Cardiac resynchronization therapy in patients with mild heart failure: a systematic review and meta-analysis


CRD summary
The review concluded that cardiac resynchronisation therapy reduced mortality and the risk of heart failure events, induced a favourable left ventricular reverse remodelling and slowed progression of heart failure symptoms in patients with mild heart failure. The review had some methodological problems and there were differences between the trials so caution is warranted when interpreting the authors' conclusions.

Authors' objectives
To investigate the effectiveness of cardiac resynchronisation therapy in asymptomatic or mildly symptomatic heart failure patients.

Searching
PubMed, BioMed Central, Cardiosource, ClinicalTrials.gov and Web of Science were searched from January 1970 to January 2011 with no language restrictions. Search terms were reported. Five conference proceedings were searched for the previous five years.

Study selection
Randomised controlled trials (RCTs) of cardiac resynchronisation therapy versus no cardiac resynchronisation therapy in patients with heart failure and left ventricular ejection fraction of up to 40% and New York Heart Association functional class I to II were eligible for inclusion. The relevant outcomes were death, heart failure, worsening of clinical status, exercise tolerance and adverse events.

The included trials studied cardiac resynchronisation therapy (on or off pump) alone or in combination with implantable cardioverter-defibrillator. New York Heart Association criteria ranged from I/II to II to IV. Mean age of patients ranged from 62 to 66 years, 75% to 89% of the patients were male and 63% to 95% of the patients were on beta blockers. Two trials used a cross-over design.

Two reviewers independently performed study selection. Disagreements were resolved by a third reviewer.

Assessment of study quality
Trial quality was assessed using the Cochrane Collaboration risk of bias tool for risk of selection bias, performance bias, detection bias and attrition bias.

The authors did not state how many reviewers undertook quality assessment.

Data extraction
Data were extracted on clinical outcomes and adverse events and used to calculate mean differences and odds ratios, together with 95% confidence intervals.

Two reviewers independently extracted data. Disagreements were resolved by a third reviewer.

Methods of synthesis
Mantel-Haenszel random-effects meta-analysis was used to calculate pooled odds ratios (ORs) and weighted mean differences (WMDs), together with 95% confidence intervals. Statistical heterogeneity was assessed using the I² statistic. Meta-regression was used to assess impact of covariates such as age and gender on overall mortality and heart failure. Publication bias was assessed using funnel plots. Sensitivity analyses were conducted.

Results of the review
Five trials (4,904 patients; 4,213 included in the analysis, range 186 to 1,820) were included in the review. All five trials
were of comparable quality but three trials randomised patients only after successful cardiac resynchronisation therapy implantation (which may have biased results). Follow-up ranged from six to 40 months.

Compared with control, cardiac resynchronisation therapy was associated with statistically significant reduced risk of death (OR 0.78, 95% CI 0.63 to 0.97; four RCTs), heart failure events (OR 0.63, 95% CI 0.52 to 0.76; three RCTs) and progression of heart failure (OR 0.54, 95% CI 0.31 to 0.93; two RCTs). There was no significant difference in exercise tolerance in patients with asymptomatic to mild heart failure. Compared with control, cardiac resynchronisation therapy was associated with statistically significantly reduced left ventricular reverse remodelling (WMDs -19.4mL/m², 95% CI -18.2 to -20.7; three RCTs).

Rates of complications with cardiac resynchronisation therapy ranged from 13.2% to 53% and appeared to be higher than with control. Sensitivity analysis did not significantly affect the results except that mortality was highly influenced by one trial.

**Authors’ conclusions**
Cardiac resynchronisation therapy reduced mortality and the risk of heart failure events, induced a favourable left ventricular reverse remodelling and slowed the progression of heart failure symptoms in patients with mild heart failure.

**CRD commentary**
Inclusion criteria for the review were clearly defined. Several relevant databases were searched without language restrictions. Publication bias was assessed but the results were not presented and the meaningfulness of an analysis with fewer than 10 trials was questionable. Attempts were made to reduce error and bias during study selection and data extraction; it was unclear whether the same attempts were made for quality assessment. Two trials were included in which some patients did not fully meet the inclusion criteria; one of these was excluded from some analyses. Results of the quality assessment were not fully presented and this made it difficult to assess the validity of the evidence base. The authors noted that three trials randomised patients only after successful cardiac resynchronisation therapy implantation and this may have biased results. Trials were combined using random-effects meta-analysis. It was unclear whether statistical heterogeneity was assessed and this was especially problematic given the clinical and methodological differences between the trials. The authors noted that there was evidence of clinical differences between trials. It may not have been appropriate to pool cross-over design trials with parallel group trial.

The review had some methodological problems and there were differences between the trials so caution is warranted when interpreting the authors’ conclusions.

**Implications of the review for practice and research**
The authors did not state any implications for practice or research.

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