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)

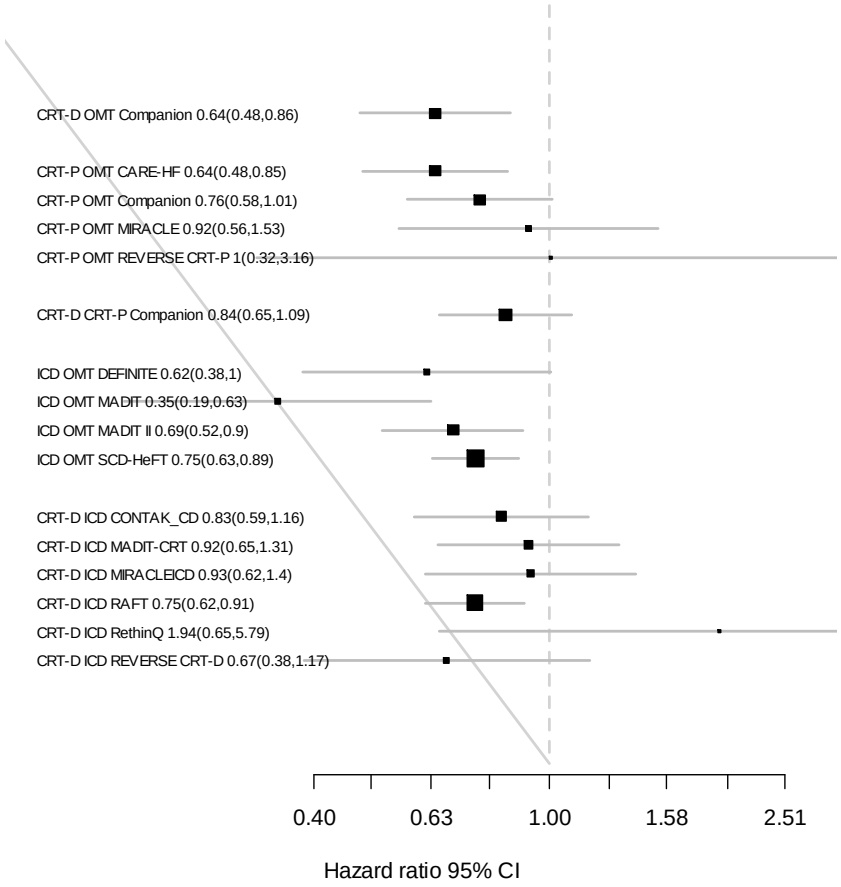


Figure S1: Hazard ratios on all-cause mortality for individual studies included in individual patient data

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

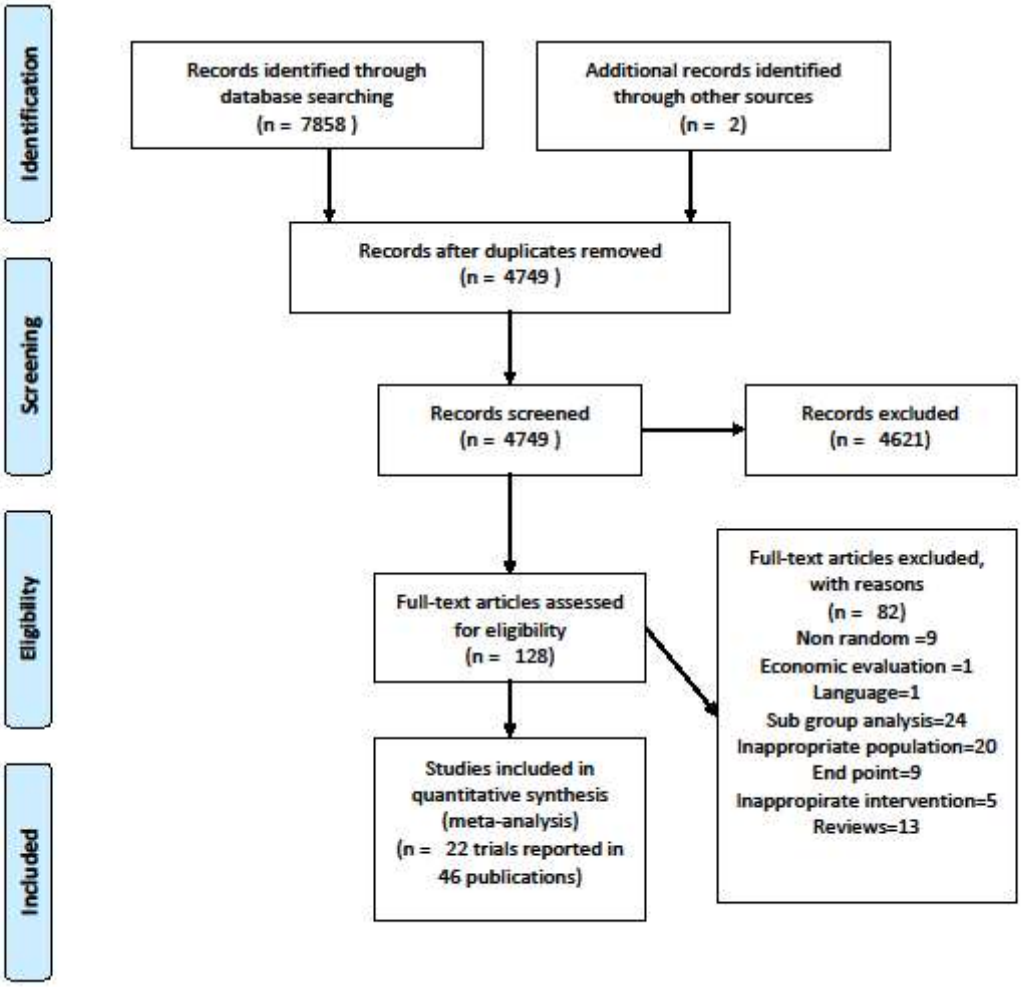
#1	(CRT or cardiac resynchron* therap*):ti,ab,kw in Clinical Trials	647
#2	(resynchron* therap*):ti,ab,kw in Clinical Trials	204
#3	(BVP):ti,ab,kw in Clinical Trials	14

#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

For more information, visit www.prisma-statement.org.

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