Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that cardiac resynchronization therapy effectively reduced adverse events in heart failure patients with a baseline QRS interval of 150 milliseconds or more, but not in patients with a QRS of less than 150 milliseconds. Given the small evidence base of uncertain quality and potential for review bias, the authors' conclusions should be interpreted with some caution.

Authors' objectives
To assess the effects of cardiac resynchronization therapy on adverse clinical events in patients with heart failure and moderate versus severe prolonged QRS duration.

Searching
MEDLINE and SCOPUS were searched up to March 2011. Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to the first quarter of 2010; search terms were available online.

Study selection
Randomised controlled trials (RCTs) that assessed the effects of cardiac resynchronisation therapy on clinical end points (death and hospitalisation) in patients with heart failure and moderate (<150 milliseconds) versus severe (≥150 milliseconds) prolonged QRS duration were eligible for inclusion if they had a non-cardiac resynchronisation therapy control. Eligible trials were required to enable implantable cardioverter defibrillator implantation in both trial arms. Crossover designs were excluded.

Included studies were of patients in New York Heart Association (NYHA) classes one to four. Mean/median age of patients ranged from 63 to 67 years. Most patients were male. Mean or median ejection fraction at baseline ranged from 21% to 27%. Between 23% and 41% of patients had diabetes. Between 33% and 62% had no-ischaemic heart failure. Approximately two thirds of the patients were in the severely prolonged QRS group and approximately one third were in the moderately prolonged QRS group. Where reported, most patients' heart failure was due to left bundle branch block, but in some it was due to right bundle branch block. Included trials compared cardiac resynchronisation therapy with medical therapy or no cardiac resynchronisation therapy. At baseline, patients received angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker, β-blocker or spironolactone. Outcomes, including all-cause mortality and heart failure hospitalisation, were combined to report a composite clinical end point.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
The authors did not state that they formally assessed study quality, but they reported on blinding, withdrawals and intention-to-treat (ITT) analysis.

Data extraction
Two reviewers independently extracted effect sizes (hazard ratios and odds ratios) and 95% confidence intervals (CIs) from the primary studies. Primary authors were contacted for further data, where necessary.

Methods of synthesis
A fixed-effect model was used to pool hazard ratios and odds ratios, along with their 95% CIs, to calculate log-transformed risk ratios (RRs) for the composite clinical end point; a random-effects model where there was evidence of statistical heterogeneity (I²>40%). Statistical heterogeneity was assessed using the Cochran Q and I² statistics.

Meta-regression was undertaken to assess the impact of baseline QRS duration on the effect of cardiac resynchronisation therapy.
Resynchronisation therapy on composite clinical events (log RR). Sensitivity analyses were performed to assess the effects of NYHA class (NYHA classes III and IV only versus NYHA classes I and II only), use of implantable cardioverter defibrillator versus no implantable cardioverter defibrillator, inclusion only of trials that reported hazard ratios (HRs) and by removal of one trial at a time.

Publication bias was assessed using funnel plots and Begg’s test.

**Results of the review**

Five RCTs were included in the review. These included 5,813 participants overall, 3,624 with severely prolonged QRS and 2,189 with moderately prolonged QRS. Mean follow-up duration ranged from 11.9 to 40 months. Two trials were double-blinded. All trials used ITT analysis. Withdrawals and crossovers were reported in the review.

Cardiac resynchronisation therapy significantly reduced the risk of composite clinical events in patients with severely prolonged QRS (RR 0.60, 95% CI 0.53 to 0.67, I²=32.1%), but had no effect on patients with moderately prolonged QRS. The difference between the two prolonged durations was significantly different (p<0.001).

Meta-regression showed a statistically significant relationship between baseline QRS duration and log RR (p<0.001); beneficial effects of cardiac resynchronisation therapy were evident with QRS intervals of 150 milliseconds and the magnitude of benefit increased with further increases in QRS duration. Sensitivity analyses did not significantly alter the findings.

There was no evidence of publication bias according to funnel plots and Begg's test.

**Authors' conclusions**

Cardiac resynchronisation therapy was effective in reducing adverse clinical events in patients with heart failure and a baseline QRS interval of 150 milliseconds or more, but did not reduce events in patients with a QRS of less than 150 milliseconds. This has implications for the selection of patients for this treatment.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. Appropriate databases were searched for eligible trials. It was unclear whether there were language restrictions and whether or not unpublished data were sought and so potentially relevant studies may have been missed. Formal assessment showed no evidence of publication bias, but the reliability of the assessment was questionable as only five studies were assessed. The authors reported on some areas of quality, but it was difficult to determine the overall quality of the trials. Data extraction was undertaken in duplicate. The authors did not state whether the quality criteria and study selection were performed in duplicate, so reviewer error and bias could not be ruled out. Details on the intervention and control regimens were limited and trials differed in terms of patients receiving implantable cardioverter defibrillator implantation. There was some evidence of statistical heterogeneity and this was investigated further using appropriate methods. The authors highlighted some limitations with the review, which included variations in composite end points across trials, approximation of cutoff values and use of different statistical measures.

The authors’ conclusions appeared to reflect the evidence, but given the small number of trials of uncertain quality and potential for review bias, the conclusions should be interpreted with some caution.

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

**Practice:** The authors stated that lack of benefit in patients with QRS of less than 150 milliseconds was not limited to patients with NYHA I and II but also appeared in NYHA III and IV patients. This had important implications for patient selection for this treatment technique.

**Research:** The authors stated that individual patient level analysis of existing clinical trials was needed to examine whether a subset of patients with moderately prolonged QRS may benefit from cardiac resynchronisation therapy, in order to inform new recommendations and refine QRS cutoffs.

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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.