

# Combined resynchronisation and implantable defibrillator therapy in left ventricular dysfunction: Bayesian network meta-analysis of randomised controlled trials

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## ABSTRACT

**Objective** To review the evidence base from randomised controlled trials of combined cardiac resynchronisation therapy and implantable cardioverter defibrillator therapy in left ventricular impairment and symptomatic heart failure.

**Design** Bayesian network meta-analysis.

**Data sources** Medline, Embase, and Cochrane databases up to June 2006.

**Review methods** Two reviewers independently assessed trial eligibility and quality. Included trials compared cardiac resynchronisation therapy, implantable cardioverter defibrillator therapy, combined resynchronisation and implantable defibrillator therapy, and medical therapy alone, in patients with impaired left ventricular systolic function. Bayesian random effects network models were used to examine overall number of deaths.

**Results** 12 studies including 1636 events in 8307 patients were identified. Combined cardiac resynchronisation and implantable cardioverter defibrillator therapy reduced the number of deaths by one third compared with medical therapy alone (odds ratio 0.57, 95% credible interval 0.40 to 0.80) but did not further improve survival when compared with implantable defibrillator therapy (0.82, 0.57 to 1.18) or resynchronisation (0.85, 0.60 to 1.22) therapy alone.

**Conclusion** Evidence from randomised controlled trials is insufficient to show the superiority of combined cardiac resynchronisation and implantable cardioverter defibrillator therapy over cardiac resynchronisation therapy alone in patients with left ventricular impairment.

## INTRODUCTION

Advances in medical therapy have improved the symptoms, quality of life, and survival of patients with symptomatic heart failure, but the prognosis remains unfavorable.<sup>1</sup> Progressive pump failure and ventricular tachyarrhythmias are common causes of death in these patients despite optimal medical therapy. New pacing technologies have emerged to treat selected patients with heart failure.<sup>2</sup> Cardiac resynchronisation therapy, or biventricular pacing, improves cardiac function by reducing or even abolishing the abnormal pattern of ventricular

activation and contraction observed in some patients with left ventricular systolic dysfunction. Implantable cardioverter defibrillator therapy reduces sudden cardiac deaths by providing antitachycardia pacing and defibrillation to stop ventricular tachycardia and fibrillation in patients with heart failure who are at risk of developing malignant ventricular tachyarrhythmias.

Current evidence based guidelines<sup>3-5</sup> recommend an implantable cardioverter defibrillator for the primary prevention of sudden cardiac death in selected patients with impaired left ventricular function, and cardiac resynchronisation therapy for improvement of symptoms and survival in selected patients with abnormal ventricular conduction. Many patients may be eligible for both treatments but it does not necessarily follow that such patients would obtain additional benefit from the combined treatment over one treatment alone. There are, however, theoretical justifications for the combined treatment. Sudden cardiac deaths still account for about one third of all deaths in patients treated with resynchronisation therapy,<sup>w1 w2</sup> and adding implantable cardioverter defibrillator backup to resynchronisation therapy might further reduce mortality. Conversely, resynchronisation therapy alone reduces the risk of worsening deaths owing to heart failure as well as sudden cardiac deaths<sup>w2</sup> suggesting that the addition of such therapy to implantable cardioverter defibrillation might further reduce the risk of death. It is therefore important to ascertain the efficacy of the combined treatment, which is more expensive than either treatment alone.

Several pairwise meta-analyses have compared the independent efficacies of resynchronisation therapy<sup>6-10</sup> and of implantable cardioverter defibrillator therapy<sup>5 11-14</sup> with medical therapy, whereas the effect of cardiac resynchronisation with an implantable defibrillator device was examined in exploratory meta-regression analyses.<sup>7 9</sup> The overall evidence from randomised controlled trials for device therapy consists of pairwise comparisons between combined resynchronisation and implantable cardioverter defibrillator therapy, resynchronisation therapy, implantable cardioverter defibrillator therapy, and

medical therapy. Most studies compared devices with medical therapy, with few directly comparing combined resynchronisation and implantable defibrillator therapy with either therapy alone.<sup>w1 w3-w5</sup> This network of evidence can be examined within a mixed treatment comparison framework without breaking randomisation, using either traditional or Bayesian models,<sup>15 16</sup> to inform medical decision making by facilitating simultaneous comparison of all treatment options.<sup>17 18</sup>

The presence of three treatment groups (combined resynchronisation and implantable defibrillator therapy, resynchronisation alone, and control) in the medical therapy, pacing, and defibrillator in chronic heart failure trial<sup>w1</sup> creates an additional level of complexity in evidence synthesis because multiple pairwise comparisons (compared with a common control) are correlated.<sup>15 19</sup> Previous studies either excluded data<sup>7</sup> (because of lack of a separate implantable cardioverter defibrillator treatment arm) from the combined resynchronisation and implantable defibrillator therapy group, or divided data<sup>9</sup> from the control group to incorporate comparisons with combined resynchronisation and implantable

defibrillator therapy and resynchronisation therapy in the same analysis. These approaches are not ideally suited<sup>15</sup> to investigate the potential incremental benefits of combined therapy, particularly as this is the largest trial examining the efficacy of this type of therapy. It is important to include data from all three treatment groups of the medical therapy, pacing, and defibrillator in chronic heart failure trial to provide evidence of a higher methodological quality, and appropriate modelling of random effects in multigroup trials can be implemented using a fully Bayesian model.<sup>19 20</sup>

We systematically reviewed overall evidence from randomised controlled trials for combined cardiac resynchronisation and implantable cardioverter defibrillator therapy on survival compared with medical therapy, an implantable cardioverter defibrillator, and cardiac resynchronisation therapy in patients with left ventricular impairment, using Bayesian network meta-analysis.

## METHODS

The search strategy was based on a highly sensitive one for identifying randomised controlled trials.<sup>21</sup> We used MeSH terms and keywords to search for intervention, with combined cardiac resynchronization and implantable cardioverter defibrillator therapy/cardiac resynchronization therapy/implantable cardioverter defibrillator devices ["Cardiac Resynchronization Therapy," "Cardiac Pacing, Artificial," "Heart Pacing," "resynchroni?ation," "(biventricular or dual?chamber or multi?site) adj (pacing or stimulat \$)," "Defibrillators, Implantable," "Electric Counter-shock," "Automatic Cardioversion," "Cardioversion; Defibrillation," "(implant\$ adj (defibrillator\$ or cardioverter\$)"] and for target condition of impaired left ventricular function ["Heart Failure, Congestive," "Ventricular Dysfunction," "Cardiac Output, Low," "(cardiac or heart or ventricular or biventricular or systolic or diastolic) adj (failure or dysfunction or impair\$)"].

We searched Medline (1966 to June 2006), Embase (1988 to 2006, week 26), and the Cochrane central register of controlled trials (2nd quarter 2006). In addition, we searched for studies in reports from the US Food and Drugs Administration and reference lists of identified studies and published meta-analyses. We applied no restrictions on types of cardiac resynchronisation therapy or implantable cardioverter defibrillator devices or on language.

## Selection criteria

Studies were eligible if they were randomised parallel controlled trials or randomised crossover trials; included patients with impaired left ventricular systolic function (ejection fraction <35%); compared cardiac resynchronisation or combined resynchronisation and implantable cardioverter defibrillator therapy with medical therapy or with medical therapy plus implantable cardioverter defibrillator therapy (studies including patients with pacing leads inserted through

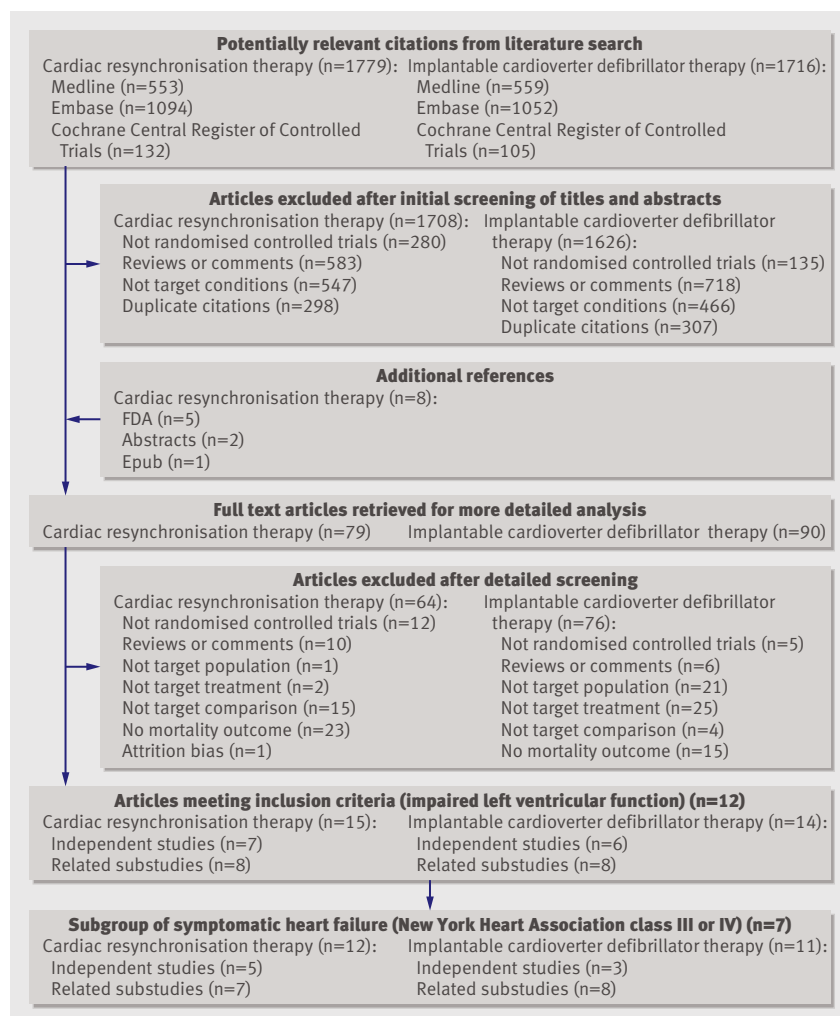


Fig 1 | Trial flow diagram of study selection

the transthoracic route were eligible, whereas we excluded trials comparing different pacing strategies in themselves), or were primary prevention trials comparing implantable cardioverter defibrillator with usual medical therapy or with oral antiarrhythmics (we excluded studies with a mandatory requirement for inducible arrhythmias and secondary prevention trials); and reported all cause mortality. We excluded trials recruiting patients who had had a myocardial infarction or undergone coronary revascularisation within the past month. Consistent with previous systematic reviews,<sup>7,9</sup> we excluded trials of less than two weeks' duration.

#### Methodological assessment

We assessed concealment of treatment allocation, blinding (patient and investigator), and analysis using intention to treat for internal validity and graded these as yes, no, or unclear. We also noted studies where randomisation occurred after implantation of the device.

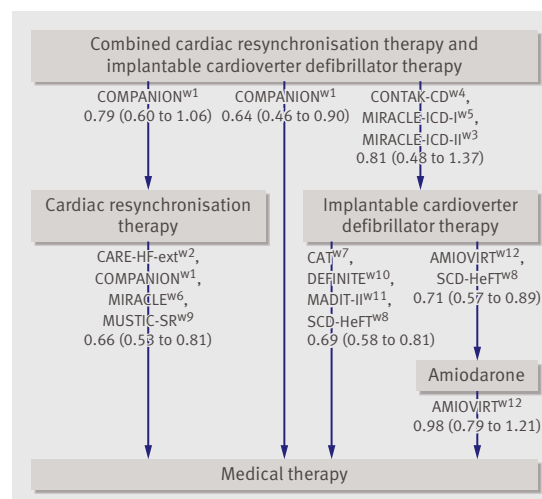
#### Data abstraction and outcomes

Both authors independently recorded trial design, recruitment criteria, baseline characteristics, efficacy outcomes, and quality assessment; any discrepancies were resolved by consensus. Primary outcomes were all cause mortality for combined resynchronisation and implantable cardioverter defibrillator therapy compared with medical therapy, with resynchronisation alone, and with implantable cardioverter defibrillator alone. For crossover trials we considered results from the first period only. We abstracted the total number of events and patients randomised to each treatment arm (intention to treat principle). Subgroup analyses were planned for patients with New York Heart Association class III or IV symptoms of heart failure at baseline.

#### Statistical analysis

For direct pairwise comparison meta-analysis we decided a priori to analyse trials using medical therapy as the control group separately from those using implantable cardioverter defibrillator therapy as the control because of prima facie evidence of clinical heterogeneity in the control groups (irrespective of estimated heterogeneity). To facilitate comparison with Bayesian network meta-analysis we expressed mortality outcomes from individual studies as odds ratios. We used random effects models to estimate the mean and 95% confidence interval for the overall treatment effect (if there were at least three studies).<sup>22</sup>

We analysed the network of randomised controlled trials within a mixed treatment comparison framework<sup>15-17</sup> using full Bayesian random effects models as described by Higgins and Whitehead<sup>19</sup> and implemented by Caldwell et al.<sup>23</sup> Specifically, we used binomial likelihood to model the probability of death within each treatment arm. In each trial we defined a study specific baseline effect using log odds of the



**Fig 2 | Bayesian network analysis of 12 randomised controlled trials (see table 1 for description of acronyms) comparing treatment strategies for patients with left ventricular dysfunction. Summary odds ratios (95% confidence intervals) are shown for each comparison, with arrowhead indicating comparator treatment. See table 1 for full titles of studies**

control group mortality, and we modelled the effect of intervention (log odds ratio) for each treatment arm. For each treatment (device) we estimated the treatment specific effect (basic variable) from the mean intervention effect for each treatment compared with the medical therapy control. We derived comparisons between treatments (functional variables) from differences between basic variables. Mean and Bayesian 95% credible intervals for treatment effects were estimated and expressed as odds ratios for presentation.

The absolute benefit for each treatment (odds of death) was estimated by adding the treatment specific effect compared with medical therapy (basic variables) to the average effect of medical therapy (baseline odds). We used standard formulas to convert the absolute odds of death to overall mortality (for the purpose of reporting).<sup>24</sup> In each simulation we ranked best the treatment option with the highest absolute odds. The probability that each treatment was best was derived from the percentage of best ranking across all simulations.

To ensure that overall effects were dominated by data from the trials and not influenced by choice of initial distribution we used low information (non-informative) prior distributions—that is, we used vague normal (mean 0, variance 10 000) and uniform (0-2) prior distributions for means and standard deviations, respectively. We examined the impact of different choices of prior distribution in sensitivity analyses.

The Bayesian models were implemented using WinBUGS version 1.4.1 (Imperial College and Medical Research Council, 2004). After convergence was achieved from an initial 5000 (burn-in)

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simulations, we constructed posterior distributions of the treatment effects from three chains of 50 000 simulations. MATLAB version 7.0 (MathWorks, Natick, MA, 2004) was used to carry out diagnostics and further data analyses.

We used funnel plots of log odds ratios against standard errors to explore the possibility of publication or other biases.<sup>25</sup> Heterogeneity was explored using the L'Abbé plot (in logarithmic scale) of the odds of death in the treatment group against that in the control group.<sup>24</sup> We used  $\chi^2$  test of Cochran's Q statistics to examine the hypothesis that all studies were evaluating the same study effect,<sup>26</sup> and we quantified the percentage of total variation across studies owing to heterogeneity ( $I^2$ ).<sup>27</sup>

The potential impact of study heterogeneity was examined in a priori sensitivity analyses excluding trials with a crossover design, less than one year's follow-up, fewer than 200 patients per group, use of less than 50%  $\beta$  blocker, early termination of trial due to futility, and requirement of previous myocardial infarction for inclusion.

## RESULTS

Figure 1 summarises the number of potential citations retrieved and the selection process. Both authors agreed on the selection and methodological assessment. Twelve independent studies met the selection criteria,<sup>w1-w12</sup> including one multigroup trial<sup>w1</sup> that compared combined cardiac resynchronisation and implantable cardioverter defibrillator therapy, resynchronisation, and medical therapy. Several studies that used univentricular pacing as the comparator for cardiac resynchronisation<sup>28-33</sup> or as the main experimental group<sup>34</sup> did not meet the selection criteria. As per protocol two trials that exclusively recruited patients who had had a recent myocardial infarction<sup>35</sup> or undergone recent coronary revascularisation were excluded.<sup>36</sup> One unpublished study<sup>37</sup> (not identified in the database search) was not included because of potential attrition bias (more than 50% of randomised patients in the control group were not available for follow-up). The potential impact of this study was examined in a post hoc sensitivity analysis.

**Table 1** | Study characteristics of included randomised controlled trials of combined cardiac resynchronisation therapy and implantable cardioverter defibrillator therapy in left ventricular impairment and symptomatic heart failure

Study	No randomised (ratio)	Interventions	Follow-up* (months)	Baseline characteristics								Quality assessment		
				Mean (SD) age	Men (%)	IHD (%)	NYHA class III (%)	LVEF (SD) %	Duration (SD) of QRS (ms)	ACEI or ARB (%)	$\beta$ blockers (%)	Concealed allocation	Analysis by intention to treat	Blinding†
CARE-HF-ext <sup>w2</sup>	813 (1:1)	MT v MT+CRT	37.4‡	67	74	38	94	25	160	95	72	Yes	Yes	No, no, yes
COMPANION <sup>w1</sup>	1520 (1:2:2)	MT v MT+CRT v MT+CRT+ICD	14.8, 16.5, 16.0	67	67	55	86	21	160	89	68	Unclear	Yes	No, no, yes
MIRACLE <sup>w6</sup>	453 (1:1)	CRT-off v CRT-on	6	64 (11)	68	54	91	22 (6)	166 (21)	92	59	Yes	Yes	Yes, yes, yes
MUSTIC-SR <sup>w9</sup>	58 (1:1)	CRT-off v CRT-on	3	64 (9)	74	45	100	23 (7)	174 (20)	96	28	Unclear	Yes	No, yes, unclear
CONTA-CD <sup>w4</sup>	490 (1:1)	ICD+CRT-off v ICD+CRT-on	4.7§	66 (11)	84	69	59	22 (7)	158 (27)	88	47	Unclear	Unclear	Unclear, unclear, unclear
MIRACLE-ICD-I <sup>w5</sup>	369 (1:1)	ICD+CRT-off v ICD+CRT-on	6	67 (10)	77	70	89	24 (6)	164 (22)	91	60	Unclear	Yes	Yes, yes, unclear
MIRACLE-ICD-II <sup>w3</sup>	186 (1:1)	ICD+CRT-off v ICD+CRT-on	6	63 (12)	89	57	0	25 (7)	165 (24)	96	63	Unclear	Yes	Yes, yes, unclear
AMIOVIRT <sup>w12</sup>	103 (1:1)	Amiodarone v MT+ICD	24	59 (12)	71	0	20	23 (9)	NA	86	52	Unclear	Yes	No, no, yes
CAT <sup>w7</sup>	104 (1:1)	MT v MT+ICD	66	52 (11)	80	0	35	24 (7)	108 (29)	96	4	Unclear	Yes	No, no, unclear
DEFINITE <sup>w10</sup>	458 (1:1)	MT v MT+ICD	29	58	71	0	21	21	115	86/11	85	Unclear	Yes	No, no, yes
MADIT-II <sup>w11</sup>	1232 (2:3)	MT v MT+ICD	20	64 (10)	85	100	24	23 (5)	NA	70	70	Unclear	Yes	No, no, unclear
SCD-HeFT <sup>w8</sup>	2521 (1:1:1)	MT+placebo v MT+ICD v MT+amiodarone	45.5	60	77	52	30	25	NA	96	69	Unclear	Yes	No, no, unclear

AMIOVIRT=amiodarone versus implantable cardioverter-defibrillator randomised trial; CAT=cardiomyopathy trial; CARE-HF-ext=cardiac resynchronisation-heart failure extension phase; COMPANION=comparison of medical therapy, pacing, and defibrillation in chronic heart failure; CONTA-CD=guidant CONTA CD CRT-D system trial; DEFINITE=defibrillators in non-ischemic cardiomyopathy treatment evaluation trial; MADIT-II=multicenter automatic defibrillator implantation trial II; MIRACLE=multicenter InSync randomised clinical evaluation; MIRACLE-ICD-I=multicenter InSync randomised clinical evaluation ICD I; MIRACLE-ICD-II=multicenter InSync randomised clinical evaluation ICD II; MUSTIC-SR=multisite stimulation in cardiomyopathies sinus rhythm; SCD-HeFT=sudden cardiac death in heart failure trial. ICH=ischemic heart disease. NYHA=New York Heart Association. LVEF=left ventricular ejection fraction; ACEI=angiotensin converting enzyme inhibitors; ARB=angiotensin receptor antagonist; CRT-on=active cardiac resynchronisation therapy; CRT-off=inactive cardiac resynchronisation therapy; ICD+CRT-on=active implantable cardioverter defibrillator therapy and active cardiac resynchronisation therapy; ICD+CRT-off=active implantable cardioverter defibrillator therapy but inactive cardiac resynchronisation therapy; MT=medical therapy; NA=not available.

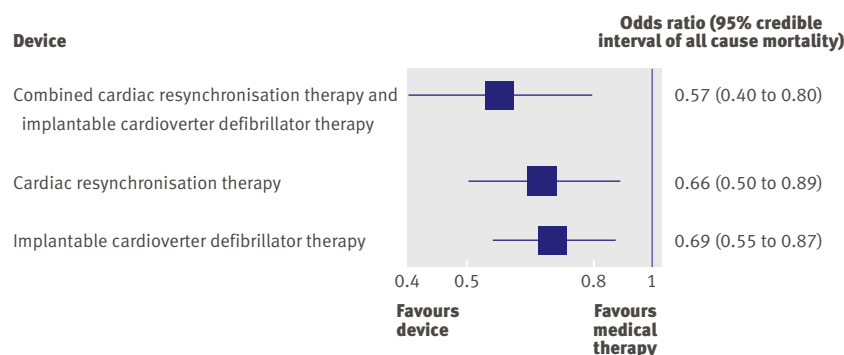
\*Duration of follow-up for mortality outcome.

†Blinding for patient, investigator, and endpoint assessment.

‡Mean follow-up for main study was 29.4 months.

§Follow-up was 3 months for 222 patients and 6 months for 279 patients implanted with investigational device.





**Fig 3** Results of Bayesian network meta-analysis of 12 randomised controlled studies of device therapies in 8307 patients with left ventricular dysfunction

Figure 2 shows the relation between the network of randomised controlled trials. In total, 1636 events occurred in 8307 patients randomised to cardiac resynchronisation therapy (245/1283), implantable cardioverter defibrillator therapy (367/2429), combined resynchronisation and implantable cardioverter defibrillator therapy (132/1112), amiodarone (247/897), and control (645/2586). Seven studies reported 1013 events in 4319 patients for subgroup analysis of New York Heart Association class III or IV heart failure, including five studies that recruited only patients with class III or IV heart failure<sup>w1 w2 w5 w6 w9</sup> and two studies that reported subgroup outcomes.<sup>w9 w11</sup>

Table 1 summarises the design, baseline characteristics, and quality assessment of the included studies. All used the transvenous approach to implantation, whereas one included 11% of patients with leads implanted transthoracically.<sup>w4</sup> Most studies were analysed using the intention to treat principle, but concealment of treatment allocation was unclear in most trials. In several studies<sup>w3 w5 w6 w9</sup> blinding of investigators or patients, or both, was possible as only patients with successful device implantations were considered for randomisation.

One study was presented in two publications reporting independent results from patients with New York Heart Association class II<sup>w3</sup> and class III or IV<sup>w5</sup> heart failure at baseline. The number of deaths reported was identical to a FDA report<sup>38</sup> but different from an earlier version<sup>39</sup> cited in previous reviews.<sup>7 9</sup> In this review published outcomes were abstracted as per two independent studies.<sup>w3 w5</sup> Mortality data were used from the extension phase of the cardiac resynchronisation heart failure trial.<sup>40 w2</sup>

Four studies accounted for 73% of patients and 88% of observed events.<sup>w1 w2 w6 w11</sup> Baseline mortality was comparable in most studies except for five.<sup>w3-w6 w9</sup> In these five studies duration of follow-up was shorter and patients only with successfully implanted devices were randomised. No major asymmetry was seen in the funnel plots to suggest publication bias (not shown).

#### Quantitative analysis

Figures 3 and 4 summarise the all cause mortality data for Bayesian network and pairwise comparisons of device therapies compared with medical therapy. Combined

resynchronisation and implantable defibrillator therapy significantly reduced mortality compared with medical therapy in one direct comparison study<sup>w1</sup> (odds ratio 0.64, 95% confidence interval 0.46 to 0.90), and in Bayesian network meta-analysis of 12 studies (0.57, 95% credible interval 0.40 to 0.80). Both resynchronisation (0.66, 95% credible interval 0.50 to 0.89) and implantable defibrillator therapy (0.69, 0.55 to 0.87) reduced mortality compared with medical therapy. Amiodarone did not have any apparent effect on mortality compared with medical therapy (0.97, 0.68 to 1.35).

The overall mortality for combined resynchronisation and implantable defibrillator therapy was 9.1% compared with 14.0% for medical therapy, corresponding to a 35% relative risk reduction (table 2). The probability determined from the Bayesian analysis that combined resynchronisation and implantable defibrillator therapy was the best option (compared with other devices and optimal medical therapy) was 0.75 in all patients with impaired left ventricular function and 0.62 in the subgroup of patients with New York Heart Association class III or IV heart failure. The corresponding probabilities for resynchronisation therapy were 0.14 and 0.27 and for implantable defibrillator therapy were 0.10 and 0.08.

Figure 5 shows the results of head to head comparisons of combined resynchronisation and implantable defibrillator therapy with either therapy alone. When combined therapy was compared with implantable defibrillator therapy no evidence was found from pairwise meta-analysis (three studies, odds ratio 0.81, 95% confidence interval 0.48 to 1.37) and Bayesian network meta-analysis (12 studies, odds ratio 0.82, 95% credible interval 0.57 to 1.18; seven studies, New York Heart Association class III or IV subgroup, odds ratio 0.74, credible interval 0.39 to 1.57) to suggest that combined therapy further improved survival (fig 4). Similarly, when combined therapy was compared with resynchronisation therapy no evidence was found from one direct comparison study (odds ratio 0.79, 95% confidence interval 0.60 to 1.06) and Bayesian network meta-analysis (odds ratio 0.85, 95% credible interval 0.60 to 1.22; New York Heart Association class III or IV subgroup, odds ratio 0.89, 95% credible interval 0.45 to 1.76) for an incremental value of combined therapy.

Estimates of treatment effects were robust for study selection criteria (including a priori and post hoc sensitivity analyses) and for statistical assumption of prior distributions (not shown).

#### DISCUSSION

The present meta-analysis, based on a Bayesian network of 12 studies including 1636 events in 8307 patients, suggests that combined cardiac resynchronisation therapy and implantable cardioverter defibrillator therapy reduces all cause mortality by one third when compared with medical therapy. Assuming an annual mortality of 15% in patients with heart failure receiving optimal medical therapy, the number needed to treat to prevent one death is 20. Although it is probable that combined therapy is the best option for reducing

mortality (probability of 0.75 in present analysis) it has not been shown to be associated with a mortality different from that with either resynchronisation therapy or implantable defibrillator therapy. These findings also apply to the subgroup of patients with New York Heart Association class III or IV heart failure, a sicker group of patients who might be expected to gain greater benefit than that of patients with class II symptoms. Thus there is

no direct evidence from clinical trials or systematic evidence from the present meta-analysis to support combined resynchronisation and implantable defibrillator therapy improving survival more than resynchronisation therapy or implantable defibrillator therapy alone in patients with left ventricular impairment.

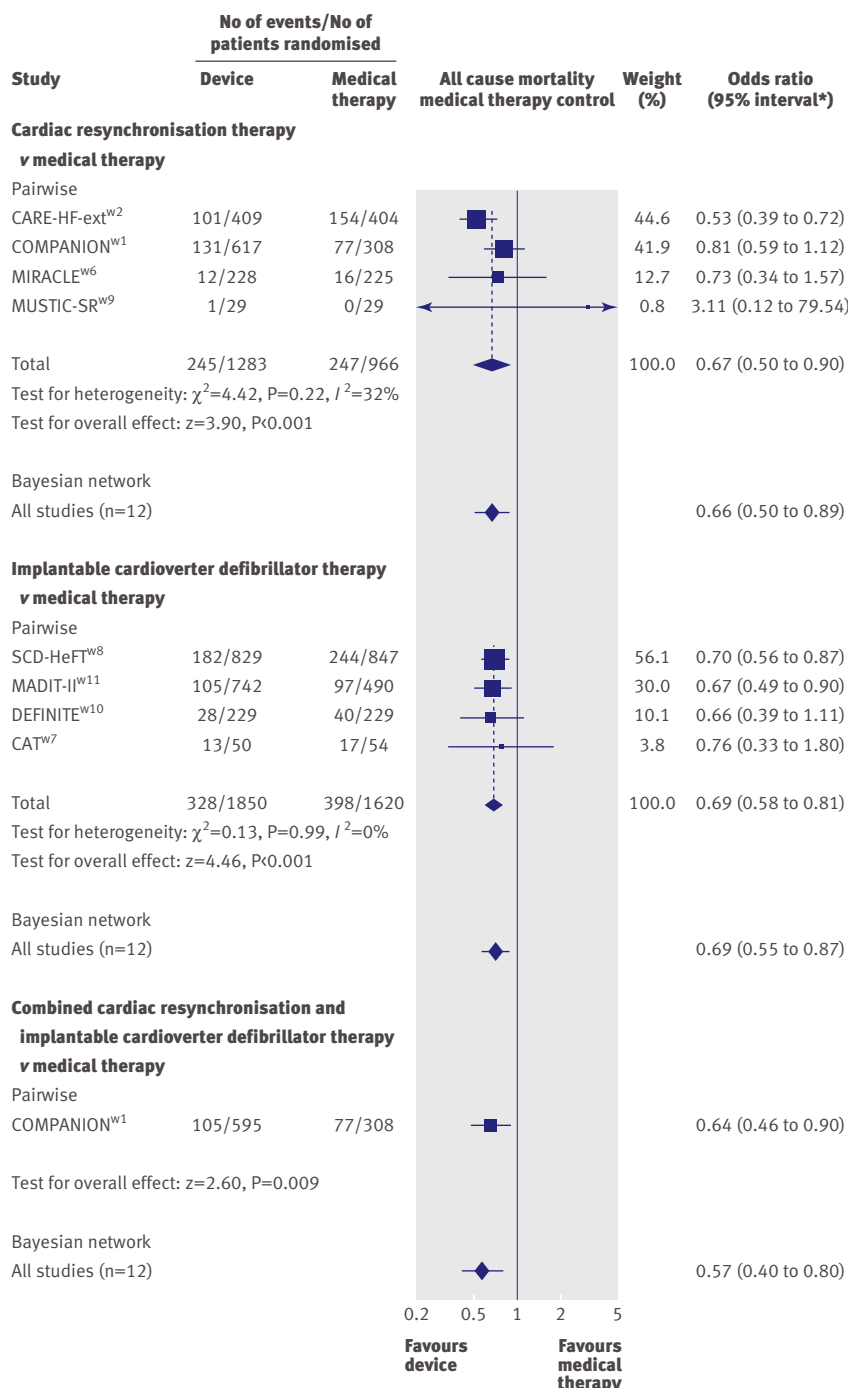
### Limitations

Limitations of the primary trials and potential confounders may affect the validity of the findings. Five studies, two of resynchronisation therapy<sup>w6 w9</sup> and three of combined therapy compared with implantable cardioverter defibrillator therapy<sup>w3-w5</sup> only randomised patients after successful implantation of the device. Although results of these studies were analysed using intention to treat (from randomisation), complications related to implantations were excluded. Event rates in these studies were lower than in other studies included in the review, but treatment effects were comparable. In addition, similar to previous meta-analyses, the present study was subject to potential publication bias,<sup>24</sup> although funnel plots did not suggest the presence of such bias and an extensive search strategy was used to identify relevant trials.

Criteria for patient selection were different but overlapping in the primary trials examining implantable cardioverter defibrillator and cardiac resynchronisation therapy. Although both sets of trials recruited patients with impaired left ventricular function, prolonged QRS interval is a prerequisite only for patients undergoing resynchronisation. Thus interpretation of the results of the present meta-analysis is subject to this potential confounder. This situation is, however, no different from everyday clinical scenarios where the doctor needs to use clinical judgment informed by the same evidence base. The point of the present meta-analysis is to use all the available evidence to tackle the clinically relevant question of whether patients independently eligible for resynchronisation and for implantable defibrillator therapy would benefit from a combined device. The current evidence base is not ideal but it is the best available pending a definitive randomised controlled trial on this subject.

We excluded studies that compared resynchronisation therapy with univentricular pacing. This reduces the total number of cases available for analysis and potentially the overall statistical power. However, this strategy avoided the ambiguity in previous reviews, where patients treated with univentricular pacing were analysed in the same group (and hence assumed to have the same prognosis) as those receiving optimal medical therapy alone. It is possible to include patients from studies using right (or left) univentricular pacing as a sixth (or seventh) treatment group in the network analysis. This approach was not adopted in the present protocol because the a priori clinical question of interest was the value of resynchronisation therapy, and not univentricular pacing, in heart failure.

Trials included in this review were carried out over a period of evolving medical management of heart



**Fig 4 | Results of pairwise meta-analysis and Bayesian network analysis of device therapies compared with medical therapy for patients with left ventricular dysfunction. \*95% confidence interval for pairwise comparison, 95% credible interval for Bayesian network comparison. See table 1 for full titles of studies**

failure;  $\beta$  blocker usage at baseline was less than 50% in several trials<sup>w4 w7 w9</sup> and the underlying risk of death in these studies might have been different had their usage been higher. In addition, the follow-up period was no more than six months for most trials of resynchronisation therapy (except the studies of cardiac resynchronisation heart failure<sup>w2</sup> and comparison of medical therapy, pacing, and defibrillator in chronic heart failure<sup>w1</sup>), potentially before the full benefits of resynchronisation therapy were realised. Several trials were underpowered to detect mortality benefits because recruitment was discontinued (owing to futility) before achieving the intended number of participants,<sup>w7 w12</sup> and some studies were primarily designed to identify functional changes.<sup>w3-w6 w9</sup> Furthermore, one trial required a history of myocardial infarction<sup>w11</sup> for inclusion, and patients with a more recent history may respond less favorably to implantable cardioverter defibrillators.<sup>41</sup> However, multiple sensitivity analyses suggested that these potential confounders did not affect the findings of this study.

The main efficacy outcome of interest in this study was mortality, but many primary trials did not report outcome in sufficient detail to permit abstraction of data on subgroups. Previous reviews<sup>7 9</sup> provided good evidence that resynchronisation therapy improved functional outcomes and quality of life, but these outcomes were not reported in any primary trials of implantable cardioverter defibrillators included in the present review, and Bayesian network meta-analyses were not planned for these outcomes. Finally, data were limited for subgroup analysis of patients with New York Heart Association class III or IV heart failure (fewer patients in implantable cardioverter defibrillator trials had class III symptoms) leading to wide credibility intervals.

#### Relation to previous studies

In previous meta-analyses that compared resynchronisation therapy with no such therapy,<sup>6-10</sup> trials with different comparison groups (resynchronisation versus medical therapy, resynchronisation versus univentricular pacing, and combined resynchronisation and implantable defibrillator versus implantable defibrillator) were combined making it impossible to determine the efficacy of combined therapy itself. The efficacy of combined therapy was inferred from

exploratory metaregression analyses implemented using likelihood estimation<sup>9</sup> or full Bayesian<sup>7</sup> techniques, which found no significant variability between trials comparing resynchronisation therapy with medical therapy (or univentricular pacing) and trials comparing combined therapy with implantable defibrillator therapy. Only two trials compared combined therapy with implantable defibrillator therapy,<sup>39 w4</sup> and data from 595 patients from the comparison of medical therapy, pacing, and defibrillator in chronic heart failure trial<sup>w1</sup> treated with combined therapy were not incorporated.<sup>7</sup> Thus results of these regression analyses may not be robust,<sup>27</sup> and the efficacy of combined resynchronisation and implantable defibrillator therapy itself cannot be quantified in these studies.

One previous meta-analysis reported that adding implantable cardioverter defibrillator to cardiac resynchronisation therapy resulted in an apparent reduction in mortality.<sup>6</sup> This claim was, however, based on the pooled estimates of data from the comparison of medical therapy, pacing, and defibrillator in chronic heart failure trial<sup>w1</sup> and a non-randomised controlled trial.<sup>42</sup> Although it is possible to include non-randomised studies within a general evidence synthesis framework<sup>43</sup> it is not generally advised in systematic reviews of device therapy<sup>44</sup> because of the possibility of introducing significant bias, especially when studies are few.<sup>45</sup>

The present Bayesian network meta-analysis permits simultaneous comparison of all treatment options, and conclusions on the efficacies of resynchronisation therapy and of implantable defibrillator therapy are similar to the results of previous meta-analyses. No evidence was found from the present network analysis, however, that combined cardiac resynchronisation and implantable defibrillator therapy is better than either resynchronisation or implantable defibrillator alone.

The full Bayesian network approach provided evidence of a higher methodological quality by taking into account the multivariate relation between intervention effects of multigroup trials. All available evidence, including data from all three treatment groups of the comparison of medical therapy, pacing, and defibrillator in chronic heart failure trial,<sup>w1</sup> was incorporated without splitting or discarding groups,<sup>15</sup> in contrast to previous exploratory metaregression analyses<sup>7 9</sup> where this was not possible. Thus conclusions of the present study are based on all available current evidence from randomised controlled trials, and multiple sensitivity analyses suggest that these findings are robust for statistical assumptions and trial inclusion criteria.

#### Implications

Current guidelines from the American College of Cardiology, American Heart Association, and European Society of Cardiology for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death<sup>46</sup> give a IIa (weight

**Table 2 | Probability of best treatment for patients with left ventricular dysfunction**

Therapy	All studies		NYHA class III or IV heart failure	
	Overall mortality (%)	Probability of best treatment	Overall mortality (%)	Probability of best treatment
Medical	14.0	0	13.7	0
Cardiac resynchronisation	10.3	0.14	10.5	0.27
Implantable cardioverter defibrillator	10.6	0.10	12.2	0.08
Combined resynchronisation and implantable defibrillator	9.1	0.75	9.7	0.62

NYHA=New York Heart Association.

of evidence in favour of efficacy), level of evidence B (data derived from a single randomised trial or non-randomised studies) recommendation for combined resynchronisation and implantable defibrillator therapy in patients with New York Heart Association class III or IV heart failure and a broad QRS complex. A case exists for using combined therapy in patients who simultaneously satisfy the criteria for both therapies, and the present Bayesian analysis suggests that it is probable that combined therapy is the best option. However, this practice is based on extrapolated evidence from trials that showed efficacy of resynchronisation therapy or implantable defibrillator therapy compared with medical therapy. No direct evidence was found from primary trials or from the present Bayesian network meta-analysis to suggest that combined therapy is better than either therapies alone in patients with left ventricular impairment. As clinical practice guidelines are becoming prescriptive rather than offering guidance, many clinicians may feel compelled (despite this lack of direct evidence of

superior efficacy) to implant a combined resynchronisation and cardioverter defibrillator device if patients fulfill criteria for both therapies.

It could be argued that cardiac resynchronisation should be added to an implantable cardioverter defibrillator in clinical practice to improve symptoms rather than survival itself, but resynchronisation therapy alone improves symptoms (as well as survival). The potential advantage of combined therapy over resynchronisation therapy alone is the theoretical incremental survival benefit (not proved in the present meta-analysis). The routine use of combined therapy in all patients eligible for both treatments, on the basis that it may prolong survival over cardiac resynchronisation therapy or implantable cardioverter defibrillator alone, would not seem to be appropriate. Trial evidence is usually required before a new treatment is used routinely.

The lack of definitive clinical evidence means that public funding bodies are unable to assess properly the comparative cost effectiveness of combined resynchronisation and implantable defibrillator therapy even if it does offer some advantage over either therapy alone. A simple pragmatic approach would be to use resynchronisation therapy, which may be more cost effective than combined therapy,<sup>47,48</sup> to reduce symptoms and extend life in patients with New York Heart Association class III or IV heart failure, with the addition of an implantable cardioverter defibrillator left to clinical judgment on an individual basis when additional indications exist. When such an addition is contemplated the hypothesised incremental benefits in survival would need to be balanced by the possible increase in morbidity due to, for example, inappropriate shocks.<sup>49</sup>

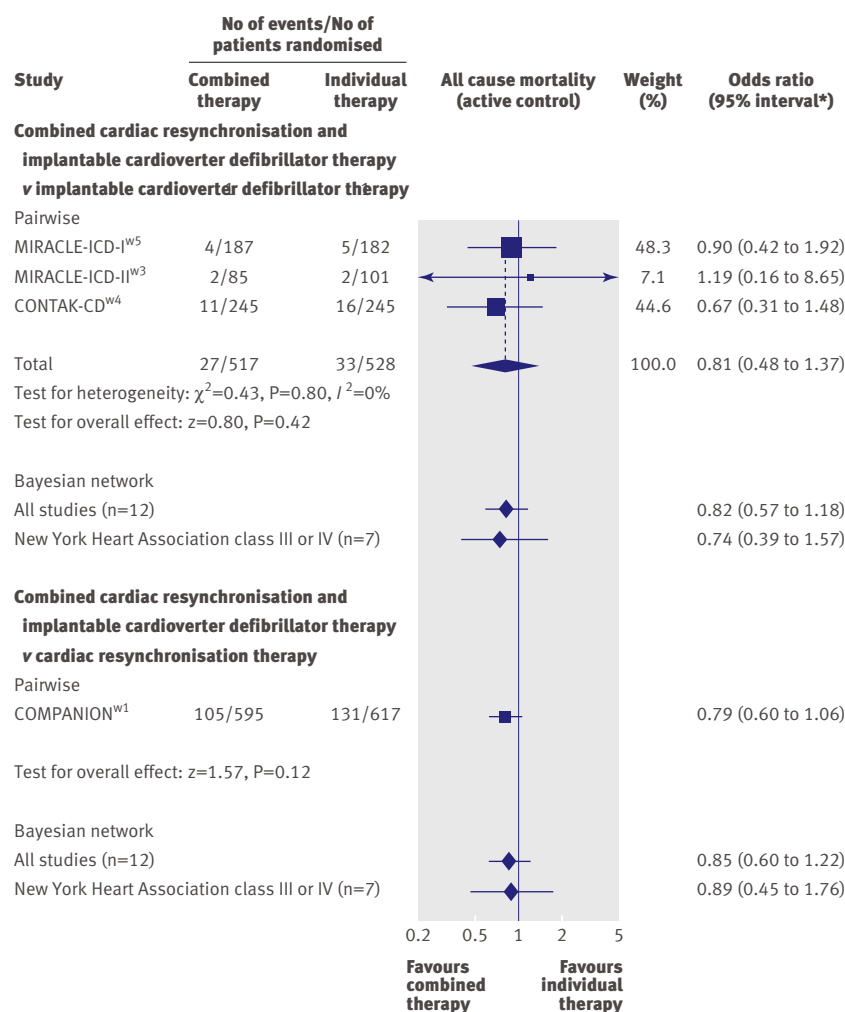
Ongoing clinical trials<sup>50,51</sup> are examining the potential value of combined therapy for patients suitable for implantable cardioverter defibrillators who are not currently eligible for cardiac resynchronisation. These studies will provide important data on the value of adding resynchronisation therapy to treat patients who currently only satisfy criteria for implantable cardioverter defibrillators, but do not inform whether combined therapy offers any survival benefits over resynchronisation therapy in patients who have heart failure with a prolonged QRS interval. In view of the additional cost of combined therapy and potential morbidity associated with inappropriate defibrillation shocks, the burden of proof (requiring a major new clinical trial of thousands of patients) should ideally be on combined therapy to show superiority over resynchronisation therapy, and further studies are needed to identify the population most likely to benefit.

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**Fig 5** | Combined cardiac resynchronisation and implantable cardioverter defibrillator therapy compared with either therapy alone. \*95% confidence interval for pairwise comparison, 95% credible interval for Bayesian network comparison. See table 1 for full title of studies



## WHAT IS ALREADY KNOWN ON THIS TOPIC

Cardiac resynchronisation and implantable cardioverter defibrillators independently improve mortality in selected patients with heart failure, but the potential incremental benefits of combined therapy remain unclear

Previous meta-analyses utilised suboptimal methodologies in dealing with trials with multiple groups

## WHAT THIS STUDY ADDS

Combined cardiac resynchronisation and implantable defibrillator therapy reduced all cause mortality of patients with heart failure by one third compared with medical therapy

Evidence from a network of 12 studies (8307 patients) is insufficient to suggest that combined therapy is superior to resynchronisation therapy

The Bayesian approach models the (multivariate) intervention effects of multigroup trials and provides evidence of a higher methodological quality than previous meta-analyses

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