Cost-effectiveness of cardiac resynchronization therapy: results from the CARE-HF trial

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of cardiac resynchronisation therapy (CRT) as an adjunct to medical therapy in the treatment of heart failure from cardiac dyssynchrony. The study assessed both CRT implants and CRT combined with an implantable defibrillator.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients aged at least 18 years who had evidence of heart failure for at least 6 weeks and were New York Heart Association (NYHA) Class III or IV with a left ventricular ejection fraction of less than 35%, a left ventricular end-diastolic dimension of at least 30 mm, and a QRS interval of greater than 120 milliseconds (ms). Patients with a QRS interval between 120 and 149 ms had to also have two of the following: an aortic pre-ejection delay of greater than 140 ms, an interventricular mechanical delay of more than 40 ms, or delayed activation of the posterolateral left ventricular wall.

Setting
The setting was secondary care. The economic study was carried out in 12 European countries.

Dates to which data relate
The effectiveness and resource use data related to 2001. The unit cost data related to 2004/05.

Source of effectiveness data
The effectiveness data were derived from a single study, details of which have been published (Cleland et al. 2001 and 2005, see ‘Other Publications of Related Interest’ below for bibliographic details).

Link between effectiveness and cost data
The resource use data were collected prospectively using the same patient sample as that used in the effectiveness study.

Study sample
The authors did not report details of power calculations or the method of sample selection in this study. The total sample size was 813, with 404 assigned to medical therapy alone and 408 assigned to CRT and medical therapy. The numbers of exclusions and patients who refused to participate were not reported.
Study design
The study was a multi-centre, randomised controlled trial (RCT) that was set in 12 European countries. The method of randomisation was not reported. The protocol specified a minimum follow-up of 18 months and the mean duration of follow-up was 29.4 months (range: 18.0 to 44.7). The authors did not report details of blinding or of the loss to follow-up. Full details of the clinical trial have been published elsewhere (Cleland et al. 2001 and 2005).

Analysis of effectiveness
The analysis of effectiveness was based on all patients included in the study. The authors did not specify that the analysis was conducted on an intention to treat basis, but the type of intervention studied means that it is almost certain to have been. The primary health outcome was time to death from any cause or unplanned hospitalisation for a major cardiovascular event. The authors did not report in this paper whether the groups were shown to be comparable at analysis.

Effectiveness results
The discounted within-trial restricted mean length of survival (until death or censorship) was 1.92 years (interquartile range, IQR: 1.51 to 2.52) with medical therapy alone and 2.02 years (IQR: 1.62 to 2.53) with CRT and medical therapy.

The gain in survival with CRT was 0.10 (95% confidence interval, CI: -0.01 to 0.21).

A discount rate of 3.5% was used.

Clinical conclusions
The authors concluded that the addition of CRT to medical therapy increases the quantity of life.

Measure of benefits used in the economic analysis
The measure of health benefits used was the quality-adjusted life-years (QALYs). The patients in the study completed the EQ-5D, a generic valuation matrix at baseline and at 90 days post-randomisation. They also completed a disease-specific quality of life questionnaire, the Minnesota Living with Heart Failure Questionnaire (MLWHF), at baseline, 90 days post-randomisation, 18 months post-randomisation and at the end of the study. The authors modelled the relationship between the change in MLWHF score and change in EQ-5D score in order to predict utility values at 18 months and at the end of the study. Utility values of zero were applied from time of death or censorship.

Direct costs
The study included the direct costs to the health service. The comprised the costs of implantation procedures and the type of implant, the costs of hospital inpatient stay according to ward type, the costs of outpatient, cardiologist and primary care visits, the length of stay in nursing or residential homes or in a rehabilitation centre, and the costs of cardiovascular medication. The resource quantities and the costs were reported separately. The implant costs were estimated from the average list price across the countries included in the study. Other unit costs were based on UK National Health Service reference costs and published drug pricing lists. Discounting was relevant and a rate of 3.5% per annum was used, in line with recommendations by the UK Treasury. The study reported the average costs. The price year was not stated but it may be assumed to be 2004/05.

Statistical analysis of costs
The authors used bootstrapping to calculate CIs for the costs. Patients were assumed to incur zero further costs following censoring. Administrative censoring may have been informative for costs as they accumulated over time, so this approach was not appropriate.
**Indirect Costs**
The indirect costs were not included in the analysis, which was appropriate given the study perspective.

**Currency**
Euros (EUR). A conversion rate of EUR 1.47 to 1.00 was used.

**Sensitivity analysis**
Several one-way sensitivity analyses were conducted to investigate uncertainty in modelling assumptions and variability in the unit costs.

**Estimated benefits used in the economic analysis**
The authors estimated that patients receiving medical therapy alone gained 1.19 QALYs (IQR: 0.65 to 1.73) within the trial, compared with 1.42 QALYs (IQR: 1.01 to 1.92) for patients receiving CRT and medical therapy. A discount rate of 3.5% per annum was used.

The mean difference in QALYs between the two groups was 0.22 (95% CI: 0.13 to 0.32).

**Cost results**
The average cost for patients receiving medical therapy alone was EUR 15,795 (IQR: 3,684 to 18,185) over the course of the trial, using a discount rate of 3.5% per annum. The corresponding cost for patients receiving CRT and medical therapy was EUR 20,110 (IQR: 9,443 to 22,540).

The mean difference in costs between the two groups was EUR 4,316 (95% CI: 1,327 to 7,485).

**Synthesis of costs and benefits**
The costs and benefits were combined to calculate the cost per QALY.

An incremental analysis was performed.

The addition of CRT to medical therapy was estimated to cost EUR 19,319 per QALY gained (95% CI: 5,482 to 45,402).

A discount rate of 3.5% per annum was applied to the costs and benefits.

The results did not appear to be sensitive to the ranges and assumptions tested in the sensitivity analyses.

**Authors' conclusions**
Cardiac resynchronisation therapy (CRT) devices represented a cost-effective use of health care resources.

**CRD COMMENTARY - Selection of comparators**
Since the study was a trial-based economic analysis, the comparators were determined by the treatments assessed in the trial. Medical therapy is also part of current practice in the study setting. You must decide whether the comparators are relevant in your own setting.

**Validity of estimate of measure of effectiveness**
The estimate of effectiveness was derived from a single study. The randomised controlled design of the study was appropriate for the study question. The authors did not discuss whether the study sample was appropriate for the study
question, but they stressed that the results of the study applied to those patients with the same characteristics as those included in the study. The authors did not discuss whether the groups were shown to be comparable at analysis. The analysis of effectiveness was handled credibly. To fully assess the internal validity of the trial, the reader should refer to the main clinical trial paper (Cleland et al. 2001).

Validity of estimate of measure of benefit
The estimation of benefits was based in part on direct measurement of utility scores using the EQ-5D, and partly on a prediction model. The prediction model might have been appropriate, but the approach to missing data was unclear. The authors stated that quality of life data were available for greater than 87% of participants, so the estimation of QALYs might have been based on a complete case analysis. The results of the trial were not extrapolated to a lifetime perspective, which the authors acknowledged might have underestimated the benefits of CRT.

Validity of estimate of costs
All the categories of cost relevant to the UK health service cost perspective were included in the analysis. The authors did not exclude any cost components. The costs were reported separately from the quantities, which improves the generalisability of the study results. The resource use data were gathered prospectively for the same patient sample as that used in the effectiveness analysis. A non-parametric bootstrap method was used to generate CIs around the costs, and this was appropriate. However, patients who were censored were assigned a cost of zero after the point of censorship. This was not appropriate as administrative censoring may be informative for costs, and so may lead to a biased estimate. The unit costs were primarily obtained from published pricing lists and cost databases in the UK. However, although a UK health service perspective was adopted, the cost of CRT and implantable defibrillator devices was based on the average price of all the countries included in the trial. A statistical analysis of the prices was not conducted. The date to which the prices related was not specified, but it could be inferred.

Other issues
The authors compared their results with those from other studies, finding them to be in disagreement with some studies that were based on other trials. A more informative analysis could be based on a synthesis of the results from all relevant trials. The authors recommended that the results only be applied to patients who could have been included in the effectiveness study. They stated that the utility scores in the UK population might be similar to those elicited in other countries. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors acknowledged that the within-trial nature of the analysis does not represent an appropriate time horizon for the analysis.

Implications of the study
The authors recommended that the effectiveness of CRT be studied in patient populations excluded from the effectiveness study. They also recommended that an incremental analysis be conducted to compare CRT alone with CRT combined with an implantable defibrillator.

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Other publications of related interest


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