Meta-analysis: cardiac resynchronization therapy for patients with less symptomatic heart failure

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CRD summary
This review concluded that cardiac resynchronization therapy was beneficial for patients with reduced left ventricular ejection fraction, symptoms of heart failure, and prolonged QRS, regardless of baseline New York Heart Association functional class. The authors’ conclusions were consistent with the evidence presented and are likely to be reliable.

Authors’ objectives
To assess the benefits and harms of cardiac resynchronization therapy in patients with advanced heart failure and those with less symptomatic disease.

Searching
PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Health Technology Assessment Database, International Pharmaceutical Abstracts, Science Citation Index Expanded, NLM Gateway, Conference Papers Index, OCLC PapersFirst, OCLC ProceedingsFirst, ProQuest Dissertations and Theses, US Food and Drug Administration website, and relevant clinical trials websites were searched from 1950 to December 2010. Search terms were reported. No language restrictions were applied to the search. Reference lists of retrieved papers and relevant proceedings booklets from meetings were reviewed. Authors and device manufacturers were contacted for additional studies and unpublished data.

Study selection
Randomised controlled trials (RCTs) that compared cardiac resynchronization therapy with inactive pacing, right or left ventricular pacing alone, implantable cardioverter-defibrillator alone, or usual care, in adult patients with heart failure and left ventricular ejection fraction (LVEF) 0.40 or less, were eligible for inclusion. To be eligible, a trial had to include more than 25 participants and report all-cause mortality (primary outcome), and at least one of the following (secondary outcomes): heart failure hospitalisation, change in LVEF, or change in functional outcomes including New York Heart Association (NYHA) class symptoms, quality of life, or six-minute walk test.

Most of the patients in included trials were male (46 to 100%) and had prolonged QRS duration. The mean age of included patients ranged from 57 to 74 years. Most trials excluded patients with atrial fibrillation. Most of the patients in control groups had an implantable cardioverter-defibrillator.

Two reviewers independently selected studies and resolved disagreements by consensus.

Assessment of study quality
Two reviewers independently assessed risk of bias of the included studies using the Cochrane Collaboration criteria and judged the risk as high, low or unclear.

Data extraction
Numbers of participants and events for dichotomous outcomes were extracted to enable the calculation of risk ratio (RR) and 95% confidence interval (CI); means and standard deviations were extracted for calculating mean difference (MD) and 95% confidence intervals for continuous outcomes. For cross-over trials, data from the last observation before cross-over were of interest. Some authors were contacted for clarification or additional data.

Two reviewers independently extracted data.

Methods of synthesis
Risk ratio or weighted mean difference (WMD), and 95% confidence intervals, were pooled in a meta-analysis by
intention-to-treat using a random-effects model. Heterogeneity between trials was assessed by the $I^2$ statistic.

Meta-regression analyses were performed to explore the efficacy of cardiac resynchronization therapy in pre-specified subgroups. Sensitivity analysis was performed to determine whether the results were robust.

Publication bias was assessed by a funnel plot.

**Results of the review**

Twenty-five RCTs ($n=9,082$ patients), of which 14 were newly identified trials from updated searches, met the inclusion criteria. Six trials were described as low risk of bias, six showed high risk of bias, and for 13 the risk of bias was unclear. Fourteen trials were double-blind, eight were single-blind, and three were open-label trials. Patients in 18 trials were randomly assigned after successful device implantation, but in six trials patients were randomised before device implantation. Sixteen RCTs used parallel study design and nine trials involved cross-over design. Duration of follow-up ranged from one to 40 months.

There was a significant reduction in all-cause mortality with cardiac resynchronization therapy (RR 0.81, 95% CI 0.72 to 0.90; 25 trials, $n=9,082$ patients). This finding did not change in any of the sensitivity analyses.

Cardiac resynchronization therapy was associated with a reduction in the risk for heart failure hospitalisation (RR 0.69, 95% CI 0.58 to 0.82; 15 trials, $n=7,012$ patients) and improved left ventricular ejection fraction (WMD 0.0364, 95% CI 0.0189 to 0.0539; 11 trials, $n=3,202$ patients).

Cardiac resynchronization therapy was associated improved functional scores on the Minnesota Living with Heart Failure Questionnaire (WMD 6.56 points, 95% CI 4.08 to 9.04; 14 trials, $n=4,283$ patients) and six-minute walk test (WMD 17.50 minutes, 95% CI 7.05 to 27.94; 15 trials, $n=3,475$ patients).

There was significant heterogeneity between trials in the outcomes assessed except for all-cause mortality.

There was no statistically significant difference in effect of cardiac resynchronization therapy between the subgroups of patients with New York Heart Association (NYHA) class I/II and NYHA class III/IV symptoms in all the outcomes assessed, except that functional outcomes did not improve appreciably in patients with milder symptoms (NYHA class I/II). Left ventricular pacing alone did not affect any of the outcomes.

The implantation success rate for cardiac resynchronization therapy was 94.4% (95% CI 93.8% to 94.8%). The rates of complications for cardiac resynchronization therapy included mechanical complications in 3.2% (95% CI 2.8 to 3.6) of patients, device malfunction in 1.9% (95% CI 1.5% to 2.4%), lead problems in 6.2% (95% CI 5.6 to 6.8), and infections in 1.4% (95% CI 1.1 to 1.7). Peri-implantation death occurred in 0.3% (95% CI 0.2 to 0.5) of patients undergoing cardiac resynchronization therapy.

The funnel plot suggested potential publication bias for heart failure hospitalisation.

**Authors’ conclusions**

Cardiac resynchronization therapy was beneficial for patients with reduced left ventricular ejection fraction, symptoms of heart failure, and prolonged QRS, regardless of baseline New York Heart Association functional class.

**CRD commentary**

This review addressed a well-defined question in terms of participants, interventions, outcomes, and study design. Published and unpublished data were sought from relevant sources. To minimise bias and errors during the review process, two reviewers independently selected trials, extracted data, and assessed the quality of the included trials.

Quality of the included studies was assessed using appropriate criteria. The characteristics of the individual trials were presented. Potential sources of heterogeneity were explored; the method of synthesis appeared to be appropriate. Sensitivity analysis demonstrated that the results were robust to changes in the factors considered.
The authors’ conclusions were consistent with the evidence presented and are likely to be reliable.

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

**Practice:** The authors stated that the current evidence supports the expansion of the indications for cardiac resynchronization therapy to less symptomatic patients with heart failure who have ventricular ejection fraction if less than 0.35 and QRS duration of 120ms and are in sinus rhythm.

**Research:** The authors stated that further research is needed to assess the effectiveness of cardiac resynchronization therapy in patients with atrial fibrillation, and to establish a uniform definition for cardiac resynchronization therapy response and case selection to enable the implantation of cardiac resynchronization therapy devices in patients who are most likely to benefit.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.