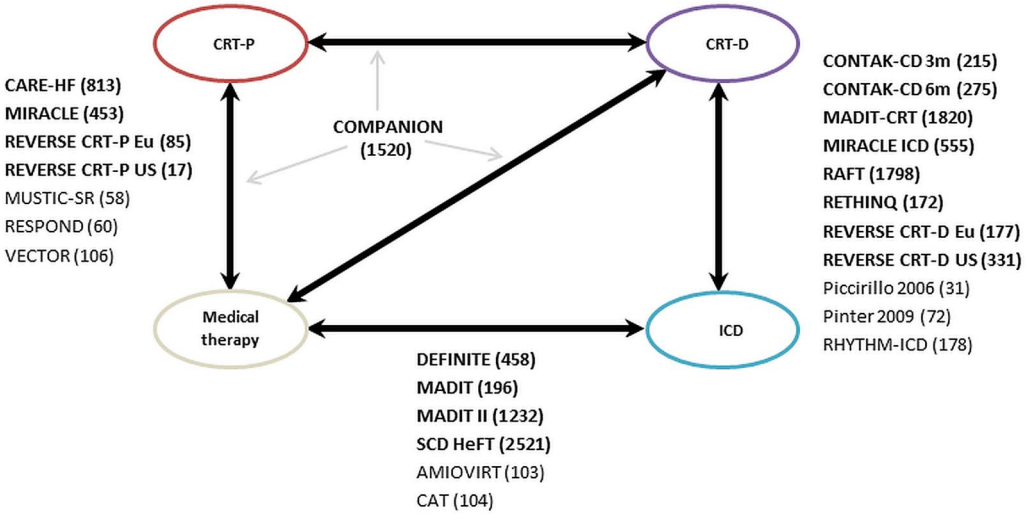

Figure 1 Network of randomised controlled trial evidence. Elipses represent comparators. Arrows represent comparisons of interventions for which trial data were available. Studies for which individual patient data were available are in bold. Patient numbers represent the total number of patients enrolled in each trial informing the comparison of interest. CRT-D, cardiac resynchronisation therapy pacemaker with defibrillation therapy; CRT-P, cardiac resynchronisation therapy pacemakers; ICD, implantable cardioverter defibrillators.

Further detail regarding the statistical methods is available in the on-line supplementary appendix.

RESULTS

Individual patient database

The 12 638 patients included in the trial database were followed up for a mean of 2.5 years (range 0–7.5 years) during which 2422 deaths were observed.

Patient characteristics stratified by trial arm are presented in table 1. There is considerable overlap in the patients randomised to the different treatment options. As expected, patients randomised to CRT-P or CRT-D had longer mean QRS duration and more frequently exhibited LBBB morphology compared with those randomised to medical therapy or ICD. The majority of patients were in NYHA class II or III, with CRT-P trials enrolling more individuals in class III and ICD trials in class II. Only 138 (1.1%) of patients had a LVEF in the 36–40% range, so the analyses presented are representative of patients with LVEF ≤35%.

Unadjusted analysis

Analysis of all trials (including those for which individual patient data were unavailable) showed CRT-D to be the most effective treatment (HR when compared against medical therapy 0.58 (95% credible interval: 0.50–0.68)), with CRT-P and ICD showing similar effects on mortality (0.72 (0.60–0.85) and 0.71 (0.63–0.80), respectively), compared with medical therapy. Head-to-head device comparisons supported a statistically significant benefit of CRT-D when compared with CRT-P (0.81 (0.67–0.99)) and ICD (0.82 (0.72–0.93)). Restricting the network to the 13 trials for which individual patient data were available did not alter the results (point estimates and CIs fell within 0.01 of the overall analysis, results not shown). Restriction of the adjusted analysis to trials for which individual patient data were available is therefore unlikely to influence the results.

Adjusted analysis

Univariate analyses suggested that age, gender, LVEF, QRS duration and LBBB morphology affected mortality benefit, with p values for the interaction effects ranging from <0.001 to 0.043. These effects were therefore included in a multivariate model. Dropping each set of interaction effects from this model in turn worsened the model significantly for age, gender, LVEF and QRS (p values <0.01 to 0.07). Dropping LBBB did not significantly worsen the model fit (p=0.27), but it was, however, retained given its known clinical importance. Adding in covariables that were not significant in the univariate analysis (USA or non-USA-based trial; NYHA class; ischaemic aetiology) did not significantly improve the model fit (p values: 0.21–0.71), and they were therefore discarded. The multivariate model and the univariate analyses suggested that lower LVEF (within the range seen in the trials) increased CRT-D efficacy but reduced CRT-P and ICD efficacy. As CRT-D is the combined device, these effects were not deemed clinically plausible. Examination of a dichotomised LVEF variable indicated that the impact of LVEF increased and decreased device effectiveness in biologically improbable patterns over the range of the variable. LVEF was therefore dropped from the final model. QRS duration was split into three categories for the final model (<120 ms, 120–149 ms and ≥150 ms), reflecting commonly accepted clinical thresholds and age was split into two categories (<60 and ≥60 years). The results of univariate network meta-analyses are shown in figure 2 for those variables included in the final multivariate model.

Final model

The final multivariate model included age, gender, QRS duration and LBBB morphology. Table 2 provides point estimates and CIs from the multivariate model for the treatment effects for each device, by subgroup. This allows estimates of risk and benefit to be made for *individual* patients with specific QRS duration and morphology, age and gender. The model parameters are reported in the on-line supplementary appendix.

Our model predicts that in *all* subgroups of patients (LVEF ≤35% and QRS ≥120 ms), CRT-D is associated with a mortality reduction, which is statistically significant in 15 of 16 subgroups, the exception being men under 60 years, with QRS duration ≥120 to <150 ms without LBBB morphology where the CI just spans unity. Estimated relative risk reductions in mortality ranged from 28% (HR 0.72 (0.51 to 1.01)) in that group to 53% (HR 0.47 (0.34 to 0.66)) in women ≥60 years with QRS duration ≥150 ms and LBBB. CRT-D is more effective in those with QRS durations ≥150 ms, in those with LBBB and in women, with minimal interaction with age.

CRT-P is more effective at reducing mortality in older patients and in women, in those with QRS duration ≥150 ms and in those with LBBB morphology. In those with the broadest QRS and LBBB, the effect size varied from relative risk

Table 1 Characteristics of patients included in trial database

Intervention	Medical therapy	CRT-D	CRT-P	ICD	Missing (%)
Number of patients	3477	3527	1328	4306	0.0
Age (mean, years)	61.9	65.0	65.0	63.5	0.0
QRS duration (mean, ms)	130.8	156.8	162.3	140.5	1.3
LVEF (mean, %)	23.7	23.4	23.4	23.3	1.4
Gender (% female)	24.0	22.5	30.1	20.7	0.0
US (%)	81.1	61.6	62.6	68.8	0.0
NYHA1 (%)	7.7	6.0	1.1	11.4	0.1
NYHA2 (%)	45.3	59.4	4.5	61.9	
NYHA3 (%)	43.5	31.1	85.3	24.9	
NYHA4 (%)	3.5	3.5	9.1	1.8	
Ischaemic (%)	58.2	60.1	52.3	64.0	6.4
LBBB morphology (%)	37.5	69.4	79.7	45.6	1.8

CRT-D, cardiac resynchronisation therapy pacemaker with defibrillation therapy; CRT-P, cardiac resynchronisation therapy pacemakers; ICD, implantable cardioverter defibrillators; LBBB, left bundle branch block; NYHA, New York Heart Association.

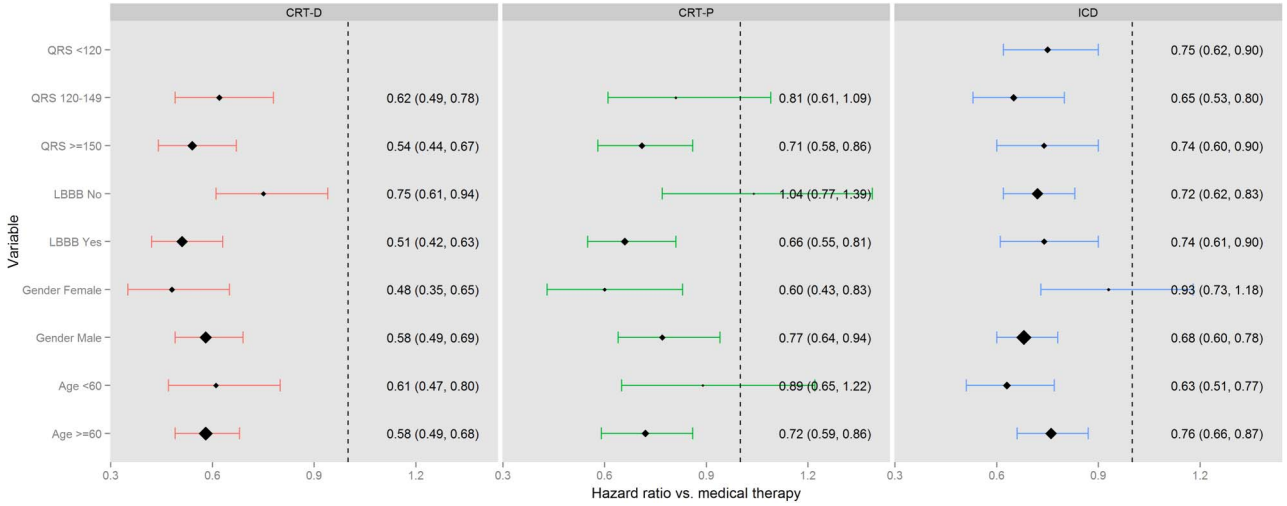

Figure 2 Treatment effect estimates from univariate network meta-analysis model for variables included in final model. The forest plots show the results of the univariate network meta-analysis incorporating individual baseline characteristics as interaction effects. HRs (mean (95% CI)) are presented relative to medical therapy with values <1.0 indicating reduced all-cause mortality. CRT-D, cardiac resynchronisation therapy pacemaker with defibrillation therapy; CRT-P, cardiac resynchronisation therapy pacemakers; ICD, implantable cardioverter defibrillators; LBBB, left bundle branch block.

reduction of 20% (HR 0.80 (0.56 to 1.14)) in younger men to 44% (HR 0.56 (0.40 to 0.79)) in older women. A substantially lower effect was observed in those with QRS duration 120–149 ms and no LBBB (varying from no benefit or potential harm (HR 1.07 (0.70 to 1.64)) in men aged <60 years to 25% relative risk reduction (HR 0.75 (0.46 to 1.21)) in women aged ≥60 years).

In contrast, the mortality benefit of ICD therapy is greater in men than in women, and less apparent in older patients. For all subgroups of men, the effect size was statistically significant with relative risk reductions between 24% and 48%. For women, the estimated mortality benefit of ICD was smaller and the CIs in 9 of the 10 subgroups spanned unity. The estimated effect sizes were smaller for all subgroups of men and women aged 60 years or more, compared with younger patients.

The sensitivity analysis restricted to patients with QRS ≥120 and NYHA II–IV produced similar results though predicted greater effectiveness of CRT-D and CRT-P in patients <60 years and no longer suggested that CRT-P effectiveness depended on age. For full results, see the on-line supplementary appendix.

DISCUSSION

This individual patient data network meta-analysis incorporated data from all major trials of ICD, CRT-P and CRT-D in patients with heart failure and reduced EF. The data set included 2422 deaths in 12 638 patients, representing 95% of all patients randomised in the clinical trials of these technologies.

Tools developed using individual patient characteristics to estimate treatment benefits are the cornerstone of personalised medicine. Unlike conventional subgroup analyses which present

Table 2 Subgroup-specific treatment effects predicted by multivariate adjusted network meta-analysis

				CRT-D vs MT	CRT-P vs MT	ICD vs MT	CRT-D vs CRT-P	CRT-D vs ICD	ICD vs CRT-P
Gender	Age	QRS	LBBB	HR (95% CI)					
Female	<60	<120	N			0.82 (0.60 to 1.13)			
		≥120 to <150	N	0.62 (0.40 to 0.96)	0.86 (0.50 to 1.48)	0.69 (0.48 to 0.99)	0.72 (0.40 to 1.30)	0.90 (0.58 to 1.39)	0.80 (0.46 to 1.39)
		≥120 to <150	Y	0.55 (0.36 to 0.84)	0.76 (0.46 to 1.25)	0.74 (0.51 to 1.07)	0.72 (0.42 to 1.25)	0.74 (0.48 to 1.13)	0.98 (0.58 to 1.64)
		≥150	N	0.55 (0.35 to 0.86)	0.74 (0.42 to 1.28)	0.77 (0.52 to 1.13)	0.74 (0.41 to 1.35)	0.71 (0.46 to 1.12)	1.04 (0.59 to 1.83)
		≥150	Y	0.48 (0.33 to 0.72)	0.65 (0.42 to 1.00)	0.82 (0.59 to 1.15)	0.75 (0.45 to 1.24)	0.59 (0.40 to 0.87)	1.27 (0.79 to 2.04)
	≥60	<120	N			1.01 (0.76 to 1.36)			
		≥120 to <150	N	0.60 (0.41 to 0.90)	0.75 (0.46 to 1.21)	0.85 (0.62 to 1.17)	0.81 (0.48 to 1.37)	0.71 (0.48 to 1.04)	1.14 (0.70 to 1.87)
		≥120 to <150	Y	0.53 (0.37 to 0.78)	0.65 (0.42 to 1.02)	0.91 (0.66 to 1.27)	0.82 (0.51 to 1.32)	0.59 (0.41 to 0.84)	1.39 (0.89 to 2.20)
		≥150	N	0.53 (0.35 to 0.80)	0.64 (0.39 to 1.03)	0.94 (0.66 to 1.34)	0.84 (0.50 to 1.40)	0.57 (0.38 to 0.84)	1.48 (0.91 to 2.41)
		≥150	Y	0.47 (0.34 to 0.66)	0.56 (0.40 to 0.79)	1.01 (0.76 to 1.35)	0.84 (0.56 to 1.27)	0.47 (0.34 to 0.64)	1.81 (1.24 to 2.64)
Male	<60	<120	N			0.62 (0.48 to 0.79)			
		≥120 to <150	N	0.72 (0.51 to 1.01)	1.07 (0.70 to 1.64)	0.52 (0.39 to 0.69)	0.67 (0.42 to 1.06)	1.37 (0.98 to 1.92)	0.49 (0.31 to 0.76)
		≥120 to <150	Y	0.63 (0.44 to 0.91)	0.94 (0.61 to 1.43)	0.56 (0.40 to 0.78)	0.68 (0.43 to 1.07)	1.13 (0.80 to 1.61)	0.60 (0.38 to 0.93)
		≥150	N	0.63 (0.44 to 0.91)	0.91 (0.58 to 1.42)	0.58 (0.42 to 0.80)	0.69 (0.43 to 1.12)	1.10 (0.78 to 1.54)	0.63 (0.40 to 1.00)
		≥150	Y	0.56 (0.40 to 0.77)	0.80 (0.56 to 1.14)	0.62 (0.46 to 0.83)	0.70 (0.46 to 1.06)	0.90 (0.67 to 1.23)	0.77 (0.52 to 1.15)
	≥60	<120	N			0.76 (0.62 to 0.94)			
		≥120 to <150	N	0.70 (0.53 to 0.92)	0.92 (0.64 to 1.32)	0.64 (0.51 to 0.81)	0.76 (0.52 to 1.10)	1.09 (0.85 to 1.39)	0.70 (0.48 to 1.00)
		≥120 to <150	Y	0.62 (0.46 to 0.83)	0.81 (0.57 to 1.16)	0.69 (0.52 to 0.91)	0.76 (0.53 to 1.11)	0.90 (0.69 to 1.16)	0.85 (0.59 to 1.23)
		≥150	N	0.62 (0.46 to 0.83)	0.79 (0.55 to 1.12)	0.71 (0.54 to 0.93)	0.78 (0.54 to 1.13)	0.87 (0.67 to 1.12)	0.90 (0.63 to 1.30)
		≥150	Y	0.54 (0.43 to 0.69)	0.69 (0.55 to 0.87)	0.76 (0.60 to 0.96)	0.79 (0.59 to 1.05)	0.72 (0.59 to 0.87)	1.10 (0.83 to 1.46)

CRT-D, cardiac resynchronisation therapy pacemaker with defibrillation therapy; CRT-P, cardiac resynchronisation therapy pacemakers; ICD, implantable cardioverter defibrillators; LBBB, left bundle branch block; MT, medical therapy.

results stratified by a single characteristics, our multivariate analysis allows the expected relative effect of alternative devices to be assessed based on an individual patient's QRS duration, LBBB morphology, age and gender by reading off the relevant HR from table 2. These results could be integrated with a prediction model for mortality in untreated patients, to predict life expectancies for alternative devices. This could be included in a web-based decision tool[28] and integrated into a 'patient decision aid' to facilitate shared decision making and informed consent.[29]

The results for the unadjusted network meta-analysis are consistent with those published previously,[30] but, in addition, the current analysis shows a statistically significant benefit of CRT-D over both ICD and CRT-P, with the differences driven by evidence from more recently published trials.[11 12 18] Given the heterogeneity within and across the included studies, the unadjusted results may be confounded.

The adjusted analysis suggests that increasing QRS duration and LBBB morphology are associated with greater mortality benefit from CRT. This is consistent with the mechanism of mechanical cardiac resynchronisation in LBBB, and the higher risk of pump failure deaths among patients with longer QRS durations. Analyses of published data have found both variables to improve CRT efficacy in univariate analyses.[4 5] A recent meta-analysis of individual patient data from 3872 patients included in five CRT (P or D) trials found no association between LBBB morphology and CRT efficacy for all-cause mortality when QRS duration had been controlled for.[7] This meta-analysis was smaller than that presented here (662 deaths in 3872 patients compared with 2422 deaths in 12 638 patients with 1430 deaths observed in CRT trials) and pooled results from CRT-P with CRT-D and ICD with medical therapy.

We also found important effects of age and gender. These effects are likely to be related to the underlying risk of competing causes of death; sudden (presumed arrhythmic) death, pump failure or other causes. Women are less likely to experience sudden cardiac death than men.[31] Similarly, although the incidence of sudden cardiac death increases with age, the proportion of cardiac deaths that are sudden decreases owing to high numbers of other cardiac causes of death.[32 33] As CRT delivers most of its benefit through pump function and ICD by treating arrhythmias leading to sudden cardiac death, this may explain the higher efficacy of ICD therapy in younger patients and men, and the higher efficacy of CRT in women. The effects of age and gender observed by pooling these trials were not observed consistently in the individual studies. Nor have they been identified in previous meta-analyses, with one exception—an analysis of published subgroup data that showed lower efficacy of ICD on all-cause mortality in women.[9]

No evidence was found for interaction effects of devices with NYHA class, aetiology or LVEF. Of course, these variables do predict *absolute* incremental mortality benefit from therapy as they are known to be predictive of life expectancy in the absence of device intervention.[34]

Our analysis is in line with current clinical guidance (table 3), though suggests that there is no evidence to support different recommendations according to a patients aetiology. It also suggests that age and gender play a significant role in determining the relative benefit of alternative devices. For example, although CRT-D offers benefits over ICD in the overall patient population, in men strong evidence of benefit is only observed for those with the strongest indication for CRT (≥60 years, QRS ≥150 ms, LBBB). Gender is mentioned in the CRT guideline as predictive of improved effect but not in guidance for ICD use, and neither guideline mentions age.

Table 3 Summary of relevant international guidance

Device	Patient group	Recommendation	Reference
CRT-P	LVEF ≤35%, NYHA class II, III, ambulatory class IV:		35
	QRS≥150 ms with LBBB	Class I Level A	
	QRS≥150 ms without LBBB	Class IIa Level B	
	QRS ≥120 to <150 ms with LBBB	Class I Level B	
	QRS ≥120 to <150 ms without LBBB	Class IIb Level B	
ICD	LVEF ≤35%, NYHA class II–III		2
	Ischaemic	Class I Level A	
	Non-ischaemic	Class I Level B	
CRT-D	Patients in whom CRT-P is indicated and ICD is planned	Class I Level A	35
	Patients with indicators of better prognosis and/or ischaemic heart disease	Class IIa Level B	

CRT-D, cardiac resynchronisation therapy pacemaker with defibrillation therapy; CRT-P, cardiac resynchronisation therapy pacemakers; ICD, implantable cardioverter defibrillators; LBBB, left bundle branch block; NYHA, New York Heart Association.

Limitations

This analysis does not explore the impact of atrial fibrillation or chronic kidney disease on device efficacy. Of the 10 CRT trials in the individual patient database, only one included patients with permanent atrial fibrillation.[11] Earlier analyses indicated that data on serum creatinine was unavailable for approximately one third of patients. There were, therefore, insufficient data to assess the impact of either of these features on mortality.

Outcomes for the therapies studied are dependent on both device hardware and programming. This analysis reflects the

Key messages

What is already known on this subject?

- Implantable cardioverter defibrillators (ICD), cardiac resynchronisation therapy pacemakers (CRT-P) and the combination therapy (CRT-D) reduce all-cause mortality compared with medical therapy alone. Similarly, CRT-D reduces all-cause mortality compared with ICD. Limited data exist to compare CRT-D with CRT-P. Evidence of how the mortality benefit of these implantable devices varies with patient characteristics is largely limited to individual trial subgroup analyses.

What might this study add?

- This individual patient data network meta-analysis found that patients with QRS duration ≥150 ms, left bundle branch block morphology and female gender benefited more from CRT-P and CRT-D, and those <60 years and of male gender benefited more from ICD.

How might this impact on clinical practice?

- The analysis allows the survival benefit of each device to be estimated for specific patient groups.
- This information can be used directly in assessments of net clinical benefit and cost-effectiveness. This evidence has been used in this way at the National Institute for Health and Care Excellence (NICE) in their recent guidance update.

efficacy of the devices and leads available at the time and as programmed in the clinical trials. With the benefit of current technology, we would expect greater efficacy of ICD and CRT in clinical practice. Evidence regarding the impact of these factors on outcomes should be taken in to account when considering alternative interventions.

The results should not be extrapolated to patients with characteristics absent or under-represented within the data. Namely, to the effect of CRT in patients with NYHA class I or QRS duration ≤120 ms, to CRT-P in patients with NYHA class II or to any patients with LVEF >35%.

Given the different impacts of CRT and ICD therapy on pump failure and sudden cardiac death,[17 36] it would have been interesting to analyse the impact of the devices on each cause of death. This was not pursued, as there were concerns about the reliability and consistency in the assignment of mode of death.

Value for money is another important consideration at the healthcare system level. The analysis reported here alongside further analysis of this database to estimate hospitalisation rates and quality of life has been used to inform such a cost-effectiveness analysis.[3] This will be the subject of a separate publication.

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Acknowledgements Jeff Cerkvenik (Medtronic), Jennifer Duggan (St. Jude Medical), Elena Ivanova (St. Jude Medical), Andi Schaechter (Northwestern University) and Haris Subacius (Northwestern University) provided database management and statistical support in assembling trial data held by their organisations and in responding to queries relating to the delivered data. Leticia Barcena (Oxford Outcomes Ltd.) conducted the systematic review. Ben Brown (Medtronic), Mark Chapman (Medtronic), Sheri Dodd (Medtronic), Steve Fearn (St. Jude Medical), Michael Ferguson (Boston Scientific), Mark McIntyre (Boston Scientific), Parashar Patel (Boston Scientific), Rodamni Peppa (Boston Scientific), Sine Rose (St. Jude Medical), Dan Schaber (Medtronic), Antje Smala (Biotronik), Adrian Squires (Sorin) and Nathalie Verin (Boston Scientific) provided logistical support and scientific input during the course of the project. Judith Mellis (Association of British Healthcare Industries) provided logistical support throughout the project.

Contributors BW conducted the analysis under the supervision of NH and with assistance from SM. BW, NH, SM, AS, MS, CJP and MRC contributed to the design of the work and interpretation of data. WA, JB and HK contributed to acquisition of data. BW, MRC and CJP drafted the manuscript. All authors contributed to revising the manuscipt and approved it for final submission. Contributors: Jeff Cerkvenik (Medtronic), Jennifer Duggan (St. Jude Medical), Elena Ivanova (St. Jude Medical), Andi Schaechter (Northwestern University) and Haris Subacius (Northwestern University) provided database management and statistical support in assembling trial data held by their organisations and in responding to queries relating to the delivered data. Leticia Barcena (Oxford Outcomes Ltd) conducted the systematic review. Ben Brown (Medtronic), Mark Chapman (Medtronic), Sheri Dodd (Medtronic), Steve Fearn (St. Jude Medical), Michael Ferguson (Boston Scientific), Mark McIntyre (Boston Scientific), Parashar Patel (Boston Scientific), Rodamni Peppa (Boston Scientific), Sine Rose (St. Jude Medical), Dan Schaber (Medtronic), Antje Smala (Biotronik), Adrian Squires (Sorin) and Nathalie Verin (Boston Scientific) provided logistical support and scientific input during the course of the project. Judith Mellis (Association of British Healthcare Industries) provided logistical support throughout the project.

Funding This work was supported by Biotronik, Boston Scientific, Medtronic, Sorin and St. Jude Medical. MRC's salary is funded by the National Institute for Health Research Cardiovascular Biomedical Research Unit at the Royal Brompton Hospital, London. CJP's salary is funded by Newcastle upon Tyne Hospitals NHS Foundation Trust.

Competing interests BW, SM and NH were employees of Oxford Outcomes Ltd during the period of this work. MS is a consultant to Oxford Outcomes Ltd and received payment for his involvement in this work. AS was a paid consultant to Oxford Outcomes Ltd for this work. MRC provides consultancy advice to Medtronic, Boston Scientific and St. Jude Medical and has had research grants from Medtronic. CJP has received research funding and travel grants to attend scientific meetings and has provided consultancy advice to Medtronic, Boston Scientific and St. Jude Medical. HK has provided consultancy advice and has received research funding from Boston Scientific. William Abraham has received consulting fees from St. Jude Medical and Biotronik.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary data

Systematic review and distinct trial designs

A systematic review was carried out to identify relevant data. Searches were carried out in Medline and Medline in process (Ovid SP, from 1948 to present), Embase (Ovid SP, from 1988 to present) and the Cochrane Central Register of Controlled Trials (CENTRAL) and were run from 1990 to 27th June 2011 (28th June for CENTRAL). Abstracts were screened by two reviewers. Reference lists of included trials were also reviewed. Search strategies and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram are provided at the end of this document.

Twenty-two trials were included in the review. Characteristics of the trials are provided as Table S1, along with references to the associated publications. These data were extracted from the trial publications identified by the systematic review. Missing data may therefore reflect incomplete reporting rather than the actual data collected. Missing data for the individual patient database is recorded in Table 1 of the main text.

There is variation in patient characteristics across trials with respect to age, gender, New York Heart Association (NYHA) class, QRS duration, left bundle branch block (LBBB) morphology and the proportion of patients with disease of ischaemic aetiology. Less difference was seen with respect to mean left ventricular ejection fraction (LVEF) (21-27% across all trials). These differences in average patient characteristics reflect differences in the trial inclusion criteria. However, the differences in average characteristics should not obscure the real similarities across subgroups of the trials. For example, four of the five largest trials (Companion, Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), Resynchronisation-defibrillation for Ambulatory heart Failure Trial (RAFT), and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)) all contained some proportion of patients with NYHA III, QRS duration≥120ms and LVEF≤30%. Study quality was assessed using the risk of bias assessment tool recommended by the National Institute for Health and Care Excellence[1], and is summarised in Table S2.

Of the eight studies not included in the individual patient data set, two were not sponsored by the manufacturers (Cat and Piccirillo *et al*.); two were not available (Amiovirt, Pinter *et al*.); two data sets could not be reconciled with the published data and were therefore not considered of sufficient quality

for inclusion in the analysis (MUltisite STImulation in Cardiomyopathies (MUSTIC); Resynchronisation for HemodYnamic Treatment for Health failure Management ICD (RHYTHM-ICD)) and two were not identified by the systematic review until data requests had been sent out and the analysis had started (Vector; Respond).

The dataset holder for MUSTIC (Medtronic) was unable to reconcile the available datasets (which were locked over 10 years ago) with the data in the public domain. These data were therefore not supplied to the authors for analysis. The data for RHYTHM-ICD were released to the authors however the authors in collaboration with the data holder (St. Jude Medical) were unable to reconcile the number of deaths between the FDA report for this study (9 deaths for CRT-D and 3 for ICD) with the individual patient data sets (which showed 7 and 2 deaths respectively). Given these concerns regarding the individual patient data this data was not included in the adjusted analysis. The unadjusted analysis was however run with and without data from the studies for which individual patient data were unavailable in order to assess the potential for omission of these studies to influence the study results.

Contak-CD and REsynchonization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) were not straightforward parallel-group designs comparing the devices of interest. Patient allocation in REVERSE was to either CRT-D or CRT-P implantation based on clinical guidelines or physician judgement. Patients were then randomised to resynchronisation therapy "on" or "off". In addition, patients were programmed to have CRT switched "on" after 12 months in the US and 24 months in Europe. REVERSE is, therefore, considered as four trials: US and European trials in CRT-D implanted patients comparing CRT-D to ICD (representing the majority of patients); and US and European trials in CRT-P implanted patients comparing CRT-P to medical therapy.

Contak-CD initially randomised patients to CRT-P or medical therapy with cross-over to the other therapy after 3 months. Part way through the trial, patients enrolled into a six-month parallel group trial. These designs can, therefore, be considered as two separate trials (Contak-CD Ph1 (up to 3 months) and Contak-CD Ph2, respectively).

The SCD-HeFT trial randomised patients to three arms: conventional therapy plus placebo; conventional therapy plus amiodarone and conventional therapy plus ICD. As the focus of this

analysis was to compare device therapies this posed the question of whether one or both of the non-device arms should be included in the analysis. Based on clinical advice and the all-cause mortality endpoint results from this study (amiodarone vs. placebo hazard ratio 1.06 (95% CI 0.86-1.30)), the amiodarone and placebo arms of this trial were pooled in the analysis.

Miracle ICD and Miracle ICD II, although reported in separate publications, actually describe a single trial so this is considered as a single trial in the analysis.

Data from publications were extracted by one reviewer and checked by another. Individual patient data were requested in a standardised format from the three device manufacturers. A wide range of patient characteristic, study characteristic and outcome data were extracted from the trials. However, the focus of the network meta-analysis is the all-cause mortality outcome.

Statistical methods

Methods for combining binary and hazard ratio data

Binary data were included using a binomial likelihood for the cumulative probability of death in arm *k* of study *s* ($F_{s,k}$). From this, the log-cumulative hazard $\ln(H_{s,k})$ is derived using a complementary log-log link transformation [2] . The log-cumulative hazard is estimated as the sum of a study-specific 'baseline' term α_s and a treatment effect coefficient β_k where $\beta_1 = 0$ and β_b represents the treatment effect for the baseline treatment in study *s*.

$$\ln(H_{s,k}) = \alpha_s + \beta_k - \beta_b$$

Equation 1

Hazard ratio data were incorporated into the NMA model using a normal likelihood for the log-hazard ratio $\ln(HR_{s,k,b})$ for study *s* comparing treatment *k* to treatment *b*. These were estimated from each study using a cox proportional hazards model. The log-hazard ratio estimates are then included in a treatment effect model to allow the hazard ratio data to also inform the β_k :

$$\ln(HR_{s,k,b}) = \beta_k - \beta_b$$

Equation 2

Equations 1 and 2 are replaced by equations 3 and 4 for the random effects model where $re_{s,k}$ is the random effect deviation for arm k of study s and is assumed to be normally distributed with zero mean and variance $\sigma^2/2$, where σ^2 is the random effect variance for a treatment comparison.

$$\ln(H_{s,k}) = \alpha_s + \beta_k - \beta_b + re_{s,k} - re_{s.b}$$

Equation 3

$$\ln(HR_{s,k,b}) = \beta_k - \beta_b + re_{s,k} - re_{s.b}$$

Equation 4

For ease of implementation this model was implemented in Winbugs and is a Bayesian analysis. Vague priors were used in this analysis. Two sets of initial values were used and convergence was assessed by examining caterpillar plots and Brooks Gelman-Rubin (BGR) statistics [3]. Fixed and random effects models were fitted and the deviance information criteria (DIC) was used to compare

their fit [4]. Autocorrelation was also examined. Fixed effects models were preferred according to the deviation information criterion (DIC) in the unadjusted analysis and are presented in the main text.

Methods for adjusted analysis

The unadjusted model takes the following form:

$$\lambda_{is} = \lambda_s(t) \cdot \exp(\beta_{CRT-P} D_{CRT-P\ is} + \beta_{CRT-D} D_{CRT-D\ is} + \beta_{ICD} D_{ICD\ is})$$

Equation 5

Where λ_{is} is the hazard for patient *i* in study *s*, $\lambda_s(t)$ is the baseline hazard function in study *s* which will vary over time *t*, the β's are the treatment coefficients expressing the efficacy of the devices vs. medical therapy and the D_{DEVis} are device dummy variables which take the value 1 if patient *i* in study *s* was randomised to that device and 0 otherwise. This model is equivalent to Equation 2 where the hazard ratio data from each trial is synthesised.

When device-by-baseline characteristic interaction effects are included the model expands to take the following form:

$$\lambda_{is} = \lambda_s(t) \cdot \exp(\beta_X X_{is} + \beta_{CRT-P} D_{CRT-P\ is} + \beta_{CRT-D} D_{CRT-D\ is} + \beta_{ICD} D_{ICD\ is} + \beta_{X.CRT-P} D_{CRT-P\ is} X_{is} + \beta_{X.CRT-D} D_{CRT-D\ is} X_{is} + \beta_{X.ICD} D_{ICD\ is} X_{is})$$

Equation 6

Where X_{is} and β_X are the baseline variable (or vector of covariables) and coefficient on the baseline variable respectively and $\beta_{X.DEV}$ is the coefficient on the device by baseline variable interaction. The β_X are nuisance parameters in this model. This model was fitted using the coxph function in the R package *survival*.

Continuous variables were dichotomised to facilitate presentation. A quadratic model was fitted which showed that the efficacy of CRT-P and CRT-D increases broadly linearly between QRS durations of 120ms and 150ms and then levels off after 150ms. This suggests that these categories are reasonable, though they may not fully reflect heterogeneity in response between QRS duration of 120 and 150ms. For age, efficacy of ICD increases and efficacy of CRT-P decreases with age, until a plateau is observed after approximately 60 years. For simplicity, age was therefore converted to a two level variable of <60 and ≥60 years. Again this may miss some of the heterogeneity in response to therapy in the <60 category.

Multiple imputation methods

The exploratory analyses used a complete case approach; prior-MI was used as a proxy for ischaemic aetiology when data on ischaemic aetiology was missing. For the final adjusted model, multiple imputation was used to address missing baseline variables. Imputation was carried out in the Amelia package[1]. Five imputed data sets were created. The approach used assumes that the complete (unobserved) data set has a multivariate normal distribution and that data are missing at random. Draws from the estimated complete data multivariate normal distribution are made using a combination of an expectation-maximisation algorithm and bootstrapping.

Individual study results

Individual study results for studies included in the individual patient dataset are shown in Figure S1. Q tests were conducted to assess the significance of any heterogeneity in the trials and the I^2 statistic was calculated to quantify the degree of heterogeneity.[5] Multiple studies were reported for three of the pairwise comparisons (see Figure S1). The p-values for the Q test were 0.56, 0.10 and 0.48 for CRT-P vs. OMT, ICD vs. OMT and CRT-D vs. ICD respectively. The I^2 statistics for the same comparisons were 0%, 52% and 0% respectively. There is therefore moderate evidence of heterogeneity within the ICD vs. OMT comparison.

Final model

All coefficients for the final model are presented as Table S3.

Proportional hazards tests were run for all main effects and interaction effects. The Schoenfeld residual-based test suggested by Grambsch and Therneau was used.[6] Tests of the proportional hazards assumption did not suggest that this was violated (global p-value = 0.684), nor did plots of the Schoenfeld residuals suggest time trends.

[1] http://cran.r-project.org/web/packages/Amelia/vignettes/amelia.pdf

Sensitivity analysis

The patients included in the current analysis are highly heterogeneous and this heterogeneity is expected to result in differences in treatment effects. The adjusted analysis presented aims to reflect this heterogeneity via the inclusion of interactions between the device effects and a series of covariables. These covariables are assumed to have multiplicative and independent impacts on the hazard ratio of each device, however it is possible (and likely) that these relationships do not perfectly hold. A sensitivity analysis was therefore run restricting the main analysis to those patients with QRS≥120ms and with NYHA II-IV as this group were expected to be more homogeneous with respect to treatment effects. The results are presented as Table S4 and Table S5. The results are very similar with the exception of the main effects of CRT-D, CRT-P and age and the interaction of age with CRT-D and CRT-P effectiveness (Table S4) which are somewhat different although confidence intervals from the two analyses are overlapping. The net impact of these changes to the model coefficients for predictions in specific patient groups is shown in Table S5. This shows that predictions in the majority of patients remain similar with the exception of patients with age <60 years. The sensitivity analysis suggests that these patients experience higher effects of CRT-P and CRT-D. The sensitivity analysis is associated with increased uncertainty as shown by generally wider confidence intervals in Table S3 and S4, this reflects the smaller number of patients analysed.

Supplemental Tables

Table S1. Baseline characteristics of studies included in systematic review

Study	Arm	N *	Age- mean (SD)	Male- n (%)	NYHA I n (%)				Mean LVEF (SD)	QRS duration (ms)- Mean (SD)	LBBB morphology -n (%)	Ischaemic -n(%)
					I	II	III	IV				
AMIOVIRT [7 8]	ICD	103	58 (11)	34 (67)	10 (18)	33 (64)	8 (16)	0	22 (10)	NR	21 (42)	0
	MT		60 (12)	38 (74)	7(13)	33 (63)	12 (24)	0	23 (8)	NR	28 (53)	0
CARE-HF [9-13]	CRT-P	813	67 (60-73)†	304 (74)	0	0	386 (94)	23 (6)	25 (21-29)†	160 (152-180)†	NR	165 (40)
	MT		66 (59-72)†	293 (73)	0	0	377 (93)	27 (7)	25 (22-29)†	160 (152-180)†	NR	144 (36)
CAT [14-16]	ICD	104	52 (12)	43 (86)	0	33 (66.7)	17 (33.3)	0	24 (6)	102 (29)	42 (84.6)	NR
	MT		52 (10)	40	0	35 (64.1)	19 (35.8)	0	25 (8)	114 (29)	44 (81.8)	NR

Study	Arm	N *	Age- mean (SD)	Male- n (%)	NYHA I n (%)				Mean LVEF (SD)	QRS duration (ms)- Mean (SD)	LBBB morphology -n (%)	Ischaemic -n(%)
					I	II	III	IV				
COMPANION [17-20]	CRT-P	1520	67	(74) 413 (67)	0	0	537 (87)	80 (13)	20.2	160[2]	426 (69)	333 (54)
	CRT-D		66	399 (67)	0	0	512 (86)	83 (14)	22.2	160[2]	434 (73)	327 (55)
	MT		68	213 (69)	0	0	253 (82)	55 (18)	22.2	158†	216 (70)	182 (59)
Contak-CD [21 22]	CRT-D	490	66 (11)	208 (85)	0	78 (32)	147 (60)	20(8)	21 (7)	160(27)	132 (54)	164 (67)
	ICD		66 (11)	203 (83)	0	81 (33)	140 (57)	25 (10)	22 (7)	156(26)	135 (55)	174 (71)
DEFINITE [23 24]	ICD	458	58.4 (20.3-83.9) ‡	166 (72.5)	58 (25.3)	124 (54.2)	47 (20.5)	0	20.9 (7 - 35) ‡	114.7 (78 - 196) ‡	45 (19.7)	0

Study	Arm	N *	Age- mean (SD)	Male- n (%)	NYHA I n (%)				Mean LVEF (SD)	QRS duration (ms)- Mean (SD)	LBBB morphology -n (%)	Ischaemic -n(%)
					I	II	III	IV				
MADIT [25 26]	MT	196	58.1 (21.8-78.7) ‡	160 (69.9)	41 (17.9)	139 (60.7)	49 (21.4)	0	21.8 (10 - 35) ‡	115.5 (79 - 192) ‡	45 (19.7)	0
	ICD		62 (9)	92 (97)	35 (37)	60 (63)	0	27 (7)	NR	7 (7)	95 (100)	
	MT		64 (9)	92 (91)	33 (33)	68 (67)	0	25 (7)	NR	8 (8)	101 (100)	
MADIT II [27 28]	ICD	123 2	64 (10)	623 (84)	260 (35)	260 (35)	186 (25)	37 (5)	23 (5)	NR	141 (19)	742 (100)
	MT		65 (10)	417 (85)	191 (39)	167 (34)	113 (23)	20 (4)	23 (6)	NR	88 (18)	490 (100)
MADIT-CRT [29-31]	CRT -D	182 0	65 (11)	814 (74.7)	152 (14.0)	937 (86.0)	0	0	24 (5)	NR	761 (69.9)	598 (55)
	ICD		64 (11)	553	113 (15.5)	618 (84.5)	0	0	24 (5)	NR	520 (71.3)	401 (55)

Study	Arm	N *	Age- mean (SD)	Male- n (%)	NYHA I n (%)				Mean LVEF (SD)	QRS duration (ms)- Mean (SD)	LBBB morphology -n (%)	Ischaemic -n(%)
					I	II	III	IV				
MIRACLE [32-34]	CRT-P	453	63.9 (10.7)	155 (75.6) (68)	0	0	205 (90)	23 (10)	21.8 (6.3)	167 (21)	NR	114 (50)
	MT		64.7 (11.2)	153 (68)	0	0	205 (91)	20 (9)	21.6 (6.2)	165 (20)	NR	131 (58)
MIRACLE-ICD [35]	CRT-D	369	66.6 (11.3)	142 (75.9)	0	0	165 (88.2)	22 (11.8)	24.2 (6.5)	165 (22)	NR	119 (64)
	ICD		67.6 (9.2)	141 (77.5)	0	0	163 (89.6)	19 (10.4)	23.9 (6.0)	162 (22)	NR	138 (75.8)
MIRACLE-ICD II [36]	CRT-D	186	63.0 (12.8)	75 (88.2)	0	85 (100)	0	0	24.4 (6.6)	166 (25)	NR	47 (55.3)
	ICD		63.1 (12.1)	91 (90.1)	0	101 (100)	0	0	24.6 (6.7)	165 (23)	NR	59 (58.4)

Study	Arm	N *	Age- mean (SD)	Male- n (%)	NYHA I n (%)				Mean LVEF (SD)	QRS duration (ms)- Mean (SD)	LBBB morphology -n (%)	Ischaemic -n(%)
					I	II	III	IV				
MUSTIC [37]	CRT-P‖	58	64 (11)	19 (66)	0	0	29 (100)	0	23 (7) §	172 (22)	58 (87%)	25 (37%)
	MT‖		64 (8)	24 (83)	0	0	29 (100)	0		175 (19)		
Piccirillo *et al* [38]	ICD	31	65 (8)	12 (80)	0	0	5 (33)	10 (67)	22 (8)	159 (8)	NR	15 (100)
	CRT-D		65 (4)	13 (81)	0	0	5 (31)	11 (69)	23 (4)	160 (4)	NR	16 (100)
Pinter *et al* [39]	CRT-D	72	66.3 (8.6)	28 (77.8)	NR	NR	NR	NR	21.2 (7.9)	NR	NR	NR
	ICD		66.1 (8.8)	29 (80.6)	NR	NR	NR	NR	24 (8.3)	NR	NR	NR
RAFT [40 41]	CRT	179	66.1 (9.3)	758	0	708 (79.2)	186	0	22.6	157 (23.6)	652 (72.9)	614 (68.7)

Study	Arm	N *	Age- mean (SD)	Male- n (%)	NYHA I n (%)				Mean LVEF (SD)	QRS duration (ms)- Mean (SD)	LBBB morphology -n (%)	Ischaemic -n(%)
					I	II	III	IV				
	-D	8		(84.8)			(20.8)		(5.4)			
	ICD		66.2 (9.4)	732 (81.0)	0	730 (80.8)	174 (19.2)	0	22.6 (5.1)	158.3 (24)	643 (71.1)	587 (64.9)
	CRT -P		66.7 (7.86)	25 (86.2)	0	0	19 (65.5)	10 (34.5)	22.3 (8.42)	91.5 (10.6)	NR	22 (75.9)
RESPOND [42]		60										
	MT		69.3 (10.2)	24 (77.4)	0	0	26 (83.9)	5 (16.1)	22.1 (10.2)	97.8 (12.9)	NR	28 (90.3)
	CRT -D		60 (12)	62 (12)	0	0	87 (100)	0	25 (5)	107 (12)	NR	47 (54)
RETHINQ [43 44]		172										
	ICD		58 (14)	49 (58)	0	0	84 (99)	0	26 (6)	106 (13)	NR	43 (51)
REVERSE [45-48]	CRT -D	610	62.9 (10.6)	327 (78)	75 (18)	344 (82)	0	0	26.8 (7.0)	153 (21)	470 (77)	236 (56)

Study	Arm	N *	Age- mean (SD)	Male- n (%)	NYHA I n (%)				Mean LVEF (SD)	QRS duration (ms)- Mean (SD)	LBBB morphology -n (%)	Ischaemic -n(%)
					I	II	III	IV				
Rhythm-ICD [49]	ICD	178	61.8 (11.6)	152 (80)	32 (17)	159 (83)	0	0	26.4 (7.1)	154 (24)		97 (51)
	CRT-D		NR	NR	1 (0.8)	6 (5.0)	104 (87.4)	8 (6.7)	25.6 (8.3)	169 (16)	NR	NR
	ICD		NR	NR	2 (3.4)	4 (6.8)	50 (84.7)	3 (5.1)	23.3 (6.4)	167 (15)	NR	NR
SCD-HeFT [50 51]	ICD	2521	60.1 (51.9-69.2) †	639 (77)	0	566 (68)	263 (32)	0	24 (19.0-30.0) †	NR	NR	431 (52)
	Amiodarone		60.4 (51.7-68.3) †	639 (76)	0	601 (71)	244 (29)	0	25 (20.0-30.0) †	NR	NR	426 (50)
	Placebo		59.7 (51.2-	655	0	594 (70)	253 (30)	0	25 (20.0-	NR	NR	453 (53)

Study	Arm	N *	Age- mean (SD)	Male- n (%)	NYHA I n (%)				Mean LVEF (SD)	QRS duration (ms)- Mean (SD)	LBBB morphology -n (%)	Ischaemic -n(%)
					I	II	III	IV				
	ebo		67.8) †	(77)					30.0) †			
Vector [52][#]	CRT -P MT	106	67.1 (9.7)	90 (62.5)	0	42 (29%)	94 (65%)	9 (6%)	NR NR	NR NR	NR NR	NR NR

* randomised; †Median (inter quartile range); ‡Mean (range); § data reported for 67 patients at baseline rather than 58 randomised; ‖ group allocation prior to cross-over; [#]baseline characteristics include 38 non-randomised patients in addition to the 106 randomised.

SD=standard deviation; NYHA = New York Heart Association functional class; LVEF = left ventricular ejection fraction; LBBB = left bundle branch block.

Table S2: Assessment of risk of bias of included studies

Study reference	Reporting of randomization	Reporting of allocation concealment	Reporting of blind treatment assignment/ blind outcome assessment	Description of pts. baseline characteristics/ group balance	Analysis based on ITT
AMIOVIRT	Unclear	Unclear	Adequate	Adequate	Adequate
CARE-HF	Adequate	Adequate	Adequate	Adequate	Adequate
CAT	Unclear	Adequate	Unclear	Adequate	Unclear
COMPANION	Unclear	Unclear	Adequate	Adequate	Adequate
Contak-CD	Unclear	Unclear	Unclear	Adequate	Unclear
DEFINITE	Unclear	Unclear	Adequate	Adequate	Adequate
MADIT	Unclear	Unclear	Unclear	Adequate	Adequate
MADIT-CRT	Unclear	Adequate	Adequate	Adequate	Adequate
MADIT II	Unclear	Adequate	Unclear	Adequate	Adequate
MIRACLE	Unclear	Adequate	Adequate	Adequate	Adequate
MIRACLE-ICD	Adequate	Adequate	Adequate	Adequate	Adequate
MIRACLE-ICD II	Adequate	Adequate	Adequate	Adequate	Adequate
MUSTIC	Unclear	Unclear	Inadequate	Adequate	Adequate
Piccirillo et al	Unclear	Unclear	Unclear	Adequate	Unclear
Pinter et al	Unclear	Unclear	Adequate	Adequate	Unclear
RAFT	Unclear	Adequate	Adequate	Adequate	Adequate
RESPOND	Adequate	Adequate	Unclear	Adequate	Adequate
RETHINQ	Adequate	Adequate	Adequate	Adequate	Adequate
REVERSE	Unclear	Unclear	Adequate	Adequate	Adequate

RHYTHM ICD	Unclear	Unclear	Unclear	unclear	Unclear
SCD- HeFT	Unclear	Unclear	Adequate	Adequate	Adequate
Vector	Unclear	Unclear	Unclear	Unclear	Unclear

Table S3. Multivariate adjusted model

Variable	Hazard ratio	Lower 95% CI	Upper 95% CI
ICD*	0.77	0.52	1.13
CRT-P*	0.74	0.42	1.28
CRT-D*	0.55	0.35	0.86
QRS<120	0.73	0.59	0.91
QRS>=120	1.05	0.86	1.27
LBBB	0.85	0.70	1.03
AGE>=60	1.82	1.57	2.11
GENDER=M	1.35	1.14	1.60
ICD*QRS<120	1.08	0.78	1.49
ICD*QRS>=120	0.90	0.70	1.17
ICD*LBBB	1.07	0.82	1.39
ICD*GENDER=M	0.75	0.59	0.97
ICD*AGE>=60	1.23	0.98	1.55
CRTP*QRS>=120	1.17	0.83	1.65
CRTP*LBBB	0.88	0.62	1.25
CRTP*GENDER=M	1.24	0.86	1.77
CRTP*AGE>=60	0.86	0.62	1.21
CRTD*QRS>=120	1.13	0.87	1.48
CRTD*LBBB	0.88	0.67	1.16
CRTD*GENDER=M	1.16	0.84	1.58
CRTD*AGE>=60	0.98	0.74	1.28

* Reference category is a patient receiving OMT, <60 years of age, female, QRS duration ≥150ms and non-LBBB conduction abnormality. CI = confidence interval.

ICD = implantable cardioverter defibrillator; CRT-P = cardiac resychronisation therapy pacemaker; CRT-D = cardiac resychronisation therapy defibrillator; LBBB = left bundle branch block.

Table S4. Multivariate adjusted model – sensitivity analysis excluding patients with QRS<120 or NYHA Class I

Variable	Hazard ratio	Lower 95% CI	Upper 95% CI
ICD*	0.78	0.50	1.21
CRT-P*	0.66	0.37	1.18
CRT-D*	0.49	0.30	0.79
QRS>=120	1.08	0.89	1.31
LBBB	0.84	0.69	1.03
AGE>=60	1.59	1.31	1.94
GENDER=M	1.39	1.12	1.73
ICD*QRS>=120	0.90	0.69	1.18
ICD*LBBB	1.04	0.79	1.37
ICD*GENDER=M	0.76	0.56	1.03
ICD*AGE>=60	1.19	0.89	1.58
CRTP*QRS>=120	1.14	0.80	1.61
CRTP*LBBB	0.92	0.64	1.31
CRTP*GENDER=M	1.20	0.82	1.76
CRTP*AGE>=60	0.97	0.68	1.39
CRTD*QRS>=120	1.12	0.86	1.48
CRTD*LBBB	0.89	0.67	1.18
CRTD*GENDER=M	1.11	0.79	1.56
CRTD*AGE>=60	1.14	0.84	1.55

* Reference category is a patient receiving OMT, <60 years of age, female, QRS duration ≥150ms and non-LBBB conduction abnormality. CI = confidence interval.

ICD = implantable cardioverter defibrillator; CRT-P = cardiac resychronisation therapy pacemaker; CRT-D = cardiac resychronisation therapy defibrillator; LBBB = left bundle branch block.

Table S5. Subgroup-specific treatment effects predicted by multivariate adjusted network meta-analysis – sensitivity analysis excluding patients with QRS<120 or NYHA Class I

Gender	Age	QRS	LBBB	CRT-D vs. MT	CRT-P vs. MT	ICD vs. MT	CRT-D vs. CRT-P	CRT-D vs. ICD	ICD vs. CRT-P
				Hazard ratio (95% confidence interval)					
Female	<60	<120	N						
		≥120-<150	N	0.55(0.34 ,0.87)	0.76(0.43 ,1.33)	0.71(0.47 ,1.07)	0.72(0.40 ,1.31)	0.77(0.49 ,1.23)	0.93(0.53 ,1.65)
		≥120-<150	Y	0.48(0.31 ,0.76)	0.69(0.41 ,1.17)	0.74(0.49 ,1.12)	0.70(0.40 ,1.21)	0.66(0.42 ,1.03)	1.06(0.62 ,1.81)
		≥150	N	0.49(0.30 ,0.79)	0.66(0.37 ,1.18)	0.78(0.50 ,1.21)	0.73(0.40 ,1.34)	0.62(0.39 ,0.99)	1.18(0.66 ,2.10)
		≥150	Y	0.43(0.28 ,0.66)	0.61(0.38 ,0.97)	0.81(0.55 ,1.20)	0.71(0.42 ,1.18)	0.53(0.35 ,0.80)	1.34(0.82 ,2.18)
	≥60	<120	N						
		≥120-<150	N	0.62(0.41 ,0.95)	0.73(0.44 ,1.22)	0.84(0.58 ,1.21)	0.85(0.50 ,1.44)	0.74(0.50 ,1.11)	1.14(0.69 ,1.9)
		≥120-<150	Y	0.55(0.37 ,0.82)	0.67(0.43 ,1.06)	0.88(0.61 ,1.26)	0.82(0.51 ,1.33)	0.63(0.43 ,0.92)	1.30(0.81 ,2.07)
		≥150	N	0.56(0.36 ,0.86)	0.65(0.39 ,1.06)	0.93(0.63 ,1.38)	0.86(0.51 ,1.45)	0.60(0.40 ,0.90)	1.44(0.87 ,2.38)
		≥150	Y	0.49(0.35 ,0.70)	0.59(0.41 ,0.85)	0.97(0.70 ,1.34)	0.83(0.55 ,1.25)	0.51(0.36 ,0.71)	1.64(1.10 ,2.43)
Male	<60	<120	N						

	≥120-<150	N	0.61(0.42 ,0.87)	0.91(0.58 ,1.41)	0.53(0.39 ,0.73)	0.67(0.42 ,1.06)	1.13(0.80 ,1.61)	0.59(0.38 ,0.92)
	≥120-<150	Y	0.54(0.36 ,0.79)	0.83(0.54 ,1.28)	0.56(0.39 ,0.80)	0.65(0.41 ,1.03)	0.96(0.67 ,1.39)	0.67(0.43 ,1.06)
	≥150	N	0.54(0.37 ,0.79)	0.80(0.50 ,1.26)	0.59(0.42 ,0.84)	0.68(0.42 ,1.09)	0.91(0.64 ,1.30)	0.74(0.46 ,1.19)
	≥150	Y	0.48(0.34 ,0.67)	0.73(0.50 ,1.06)	0.62(0.44 ,0.85)	0.65(0.43 ,0.99)	0.77(0.56 ,1.07)	0.84(0.56 ,1.27)
	<120	N						
	≥120-<150	N	0.69(0.52 ,0.92)	0.88(0.61 ,1.27)	0.64(0.50 ,0.81)	0.79(0.54 ,1.15)	1.09(0.85 ,1.40)	0.72(0.50 ,1.05)
≥60	≥120-<150	Y	0.61(0.45 ,0.83)	0.81(0.56 ,1.16)	0.66(0.49 ,0.89)	0.76(0.52 ,1.11)	0.93(0.71 ,1.21)	0.82(0.56 ,1.20)
	≥150	N	0.62(0.46 ,0.83)	0.77(0.54 ,1.11)	0.70(0.53 ,0.94)	0.80(0.55 ,1.15)	0.88(0.67 ,1.14)	0.91(0.63 ,1.32)
	≥150	Y	0.55(0.43 ,0.70)	0.71(0.56 ,0.90)	0.73(0.57 ,0.94)	0.77(0.58 ,1.02)	0.74(0.61 ,0.91)	1.03(0.77 ,1.38)

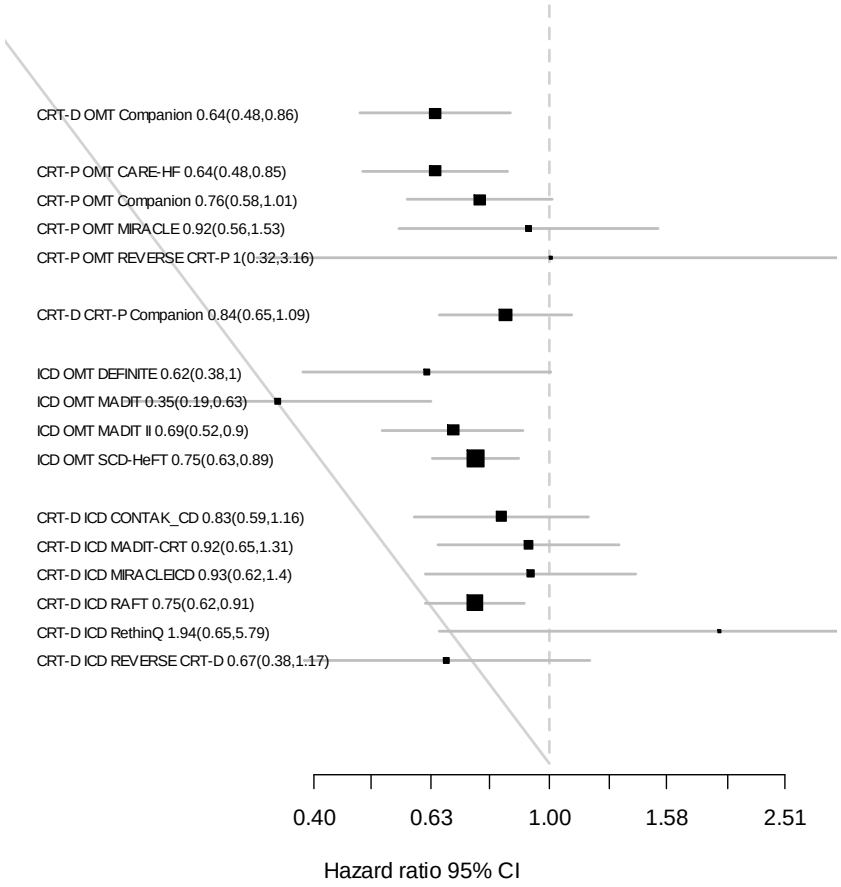


Figure S1: Hazard ratios on all-cause mortality for individual studies included in individual patient data

Further information on searches

Search syntax

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to Present>

Search run on 27/06/2011

1 (CRT or "cardiac resynchron$ therap$").tw. (6517)

2 resynchron$ therap$.tw. (2829)

3 BVP.tw. (170)

4 Cardiac Resynchronization Therapy/ (228)

5 (biventricular adj10 pac$).tw. (1261)

6 (biventricular adj10 stimulat$).tw. (157)

7 ((cardiac or heart) adj10 resynch$).tw. (3034)

8 (coronary adj10 resynch$).tw. (131)

9 (atriobiventricular adj10 pac$).tw. (14)

10 (atrio biventricular adj10 pac$).tw. (23)

11 CRT-P.tw. (133)

12 CRT-D.tw. (176)

13 cardioversion.tw. (4098)

14 cardioverter.tw. (6545)

15 Defibrillators, Implantable/ (8786)

16 (internal adj3 (defibrillat$ or cardioverter)).tw. (422)

17 (implant adj3 (cardioverter or defibrillat$)).tw. (122)

18 (cardiac adj3 defibrillat$).tw. (1061)

19 ((implant or internal or cardiac) and defib$).tw. (7618)

20 icd.tw. (14797)

21 or/1-20 (35301)

22 Intraventricular conduction delay$.tw. (271)

23 Dilated cardiomyopathy.tw. (10812)

24 (Sudden death adj3 cardiac).tw. (801)

25 ((prolonged or wide) adj2 QRS).tw. (1056)

26 (Premature ventricular adj1 (complex$ or contraction)).tw. (794)

27 ((Reduced or low) adj ejection fraction).tw. (1045)

28 ((impaired or dysfunction or function) adj3 (left ventric$ or LVEF or LV)).tw. (37111)

29 (ventricular adj1 (tachycardia or fibrillation)).tw. (25008)

30 arrhythmi$.tw. (57496)

31 heart failure.tw. (85570)

32 ((cardiac or ventricular or intraventricular) adj5 asynchron$).tw. (444)

33 ((cardiac or ventricular or intraventricular) adj5 dyssynchron$).tw. (882)

34 cardiac arrest.tw. (16215)

35 tachycardia, ventricular/ (8877)

36 Arrhythmias, Cardiac/ (47995)

37 Heart Failure/ (71586)

38 Death, Sudden, Cardiac/ (9017)

39 Ventricular Dysfunction, Left/ or Bundle-Branch Block/ (23476)

40 Bundle Branch Block.tw. (6055)

41 Ventricular Fibrillation/ (13640)

42 Heart Arrest/ (19743)

43 Myocardial Infarction/ (126739)

44 or/22-43 (368895)

45 Randomized controlled trials as Topic/ (73673)

46 Randomized controlled trial/ (309567)

47 Random allocation/ (71762)

48 Double blind method/ (110773)

49 Single blind method/ (15106)

50 Clinical trial/ (463846)

51 exp Clinical Trials as Topic/ (242485)

52 clinical trial/ or clinical trial, phase i/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or multicenter study/ (558228)

53 or/45-52 (851498)

54 randomized controlled trial.pt. (309567)

55 controlled clinical trial.pt. (82654)

56 random allocation.sh. (71762)

57 double blind method.sh. (110773)

58 single blind method.sh. (15106)

59 (clin$ adj25 trial$).tw. (200910)

60 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$ or dummy$)).tw. (114910)

61 Placebos/ (29766)

62 Placebo$.tw. (133939)

63 Random$.tw. (553900)

64 or/54-63 (914706)

65 53 or 64 (1220129)

66 Case report.tw. (168393)

67 Letter/ (733158)

68 Historical article/ (275454)

69 or/66-68 (1167008)

70 65 not 69 (1192243)

71 21 and 44 and 70 (3760)

72 animals/ not (animals/ and humans/) (3520949)

73 71 not 72 (3508)

74 limit 73 to english language (3198)

75 limit 74 to yr="1990 -Current" (3152)

Database: Embase<1988 to 2011 Week 25>

Search run on 27/06/2011

1 (CRT or "cardiac resynchron$ therap$").tw. (9071)

2 resynchron$ therap$.tw. (4112)

3 BVP.tw. (178)

4 cardiac resynchronization therapy/ (5525)

5 (biventricular adj10 pac$).tw. (1670)

6 (biventricular adj10 stimulat$).tw. (219)

7 ((cardiac or heart) adj10 resynch$).tw. (4377)

8 (coronary adj10 resynch$).tw. (167)

9 (atrio biventricular adj10 pac$).tw. (30)

10 (atriobiventricular adj10 pac$).tw. (20)

11 CRT-P.tw. (242)

12 CRT-D.tw. (485)

13 cardioversion.tw. (4285)

14 cardioverter.tw. (7839)

15 (internal adj3 (defibrillat$ or cardioverter)).tw. (442)

16 (implant$ adj3 (cardioverter or defibrillat$)).tw. (9516)

17 (cardiac adj3 defibrillat$).tw. (1115)

18 ((implant or internal or cardiac) and defib$).tw. (8844)

19 icd.tw. (20125)

20 *defibrillator/ (6658)

21 or/1-20 (44411)

22 *Heart arrest/ (10051)

23 *myocardial infarction/ (48787)

24 *Death,-Sudden,-Cardiac/ (8275)

25 cardiac arrest.tw. (15652)

26 Intraventricular conduction delay$.tw. (280)

27 Dilated cardiomyopathy.tw. (12299)

28 (sudden death adj3 cardiac).tw. (818)

29 ((prolonged or wide) adj2 QRS).tw. (1190)

30 (Premature ventricular adj1 (complex$ or contraction)).tw. (699)

31 ((Reduced or low) adj ejection fraction).tw. (1302)

32 ((impaired or dysfunction or function) adj3 (left ventric$ or LVEF or LV)).tw. (39565)

33 (ventricular adj1 (tachycardia or fibrillation)).tw. (22091)

34 arrhythmi$.tw. (52667)

35 *congestive cardiomyopathy/ (5894)

36 *heart muscle conduction system/ (1786)

37 *heart arrhythmia/ (18228)

38 *heart bundle branch block/ (712)

39 *heart failure/ (39054)

40 *congestive heart failure/ (17950)

41 heart failure.tw. (96051)

42 ((cardiac or ventricular or intraventricular) adj5 asynchron$).tw. (464)

43 ((cardiac or ventricular or intraventricular) adj5 dyssynchron$).tw. (1299)

44 *Bundle-Branch Block/ (712)

45 Bundle Branch Block.tw. (4682)

46 *heartventricletachycardia/ (8113)

47 *syncope/ (5496)

48 *heartventricle fibrillation/ (5098)

49 or/22-48 (273295)

50 Clinical trial/ (758285)

51 Randomized controlled trial/ (265459)

52 Randomization/ (49808)

53 Single blind procedure/ (13620)

54 Double blind procedure/ (90508)

55 Crossover procedure/ (29846)

56 Placebo/ (146356)

57 Rct.tw. (6934)

58 random*.tw. (588686)

59 (clinical trial$ or controlled clinical trial$ or major clinical stud$ or controlled stud$).tw. (219539)

60 (clinical adj25 trial$).tw. (213401)

61 ((single$ or double$ or treble$ or triple$) and (blind$ or mask$)).tw. (117874)

62 Placebo$.tw. (137596)

63 Prospective study/ (157946)

64 or/50-63 (1381558)

65 Case study/ (10159)

66 Abstract report/ or letter/ (611863)

67 or/65-66 (621895)

68 64 not 67 (1352204)

69 21 and 49 and 68 (4664)

70 limit 69 to english language (4204)

71 animal/ not (animal/ and human/) (526120)

72 animal experiment/ (1040422)

73 71 or 72 (1559640)

74 70 not 73 (3995)

75 conference.so. (435795)

76 74 not 75 (3512)

77 limit 76 to yr="1990 -Current" (3499)

Database: Cochrane

Search run on: 28/06/2011

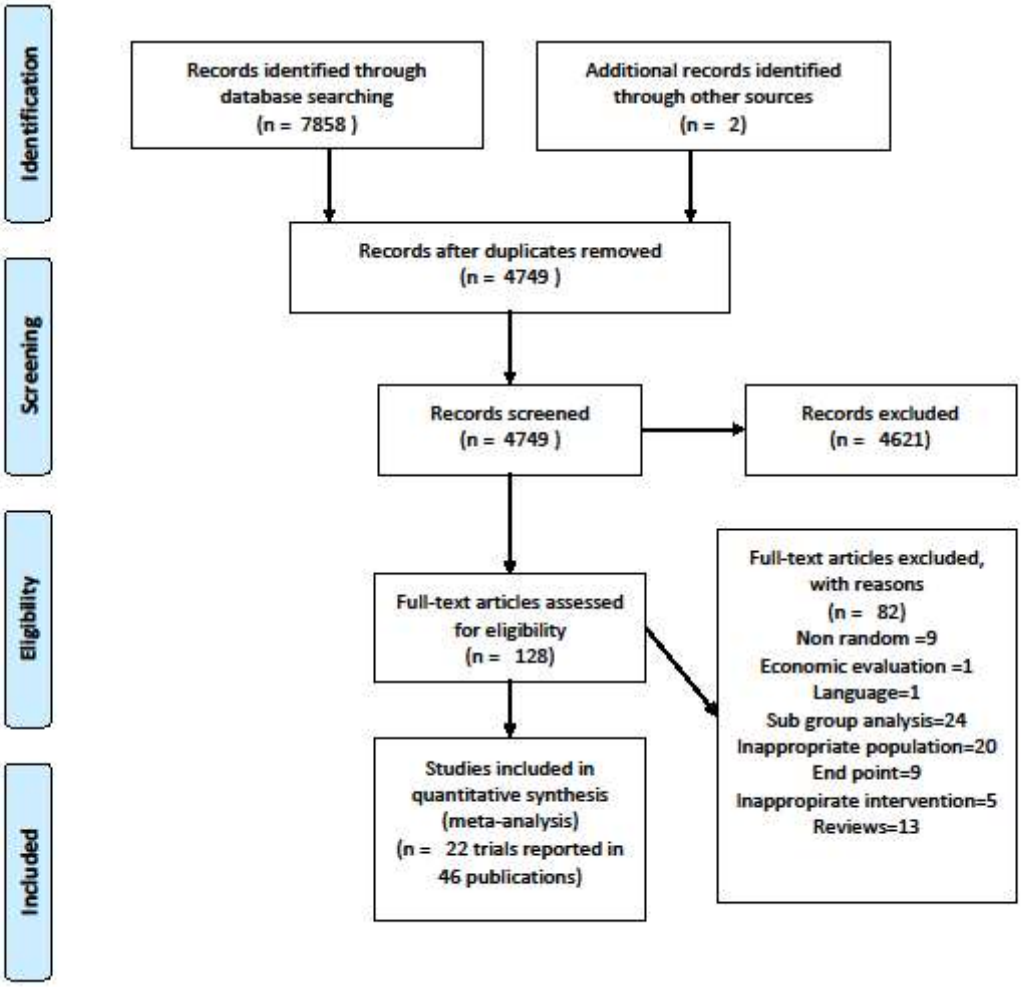
#1	(CRT or cardiac resynchron* therap*):ti,ab,kw in Clinical Trials	647
#2	(resynchron* therap*):ti,ab,kw in Clinical Trials	204
#3	(BVP):ti,ab,kw in Clinical Trials	14

#4	MeSH descriptor Cardiac Resynchronization Therapy, this term only	4
#5	(biventricular NEAR pac*):ti,ab,kw in Clinical Trials	108
#6	(biventricular NEAR stimulat*):ti,ab,kw in Clinical Trials	16
#7	((cardiac or heart) NEAR resynch*):ti,ab,kw in Clinical Trials	205
#8	(coronary NEAR resynch*):ti,ab,kw in Clinical Trials	3
#9	(atriobiventricular NEAR pac*):ti,ab,kw in Clinical Trials	3
#10	(atrio biventricular NEAR pac*):ti,ab,kw in Clinical Trials	11
#11	(CRT-P):ti,ab,kw in Clinical Trials	23
#12	(CRT -D):ti,ab,kw in Clinical Trials	58
#13	(cardioversion):ti,ab,kw in Clinical Trials	546
#14	(cardioverter):ti,ab,kw in Clinical Trials	470
#15	MeSH descriptor Defibrillators, Implantable, this term only	734
#16	(internal NEAR (defibrillat* or cardioverterter)):ti,ab,kw in Clinical Trials	19
#17	(implant NEAR (cardioverter OR defibrillat*)):ti,ab,kw in Clinical Trials	119
#18	(cardiac NEAR defibrillat*):ti,ab,kw in Clinical Trials	283
#19	((implant OR internal OR cardiac) AND defib*):ti,ab,kw in Clinical Trials	709
#20	(icd):ti,ab,kw in Clinical Trials	780
#21	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)	2746
#22	(intraventricular conduction delay):ti,ab,kw in Clinical Trials	31
#23	(Dilated cardiomyopathy):ti,ab,kw in Clinical Trials	551
#24	(Sudden death NEAR cardiac):ti,ab,kw in Clinical Trials	641

#25	((prolonged or wide) NEAR QRS):ti,ab,kw in Clinical Trials	84
#26	(Premature ventricular NEAR (complex* or contraction)):ti,ab,kw in Clinical Trials	415
#27	((Reduced or low) NEAR ejection fraction):ti,ab,kw in Clinical Trials	446
#28	((impaired or dysfunction or function) NEAR (left ventric* or LVEF or LV)):ti,ab,kw in Clinical Trials	4865
#29	(ventricular NEAR (tachycardia or fibrillation)):ti,ab,kw in Clinical Trials	1673
#30	(heart failure):ti,ab,kw in Clinical Trials	8459
#31	((cardiac or ventricular or intraventricular) NEAR asynchron*):ti,ab,kw in Clinical Trials	25
#32	((cardiac or ventricular or intraventricular) NEAR dyssynchron*):ti,ab,kw in Clinical Trials	56
#33	MeSH descriptor Arrhythmias, Cardiac, this term only	1604
#34	MeSH descriptor Heart Failure, this term only	4620
#35	MeSH descriptor Ventricular Dysfunction, Left, this term only	1412
#36	(Bundle Branch Block):ti,ab,kw in Clinical Trials	178
#37	(arrhythmi*):ti,ab,kw in Clinical Trials	5106
#38	(cardiac arrest):ti,ab,kw in Clinical Trials	990
#39	MeSH descriptor Heart Arrest, this term only	533
#40	MeSH descriptor Death, Sudden, Cardiac explode all trees	452
#41	MeSH descriptor Bundle-Branch Block explode all trees	79
#42	MeSH descriptor Ventricular Fibrillation explode all trees	425

#43	MeSH descriptor Myocardial Infarction explode all trees	7646
#44	(#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43)	23964
#45	(#21 AND #44), from 1990 to 2011	1418
#46	(#45)	1207

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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