Cardiac resynchronization therapy in patients with minimal heart failure: a systematic review and meta-analysis
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CRD summary
This review found that cardiac resynchronisation therapy decreased all-cause mortality, reduced hospitalisations and improved left ventricular ejection fraction in patients with NYHA Class I to II heart failure. The potential for missed studies and the limited information on study quality means the reliability of the authors’ conclusions is uncertain.

Authors’ objectives
To evaluate the use of cardiac re-synchronisation therapy (CRT) compared to implantable cardioverter-defibrillators (ICD) in patients with reduced ejection fraction, prolonged QRS interval and New York Heart Association (NYHA) functional Class I to II heart failure.

Searching
MEDLINE was searched from 1960 to January 2010 for relevant studies published in English; search terms were reported. The website ClinicalTrials.gov was searched, and the reference lists of retrieved articles were checked for additional studies.

Study selection
Eligible randomised controlled trials (RCTs) compared CRT to ICD in patients with NYHA Class I to II heart failure and reported data on mortality, heart failure, hospitalisation and left ventricular dimensions or volume. Additional inclusion criteria were that the patients ejection fraction was 40% or below and the QRS duration was 120ms or above.

Mean age of the patients in the included trials was 65 years and 80% of the patients were males. Most patients had NYHA functional Class II symptoms and 60% of the patients presented with ischaemic cardiomyopathy. All the patients presented with reduced ejection fraction and wide QRS intervals; the inclusion criteria for these variables were slightly different between studies. Nearly all the patients were receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Beta-blockers were used in more than 90% of the patients in the trials published post-2008, compared to 55% of the patients in trials published prior to 2008. All the trials compared CRT plus ICD to ICD alone. Follow-up in the trials ranged from six to 40 months.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Methodological quality was assessed according to the Delphi criteria and scored using the Jadad scale. Quality factors evaluated were: randomisation; allocation concealment; similarity of groups at baseline; blinding of patients, clinicians and outcome assessors; descriptions of withdrawals and drop-outs; use of intention-to-treat analyses.

The reviewers did not state how many authors performed the quality assessment.

Data extraction
Data were extracted to calculate mean differences (MD) for continuous variables, risk ratios (RR) for categorical variables and 95% confidence intervals (CI) for each outcome. The reviewers contacted the authors for additional information where data were missing or incomplete.

Data were extracted by two independent reviewers; any discrepancies between reviewers were resolved by discussion.

Methods of synthesis
Pooled weighted mean differences (WMD), risk ratios and 95% confidence intervals for each outcome were calculated using a DerSimonian and Laird random-effects model. Statistical heterogeneity was evaluated using $I^2$. The numbers-needed-to-treat (NNT) were also calculated for each outcome. Subgroup analyses were also conducted for patients on
the basis of NYHA status.

**Results of the review**

Five RCTs (4,317 patients) were included in the review. Sample sizes ranged from 186 to 1,820 patients. Two RCTs had a Jadad score of 5 points; the remaining trials scored 4 points. Allocation concealment was adequately reported in three trials. Intention-to-treat analyses were performed in four trials. Drop-outs were reported in all the RCTs. Patients and clinicians were not blinded in one RCT, but the outcome assessors were blinded in all the trials. Baseline characteristics were reported to have been similar across the groups but no results were reported on randomisation.

There were significant benefits observed in the five RCTs with CRT compared to ICD implantation in mortality (RR 0.81, 95% CI 0.65 to 0.99; NNT 29 patients; five RCTs), heart failure events and hospitalisation (RR 0.68, 95% CI 0.59 to 0.79; NNT 15; five RCTs) with a 28% reduction in the risk of a composite of mortality and hospitalisation for heart failure (RR 0.72, 95% CI 0.65 to 0.81) and improvements in left ventricular ejection fraction (WMD 4.1% 95% CI 0.1 to 8.0%; p<0.001).

For patients with NYHA Class II heart failure (five trials, 3,915 patients), there were significant benefits observed with CRT for mortality (RR 0.78, 95% CI 0.65 to 0.95; NNT 28) and hospitalisation due to heart failure (RR 0.67, 95% CI 0.57 to 0.79; NNT 14) compared to ICD implantation. In the three trials that included asymptomatic NYHA Class I patients (402), significant reductions in the risk of hospitalisation were observed (RR 0.57, 95% CI 0.34 to 0.97; NNT 12), but there were no differences between CRT and ICD for mortality.

There was no statistically significant heterogeneity observed in the results for any outcome examined.

Adverse events including implant failure, pneumothorax, pocket haematoma and infection (four studies, 4,414 patients) were significantly higher in the patients who received CRT (361 events) compared to patients receiving ICD (66 events). Most adverse events were left ventricular lead dislodgements and failure to implant the left ventricular lead.

**Authors' conclusions**

Cardiac resynchronisation therapy decreased all-cause mortality, reduced hospitalisations and improved left ventricular ejection fraction in patients with NYHA Class I to II heart failure. Although reductions in hospitalisations were observed in NYHA Class I patients, risk compared to benefits should be carefully considered in this particular subgroup.

**CRD commentary**

The review addressed a clearly defined question and criteria for the inclusion of studies were outlined and replicable. The authors searched only one appropriate database and one web site for clinical trials, which meant the search was limited and there was the potential for missed studies and publication bias. Restriction of the review to studies published in English language meant there was risk of language bias. Steps were taken to minimise errors and bias for data extraction, but the methods were not reported for study selection and quality assessment.

Methodological quality was assessed and the quality of the included studies was generally good. However, details of randomisation in the studies, and the number of patients who dropped out or who were lost to follow-up were not reported. The authors’ decision to combine the results in a meta-analysis appeared to be justified, as the differences in participants between studies were small. The authors’ conclusions are based on the evidence presented, but the potential for missed studies because of the limited search and the limited information presented on study quality means the results should be interpreted with some caution.

**Implications of the review for practice and research**

**Practice:** The authors stated that potential benefits of CRT should be carefully measured against the risk of adverse events associated with device implantation in asymptomatic patients.

**Research:** The authors did not state any implications for research.

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