ORIGINAL ARTICLE

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

B Woods,[1,2] N Hawkins,[2,3] S Mealing,[2] A Sutton,[4] W T Abraham,[5] J F Beshai,[6] H Klein,[7] M Sculpher,[1,2] C J Plummer,[8] M R Cowie[9]

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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 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. REsynchronization 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.
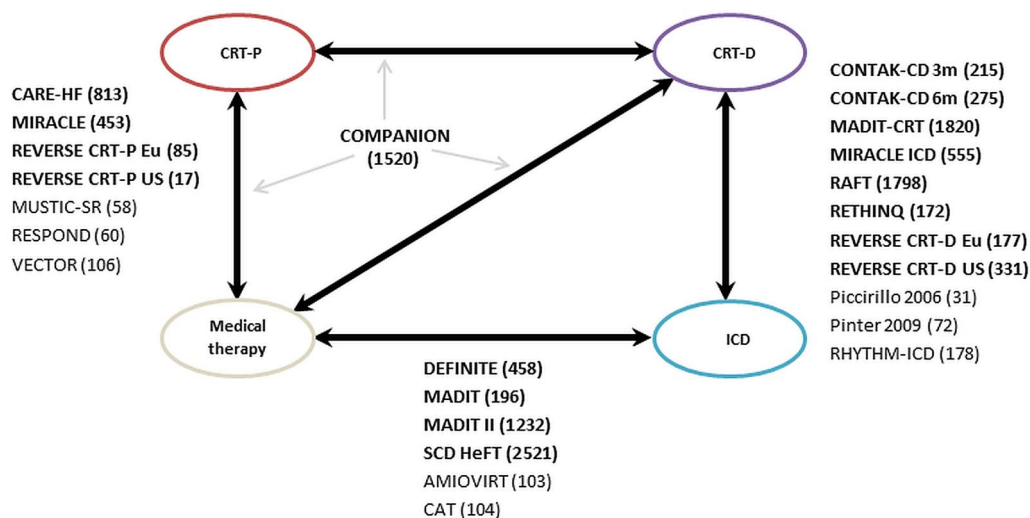

Figure 1 Network of randomised controlled trial evidence. Elipses represent comparators. Arrows represent comparisons of interventions for which trial data were available. Studies for which individual patient data were available are in bold. Patient numbers represent the total number of patients enrolled 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.
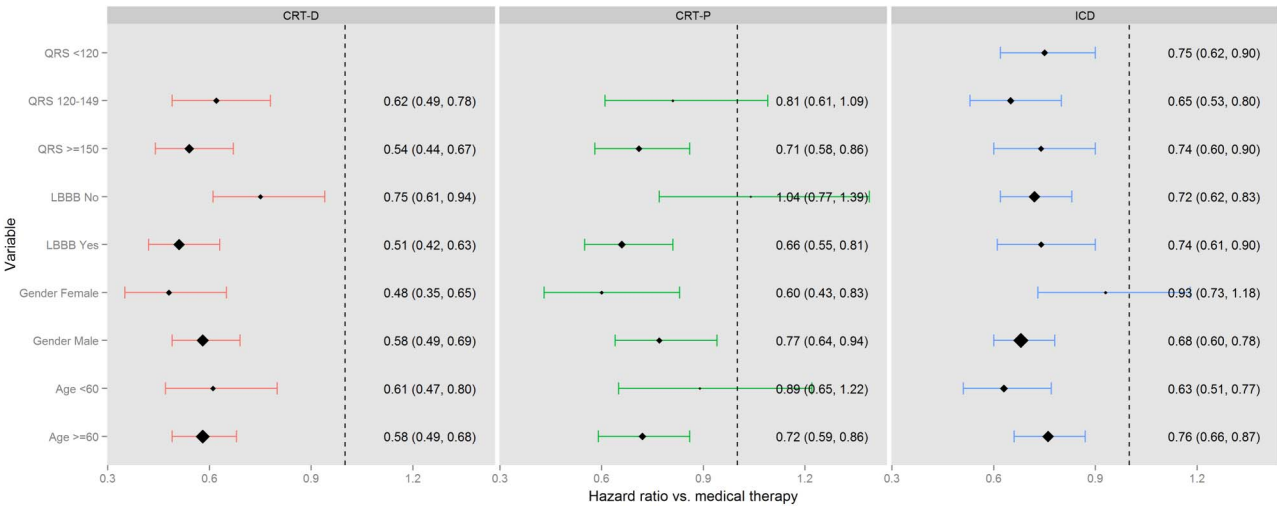
Figure 2 Treatment effect estimates from univariate network meta-analysis model for variables included in final model. The forest plots show the results of the univariate network meta-analysis incorporating individual baseline characteristics as interaction effects. HRs (mean (95% CI)) are presented 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

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
				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.

Author affiliations
[1]Centre for Health Economics, University of York, York, UK
[2]Department of Health Economics, ICON Clinical Research, Oxford, UK
[3]Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, UK
[4]Department of Health Sciences, University of Leicester, Leicester, UK
[5]Ohio State University Medical Centre, Ohio, USA
[6]Mayo Clinic, Phoenix, Arizona, USA
[7]University of Rochester, New York, USA
[8]Freeman Hospital, Newcastle upon Tyne, UK
[9]Imperial College London (Royal Brompton Hospital), London, UK

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