Cardiac resynchronization therapy: a cost or an investment?

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Cost-effectiveness estimates can help optimize use of available financial resources and this is especially relevant for implementation of cardiac resynchronization therapy (CRT), given the high upfront costs and the timescale of expected benefits. All available cost-effectiveness estimates for devices with (CRT-P) or without (CRT-D) a defibrillator are based on results of randomized trials of selected patients, with a relatively brief follow-up. Extrapolation suggests that the cost effectiveness of CRT may become more favourable as time horizons increase. Using a lifetime time horizon and comparison with optimal medical therapy, the cost effectiveness of both CRT-P and CRT-D appears to meet the $50 000/QALY benchmark commonly used for health-care interventions in the USA, as well as similar thresholds used in Europe. The absence of direct comparisons of the efficacy/effectiveness of CRT-P and CRT-D hampers cost-effectiveness comparisons, and so clinical judgment in the context of current evidence supporting the benefits of cardioverter-defibrillators may provide a rational basis for choosing between CRT-P and CRT-D. Efforts are currently being dedicated to improve CRT response rates by improved patient selection and, reasonably, any improvement in this field will translate into improved effectiveness, and therefore into improved cost effectiveness. The extended longevity of CRT devices will also positively impact cost-effectiveness estimates.

Keywords Cost • Cost effectiveness • Cost utility • Heart failure • Health economics

Introduction

In just a few years, cardiac resynchronization therapy (CRT) has emerged as a key player in the treatment of heart failure. Based on clinical evidence of efficacy and effectiveness, indications for CRT are clearly defined in consensus guidelines on heart failure management.1–3 However, the implementation of such indications is hampered by the high upfront costs of CRT devices, among other factors. This article will consider how economic tools may help address cost and equity issues that are inherent in the implementation of CRT in the ‘real-world’ setting of appropriately selected patients with moderate-to-severe heart failure.

We will address the question of how economic approaches, based on cost-effectiveness and cost-benefit analyses, could provide insights to help health-care providers decide when to implement CRT in appropriately selected patients with moderate-to-severe heart failure despite optimized medical therapy. Such an approach appears topical given the difficulties encountered by many countries in equitably implementing the current international guidelines that do not specifically address economic considerations.4,5 We will not address the issue of cost effectiveness of CRT in the setting of mild heart failure, a distinct setting where economic analysis of major trials are awaited.6,7

The clinical premise: effectiveness of cardiac resynchronization therapy

Cardiac resynchronization therapy is currently deployed to reduce morbidity and mortality rates in patients with moderate-to-severe heart failure.1–3 Solid evidence of the beneficial effects of CRT in appropriately selected patients derives from a series of major randomized clinical trials8 that provided evidence of a series of beneficial effects, summarized in Table 1. The systematic review published by McAlister et al.8 considered 14 randomized trials of CRT efficacy (involving 4420 patients), and 106 observational studies of effectiveness (9209 patients) and concluded that appropriate use of CRT has the potential to reduce all-cause mortality by 22% (95% CI, 9–33%) and hospitalizations by 37% (95% CI, 7–57%).8 In an effectiveness study of 3865 elderly Medicare patients with heart failure who were treated with a prophylactic CRT-defibrillator (CRT-D) device, comparison with matched control patients not receiving device therapy suggested long-term survival benefits similar to those reported in recent primary-prevention trials.9 So, taken together, the available evidence strongly supports widespread implementation of CRT in appropriately selected patients.

Current consensus guidelines1–3 recommend specific indications for the implementation of CRT with (CRT-D) or without...
Table I Beneficial effects of cardiac resynchronization therapy in patients with moderate-to-severe heart failure (New York Heart Association III–IV class) with ventricular dyssynchrony.

- Improvement of NYHA class (≥1 class reduction)
- Improvement of exercise capacity at 6 min walk test (by 20–30%)
- Improvement of VO₂ peak at cardiopulmonary exercise testing (by 10–40%)
- Improvement of central haemodynamic parameters
- Reduction of ventricular volumes and of mitral regurgitation
- Improvement of quality of life (by 30–60%)
- Reduction of heart failure hospitalizations
- Improvement in overall survival

Financial issues as barriers to cardiac resynchronization therapy implementation

As many as 7–20% of the patients seen by cardiologists involved in heart failure management may meet current eligibility criteria for CRT. About half the patients with an indication for CRT also fulfill eligibility for a cardioverter-defibrillator. Factors that may be implicated in the wide variations of CRT usage in ‘real-world’ routine clinical practice include the financial difficulty in accepting a treatment with such high upfront costs in the context of limited health service budgets, the increasing number of eligible patients, inappropriate reimbursement, absence of quality-of-care assurance systems, and more general cultural reservations (including limited training and familiarity with guidelines).

On financial grounds, the decision when to implant CRT devices and the choice between CRT-P and CRT-D may both have important financial implications, especially in view of the continually rising burden of heart failure in the general population. As with implantable cardioverter-defibrillators, CRT devices raise financial concerns as a consequence of the high upfront cost that administrators of implanting centres have to face when purchasing the systems (device and leads). Despite reductions in the price of CRT-D systems in the last few years, their relatively high cost in comparison with other devices (coronary stents, prosthetic cardiac valves, catheters for electrophysiologic procedures, etc.) highlights the need to move from a purely financial perspective based merely on costs to an economic perspective based on the analysis of the relationship between costs and outcomes. Despite the mounting costs that health-care systems have had to face in recent years, in most European countries outside the UK and Scandinavia the balancing of benefits against costs has not generally been a primary criterion for deciding whether a medical treatment should be covered by public services. Instead, both policymakers and health-care providers have generally focused on cost projections, with a consequent tendency to limit or even reject costly new treatments, despite their proven clinical efficacy. In other words, consideration of the effects of adopting a new treatment may often be based largely on financial concerns rather than in-depth economic analysis.

Another argument in favour of an economic approach to implementation policies regards social equity. Within Europe, marked variations in CRT implantation rates and choice of device (CRT-P vs. CRT-D) exist that cannot readily be explained only in terms of national wealth or health service budgets. Other factors may influence CRT-P and CRT-D implementation rates, including implementation policies and tools, strategies for patients’ referral, clinical cultures, etc. Policies that take into account information on cost effectiveness in conjunction with clinical effectiveness can provide an important implementation tool to redress such imbalances (in terms of both possible overtreatment and undertreatment). Treatment imbalances can raise politically relevant questions of national equity. The emerging ‘epidemic’ of heart failure and the consequent increasing cost of heart failure management at a national level may prompt less affluent contexts to address the issue of CRT-D and/or CRT-P implant coverage in a perspective of cost effectiveness. It has been authoritatively argued that global inequity in cardiovascular health-care provision is one of the greatest health-care challenges of our time.

Economic evaluations: possible approaches

Cost-effectiveness and cost-benefit analyses have been proposed in various fields of medicine to determine which alternative treatment is most likely to provide maximum health benefits for a given level of financial resources, or which treatment provides a given level of health benefits at the lowest cost. Cost-effectiveness estimates express clinical outcome in terms of ‘years of added life’ and cost utility in terms of ‘quality-adjusted life years’; on the other hand, cost-benefit analysis directly assigns a monetary value to therapeutic benefits. All are analytical methods of weighing up the benefits and costs of given medical treatments in order to provide a formal basis for implementation decisions.

Cost-effectiveness ratios

Cost-effectiveness analysis is designed to evaluate the cost of any therapeutic intervention with respect to its predictable outcome benefits. The cost of a therapy includes both the direct costs (initial cost of therapy, costs to maintain therapy, and costs caused by any adverse effects) and the indirect costs paid by...
patients, their families, and/or the community. Effectiveness is measured as the mean extra number of years survived as a result of a treatment. Incremental cost-effectiveness analysis involves comparison of alternative therapeutic strategies. The cost-effectiveness ratio is commonly expressed as dollars per year of life saved ($/YLS). Various affordability thresholds have been proposed. According to one proposal,6,20 a treatment can be considered very attractive if the cost-effectiveness ratio ranges between 0 and 20 000$/YLS; attractive between 20 000 and 40 000$/YLS; borderline between 40 000 and 60 000$/YLS; unfavourable between 60 000 and 100 000$/YLS; and absolutely unfavourable above 100 000$/YLS. Other approaches propose fixed thresholds, such as $50 000/QALY, a figure derived from renal dialysis, which is taken as a standard for decisions taken in the contest of Medicare programs.21 In the UK, the National Institute of Clinical Excellence seems to apply a cost-effectiveness threshold range of £20 000–30 000/QALY.22 The World Health Organization (WHO) proposed a rather different approach, involving calculation of country-specific cost-effectiveness thresholds, corresponding to three times the gross domestic product per capita.23 This relative approach results in over 20-fold variations between cost-effectiveness thresholds suggested for the poorest and richest countries around the world (with $ per disability-adjusted life year values ranging from a little over $4000 in some African countries to over $90 000 in North American countries).23 It can be argued that this approach recognizes the existence of wide variations in what different national economies can reasonably afford, and that it may provide a more flexible approach to the interpretation and practical use of cost-effectiveness analysis results.

Cardiac resynchronization therapy
cost-effectiveness analyses: what is available?

Available studies clearly indicate that in heart failure patients with left ventricular systolic dysfunction, prolonged QRS duration, and NYHA functional class III–IV, CRT reduces mortality (mainly through a reduction in deaths from progressive heart failure), and hospitalizations for heart failure. The reductions in relative risks of mortality and hospitalization vs. controls8 can greatly impact on the outcome of patients with moderate-to-severe heart failure fulfilling guideline indications for CRT. It is well known that the expenditures for hospitalizations are the major determinants of overall costs for heart failure.11 Thus, appropriate use of CRT may eventually exert a favourable effect on the overall costs of care for heart failure patients, accompanied by a favourable cost-effectiveness profile. Several studies have estimated the cost effectiveness and/or cost utility of CRT-P or CRT-D in comparison with optimized medical therapy within different time horizons, and using different modelling assumptions/contexts (Table 2).24–34 The diversity in the economic estimates regarding CRT-P and CRT-D is unsurprising given the differences in data sources, assumptions, modelling, time horizons, and perspectives (Table 2).

In general, the cost effectiveness of CRT appears to improve as the time horizon lengthens (extrapolating beyond the duration of available clinical trials). Furthermore, when estimated using a lifetime time horizon and compared with optimal medical therapy, the cost-effectiveness values for both CRT-P and CRT-D appear to be in line with the benchmark of $50 000/QALY, commonly used for health-care interventions in the USA, as well as with similar thresholds used in Europe21 and threshold values suggested by the WHO for many developed regions of the world.23

The choice between delivery of CRT by CRT-P or CRT-D implies a considerable (two- to three-fold) difference in device purchase costs. Unfortunately, it is difficult to compare the cost effectiveness of CRT-P and CRT-D, given the limited available data on the relative efficacy and effectiveness of these two strategies (and the consequent analytical dependence on assumptions). In our view, decision-making between CRT-P and CRT-D may be based on judgments regarding the patient’s clinical profile, in conjunction with current evidence on the added benefit of defibrillator treatment, together with cost-effectiveness considerations.20 Close multidisciplinary collaboration10,11 would be an essential premise for such an approach.

Cost-effectiveness perspectives for cardiac resynchronization therapy

Since there is no universally accepted definition of positive response to CRT, the proportion of ‘responders’ varies according to the type of response (clinical/echocardiographic) analysed.8,35 In general, between 25 and 35% of patients appear not to respond to CRT.8 However, the pattern of response can be analysed in more detail, on the basis of the extent of left ventricular reverse remodelling at mid-term follow-up, taking into account the categories of echocardiographic super-responders, responders, non-responders, and negative responders, respectively, which are related to a different outcome at long term.36 Much effort has been dedicated to enhance response rates through improved patient selection (e.g. by direct assessment of mechanical instead of electrical dysynchrony).35 It is reasonable to expect that any improvement in this field will translate into improved effectiveness of CRT, and consequently into improved cost effectiveness.

All the currently available estimates of CRT cost effectiveness have been derived from the results of randomized clinical trials, a setting focused on highly selected patients that may differ from ‘real-world’ practice of candidates selection for CRT.14,15,18 Although a sensitivity analysis is provided in all economic analyses reporting cost-effectiveness and cost-utility estimates for CRT, it is still matter of debate how reliable such assessments may be for those patients with challenging clinical pictures (advanced age, atrial fibrillation or multiple co-morbidities), who have usually been excluded from randomized clinical trials. It is reasonable to expect that the spectrum of applications of CRT in the ‘real world’ could potentially be extended to a broader population of patients than that generally enrolled in randomized clinical trials (i.e. to older patients, with more co-morbidities), implanted in less experienced centres, with a high chance of less intensive follow-ups with regard to complications, device programming optimization, and medical therapy adjustments. Attempts to estimate not only the current use of CRT in the ‘real
## Table 2 Studies from the literature reporting estimates of costs, cost utility, or cost effectiveness of cardiac resynchronization therapy (with devices with or without defibrillation capabilities)

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<td><strong>Nichol et al., 2004</strong>&lt;sup&gt;24&lt;/sup&gt;</td>
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<td><strong>Feldman et al., 2005</strong>&lt;sup&gt;25&lt;/sup&gt;</td>
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<td><strong>Calvert et al., 2005</strong>&lt;sup&gt;26&lt;/sup&gt;</td>
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<td><strong>Banz et al., 2005</strong>&lt;sup&gt;27&lt;/sup&gt;</td>
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<td>At 1 year</td>
<td>€36,600 for CRT-P vs. control</td>
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<tr>
<td><strong>Fattore et al., 2005</strong>&lt;sup&gt;28&lt;/sup&gt;</td>
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<td>5-year perspective</td>
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<td><strong>Yao et al., 2007</strong>&lt;sup&gt;30&lt;/sup&gt;</td>
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<td>Aidelsburger et al., 2008</td>
<td>HF patients (NYHA III–IV), similar to COMPANION patients, implanted with CRT-D</td>
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**Methods**

- **CRT** = cardiac resynchronization therapy; **CRT-P** = cardiac resynchronization therapy device with pacing capabilities; **CRT-D** = cardiac resynchronization therapy device with defibrillation capabilities; **HF** = heart failure; **NYHA** = New York Heart Association; **COMPANION** = Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure; **CARE HF** = Cardiac Resynchronization in Heart Failure; **RCT** = randomized controlled trial.

- CRT-P benefits assumed after 6 years. Device longevity of 5 years.

### Results

- **Per QALY gained**
- **Per LY gained**

### Notes

- In the first decade of CRT, the longevity of implanted devices has been far from optimal, with many patients requiring device replacement after 3 to 5 years. Any extension of device longevity will favourably affect cost effectiveness and this is particularly important in view of the widening of indications for CRT, now including selected patients with mild to moderate heart failure (NYHA II patients), for whom a long life expectancy is predicted (with a consequent need for several device replacements).

- Remote monitoring through the implanted device could provide another way of improving the cost effectiveness of CRT, since data transmission may involve information not only on device functions and detected/treated arrhythmias (thus markedly reducing the need for most conventional follow-up visits), but also on the haemodynamic status and fluid overload (thus potentially facilitating out-of-hospital heart failure management).

**Conclusions**

In summary, knowledge regarding cost effectiveness may help administrations optimize use of available financial resources and promote equity. The spiralling costs that our health-care systems face are prompting greater interest in cost-effectiveness estimates. Such estimates may be very relevant for implementation of CRT, given the high upfront device costs and extended timescale of the expected benefits. Economic estimates for CRT-P and CRT-D depend on data sources, theoretical assumptions, modelling decisions, time horizons, and perspective. All available cost-effectiveness estimates for CRT have been based on the results of randomized trials of carefully selected patient populations with a relatively brief follow-up. Extrapolation beyond the limited duration of available clinical trials suggests that the cost effectiveness of CRT may become more favourable as time horizons increase. Using a lifetime time horizon and comparison with optimal medical therapy, the cost effectiveness of both CRT-P and CRT-D appears to meet the $50 000/QALY benchmark.
commonly used for health-care interventions in the USA, as well as similar thresholds used in Europe and values suggested by the WHO for many developed regions of the world. As a result of such evaluations, CRT-P and CRT-D, when applied to appropriately selected patients with moderate-to-severe heart failure, should be viewed as a worthwhile investment for our health-care system.

The absence of direct comparisons of the efficacy/effectiveness of CRT-P and CRT-D hampers evaluation of the relative cost-effectiveness of these two approaches (any estimates will depend on multiple assumptions). At present, clinical judgement of the patient’s profile in the context of current evidence supporting the benefit of treatment with a cardioverter-defibrillator, including cost-effectiveness estimates, may provide the most rational basis for choosing between CRT-P and CRT-D.

More information on the effectiveness and long-term benefits of CRT in the ‘real world’ could therefore enhance the accuracy of economic estimates. Much effort is currently being dedicated to improve CRT response rates by improved patient selection (e.g. through direct mechanical rather than electrical assessment of dysynchrony). It is reasonable to expect that any improvement in this field will translate into improved effectiveness of CRT, and therefore into improved cost-effectiveness. Extended longevity of CRT devices will have a positive impact on cost-effectiveness estimates and will also be important for the assessment of CRT in the setting of mild heart failure.


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