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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 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 defibrillator therapy (0.82, 0.57 to 1.18) or resynchronisation therapy (0.85, 0.60 to 1.22) 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

Guidelines¹⁻³ recommend an implantable defibrillator in selected patients with left ventricular dysfunction, and cardiac resynchronisation therapy in selected patients with abnormal ventricular conduction. Many patients may be eligible for both treatments but not necessarily obtain additional benefit over one treatment alone.

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

METHODS

Studies were eligible if they were randomised controlled or randomised crossover trials; included patients with impaired left ventricular systolic function; compared cardiac resynchronisation or cardiac resynchronisation and an implantable cardioverter defibrillator device with medical therapy or medical therapy plus an implantable defibrillator, or were primary prevention trials comparing an implantable defibrillator with medical therapy or oral antiarrhythmics; and reported all cause mortality. (See bmj.com for the search strategy.)

Primary outcomes were all cause mortality for combined resynchronisation and implantable defibrillator therapy compared with medical therapy, with resynchronisation therapy, and with implantable defibrillator therapy. We abstracted the total number of events and patients randomised to each treatment arm (intention to

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treat). Subgroup analyses were planned for patients with New York Heart Association class III or IV 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 defibrillators as the control because of prima facie evidence of clinical heterogeneity in controls. 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).⁴

We analysed the network of randomised controlled trials on resynchronisation and implantable defibrillator therapy within a mixed treatment comparison framework⁵⁻⁷ using full Bayesian random effects models (see bmj.com).^{8,9} 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 to the average effect of medical therapy (baseline odds). We used standard formulas to convert the absolute odds of death to overall mortality.¹⁰ 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 (see bmj.com). We examined the impact of different choices of prior distribution in sensitivity analyses.

We explored the possibility of publication or other biases using funnel plots and heterogeneity using the L'Abbé plot.¹⁰ We used χ^2 test of Cochran's Q statistics to examine whether all studies evaluated the same study effect,¹¹ and we quantified the percentage of variation across studies owing to heterogeneity.¹²

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, less than 50% β blocker usage, early termination of trial due to futility, and requirement of previous myocardial infarction for inclusion.

RESULTS

Twelve studies met the selection criteria,^{w1-w12} including one multigroup trial^{w1} that compared combined resynchronisation and implantable defibrillator therapy, resynchronisation therapy, and medical therapy (see bmj.com).

The relation between the network of randomised controlled trials is on bmj.com. Overall, 1636 events occurred in 8307 patients—245/1283 after resynchronisation therapy, 367/2429 after implantable defibrillator therapy, 132/1112 after combined resynchronisation and implantable defibrillator therapy, 247/897 after

amiodarone, and 645/2586 for controls. Seven studies reported 1013 events in 4319 patients for subgroup analysis of patients with class III or IV heart failure, including five studies that recruited only patients with class III or IV heart failure^{w1 w2 w5 w6 w9} and two studies that reported subgroup outcomes.^{w9 w11}

Details of the included studies are on bmj.com. Most used the intention to treat principle, but concealment of treatment allocation was unclear in most trials. In several studies,^{w3 w5 w6 w9} blinding of investigators or patients was possible as only patients with successful implants were considered for randomisation.

One study was presented in two publications reporting independent results from patients with class II^{w3} and class III or IV^{w5} heart failure at baseline. Published outcomes were abstracted as per two independent studies.^{w3 w5} Mortality data were used from the extension phase of the cardiac resynchronisation heart failure trial.^{13 w2}

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

Quantitative analysis

All cause mortality data for device therapies compared with medical therapy are on bmj.com. Combined resynchronisation and implantable defibrillator therapy significantly reduced mortality compared with medical therapy in one direct comparison study^{w1} (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 therapy (0.66, 95% credible interval 0.50 to 0.89) and defibrillator therapy (0.69, 0.55 to 0.87) reduced mortality compared with medical therapy.

The overall mortality for combined therapy was 9.1% compared with 14.0% for medical therapy, corresponding to a 35% relative risk reduction (table). The probability determined from the Bayesian analysis that resynchronisation and implantable defibrillator therapy was the best option (compared with other devices and medical therapy) was 0.75 in all patients with impaired left ventricular function and 0.62 in patients with 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.

The results of head to head comparisons of combined resynchronisation and defibrillator therapy with either therapy alone are on bmj.com. 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, class III or IV subgroup, odds ratio 0.74, credible interval 0.39 to 1.57) to suggest that combined therapy further improved survival (see bmj.com).

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; class III or IV subgroup, odds ratio 0.89, 95% credible interval 0.45 to 1.76) for an incremental value of combined therapy.

DISCUSSION

The present meta-analysis, based on a Bayesian network of 12 studies including 1636 events in 8307 patients, suggests that combined cardiac resynchronisation with 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 or defibrillator therapy alone. These findings also apply to the subgroup of patients with New York Heart Association class III or IV heart failure, a group who might be expected to gain greater benefit than patients with class II symptoms.

Limitations

Limitations of the primary trials and potential confounders may affect the validity of the findings. Five studies^{w3-w6 w9} only randomised patients after successful implantation. Although results of these studies were analysed using intention to treat, complications related to implantations were excluded. Event rates in these studies were lower than in other included studies, but treatment effects were comparable. Funnel plots did not suggest the presence of publication bias in the present study, and an extensive search strategy was used.

Interpretation of the results may be confounded by the requirement of a prolonged QRS interval for patients undergoing resynchronisation therapy (but not for those implanted with cardioverter defibrillators). This situation is no different, however, from everyday clinical scenarios where the doctor needs to use clinical judgment informed by the same evidence base.

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. This strategy avoided the ambiguity in previous reviews, however, where patients treated with univentricular pacing were analysed in the same group (and hence assumed to have the same prognosis) as those receiving medical therapy.

Trials included in this review were carried out over a period of evolving medical management of heart failure; β blocker usage at baseline was less than 50% in several trials^{w4 w7 w9} 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, potentially before the full benefits were realised. Several trials were under-powered to detect mortality benefits because recruitment stopped before achieving the intended number of participants,^{w7 w12} and some studies were primarily designed to identify functional changes.^{w3-w6 w9} Furthermore, one trial required a history of myocardial infarction^{w11} for inclusion, and patients with a more recent history may respond less favorably to defibrillators.¹⁴ 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^{15 16} provided good evidence that resynchronisation therapy improved functional outcomes and quality of life, but these outcomes were not reported in any primary trials of 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 class III or IV heart failure (fewer patients in defibrillator trials had class III symptoms) leading to wide credibility intervals.

Relation to previous studies

One previous meta-analysis reported that adding defibrillator therapy to resynchronisation therapy resulted in a reduction in mortality.¹⁷ This claim was based on the pooled estimates of data from the comparison of medical therapy, pacing, and defibrillator in chronic heart failure trial^{w1} and a non-randomised controlled trial.¹⁸

The present Bayesian network meta-analysis permits simultaneous comparison of 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 analysis, however, that combined resynchronisation and implantable defibrillator therapy is better than either resynchronisation or implantable defibrillator therapy 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 was incorporated without splitting or

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.

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

discarding groups,⁵ in contrast to previous exploratory metaregression analyses^{15,16} where this was not possible. Thus conclusions of the present study are based on available current evidence from randomised controlled trials, and multiple sensitivity analyses suggest that these findings are robust for statistical assumptions and inclusion criteria.

Implications

Current guidelines (American College of Cardiology, American Heart Association, European Society of Cardiology) for the management of patients with ventricular arrhythmias give a IIa (weight 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 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 meta-analysis to suggest that combined therapy is better than either therapies alone in patients with left ventricular impairment.

It could be argued that resynchronisation therapy should be added to implantable defibrillator therapy 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 resynchronisation therapy or implantable defibrillator therapy alone, would not seem to be appropriate.

Ongoing clinical trials^{19,20} are examining the potential value of combined therapy for patients suitable for implantable defibrillator therapy who are not currently

eligible for resynchronisation therapy. These studies will provide important data, 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.

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