Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review

CRD summary
This review found that cardiac resynchronisation therapy added to drug therapy, compared with drug therapy alone, reduces mortality and improves symptoms and quality of life in patients with heart failure (left ventricular systolic dysfunction). This was a well-conducted review and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To evaluate the efficacy (outcomes in randomised trials), effectiveness (outcomes in clinical settings), safety and cost-effectiveness of cardiac resynchronisation therapy (CRT) in patients with left ventricular systolic dysfunction (LVSD).

Searching
MEDLINE, PubMed, the Cochrane CENTRAL Register, the Cochrane Database of Systematic Reviews, DARE, HTA, EMBASE, Science Citation Index Expanded, International Pharmaceutical Abstracts, NLM Gateway, OCLC ProceedingsFirst, OCLC PapersFirst, CRISP, various trial registries and U.S. Food and Drug Administration reports were searched. The authors also searched abstracts from Heart Rhythm Society annual meetings, screened the reference lists of included studies and review articles, and contacted study authors for additional citations. Unpublished studies and additional data were sought from device manufacturers. No language restrictions were imposed and the search terms used were reported. The searches were performed in November 2006.

Study selection
Studies that reported mortality, hospitalisation, functional outcomes, or peri- or post-implantation complications with CRT in patients with LVSD (LV ejection fraction of 0.35 or less) were eligible. Randomised controlled trials (RCTs) that compared CRT or combined CRT-implantable cardioverter defibrillator (ICD) devices with placebo pacing, right ventricular pacing or drug therapy alone were eligible for the review of efficacy; observational studies with contemporaneous comparison groups were eligible for the review of effectiveness; and RCTs and observational studies (including uncontrolled studies) were eligible for the review of safety. Inclusion criteria for the cost-effectiveness studies were not reported in the paper. Most of the participants in the included studies had prolonged QRS duration and New York Heart Association (NYHA) class 3 or 4 heart failure symptoms despite optimal drug therapy. The majority of participants (over 70%) were male and the average age was around 65 years.

Two independent reviewers selected the studies.

Assessment of study quality
Validity was assessed using the Jadad scale and evaluation of adequacy of allocation concealment for RCTs, and the Downs and Black checklist for observational studies.

Two independent reviewers performed the validity assessment.

Data extraction
For dichotomous outcomes, data on numbers of events in CRT and comparison groups were used to derive relative risks (RRs) and associated 95% confidence intervals (CIs). For continuous outcomes, means and standard deviations for each group were extracted. Data on complications and length of follow-up were used to calculate the rates of complications.

Two independent reviewers extracted the data.

Methods of synthesis
The studies were pooled by meta-analysis using random-effects models. Pooled RRs with 95% CIs were calculated for dichotomous outcomes and weighted mean differences with 95% CIs for continuous outcomes. Statistical heterogeneity was assessed using the $\chi^2$ test and $I^2$ statistic. Meta-regression analysis was used to explore the efficacy of CRT in different patient subgroups.

**Results of the review**

Fourteen RCTs (n=4,420) were included in the efficacy review, 106 studies (n=9,209) in the effectiveness review and 89 studies (n=9,677) in the safety review.

In RCTs comparing CRT plus best medical therapy with medical therapy alone and CRT plus ICD with ICD alone, CRT significantly reduced hospitalisation for heart failure (pooled RR across all studies 0.63, 95% CI: 0.43, 0.93) and all-cause mortality (pooled RR 0.78, 95% CI: 0.67, 0.91). CRT plus ICD was not significantly superior to CRT alone for either outcome. Significant heterogeneity was detected for hospitalisation. CRT was also associated with improvements in NYHA class, LV ejection fraction and quality of life. No clear subgroup effects were apparent in the RCTs of CRT.

In the effectiveness review, both survival over time in recipients of CRT and CRT plus ICD and pooled effectiveness estimates for functional outcomes were similar to those seen in RCTs.

In the safety review, implantation success rate for CRT was 93%; peri-implantation mechanical complications occurred in 4.3% of procedures and peri-implantation deaths in 0.3%. Other outcomes and analyses were reported.

**Cost information**

Based on five published decision analyses, CRT-alone devices were cost-effective compared with medical therapy alone in patients eligible for RCTs. The incremental cost per quality-adjusted life year (QALY) ranged from $107,800 in an early study to $10,192. Combined CRT-ICD devices were also cost-effective compared with medical therapy ($24,360 per QALY gained), but their cost-effectiveness relative to CRT alone was uncertain.

**Authors' conclusions**

CRT reduces morbidity and mortality in patients with LVSD and NYHA class 3 or 4 heart failure symptoms when combined with optimal medical therapy. The incremental benefits of combined CRT-ICD devices over CRT alone remain uncertain.

**CRD commentary**

This review had clear inclusion criteria for the intervention, participants and outcomes. The inclusion criteria for study designs reflected the complexity of the review, which distinguished between efficacy and effectiveness and also involved a separate review of safety. The authors searched a broad range of sources without language restrictions, and both published and unpublished studies were sought; publication bias was not reported to have been assessed. The study selection, validity assessment and data extraction were performed by two reviewers independently, thereby reducing the risk of error and bias affecting the review process. Validity was assessed using standard checklists but it is unclear whether the results were used in the analysis. Full details of the included studies were presented in the paper and the full report (see Other Publications of Related Interest). Efficacy data from RCTs were synthesised by meta-analysis. Statistical heterogeneity was assessed and differences between the studies were explored using meta-regression. Heterogeneity was significant for hospitalisation, suggesting that pooling may not have been appropriate for this outcome. Safety results were mainly presented as absolute risks in patients with a CRT device, and CRT was not compared with other interventions. Overall, this was a well-conducted review and the authors' conclusions are likely to be reliable.

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

Practice: The authors did not state any implications for practice.

Research: The authors stated that a prospective registry should be established to estimate the benefits of CRT and CRT-ICD devices in routine practice. They also recommended further studies to compare CRT devices with CRT-ICD devices and to determine which patients are most likely to benefit from each type of device.
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Record Status
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.