Cost-effectiveness of cardiac resynchronization therapy in patients with asymptomatic to mild heart failure: insights from the European cohort of the REVERSE (Resynchronization Reverses remodeling in Systolic Left Ventricular Dysfunction)

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Aims
To assess the cost-effectiveness of cardiac resynchronization therapy (CRT) compared with optimal medical therapy in patients with New York Heart Association (NYHA) II heart failure (HF) or NYHA I with previous HF symptoms.

Methods and results
A proportion in state model with Monte Carlo simulation was developed to assess the costs, life years and quality-adjusted life year (QALYs) associated with CRT-ON and -OFF over a 10 year time period. Data from 262 patients in the European cohort of the REVERSE clinical trial (QRS $\geq$ 120 ms, left ventricular ejection fraction $\leq$ 40%, CRT-ON, n = 180, CRT-OFF, n = 82) were used to model all-cause mortality, change in NYHA class and resource use. EQ-5D preference weights were taken from a previous cost-effectiveness model of CRT and unit costs from national UK databases. Costs and benefits were discounted at 3.5% p.a. Extensive deterministic and probabilistic sensitivity analyses were performed. Compared with CRT-OFF, 0.94 life years or 0.80 QALYs were gained in the CRT ON group at an additional cost of €11 455, yielding an incremental cost-effectiveness ratio of €14.278 per quality-adjusted life year (QALY) gained. At a threshold of €33 000 (£30 000) per QALY gained, the probability that CRT is cost-effective is 79.6%. Cardiac resynchronization therapy becomes cost effective after $\approx$ 4.5 years. Cardiac resynchronization therapy needs only to demonstrate a modest impact on all cause mortality (hazard ratio $= 0.82$) in order to demonstrate cost-effectiveness. The results are robust to changes in all other parameters.

Conclusion
Cardiac resynchronization therapy is a cost-effective intervention for patients with mildly symptomatic HF and for asymptomatic patients with left ventricular dysfunction and previous HF symptoms.

Keywords
Cost-effectiveness • Cardiac resynchronization therapy • REVERSE • Heart failure • NYHA class I–II

Introduction
In the USA $\sim$5 million individuals in a total population of nearly 294 million have heart failure (HF)1 and in Europe 10 million in a total of 666 million people.2 Asymptomatic left ventricular dysfunction (ALVD) is estimated to have at least the same prevalence as congestive heart failure.3,4 Overt HF symptoms generally follow ALVD and are linked to increased morbidity and mortality.5,6 If
Cardiac resynchronization therapy (CRT), either alone (‘CRT-P’) or in combination with an implantable cardioverter-defibrillator (ICD) (‘CRT-D’), has been shown to be clinically effective in patients with New York Heart Association (NYHA) classes III or IV HF, LV dysfunction and prolonged QRS duration. 11–16 In addition, CRT has been shown to be cost-effective in this patient group, with incremental cost-effectiveness ratios (ICER) ranging from €7,538 to €18,017.16–20 European and US clinical guidelines21 as well as a recent UK-based technology assessment 16 recommended CRT for use in this patient group.

Information on the clinical efficacy of CRT in patients with either asymptomatic or mild HF (NYHA III) is emerging, with evidence from the REVERSE trial indicating that CRT may prevent disease progression by reduction in clinical outcomes through reverse LV remodelling.22–24 The cost-effectiveness of CRT in these patients needs to be determined.

The aim of this study was to develop an economic model to assess the cost-effectiveness of CRT in addition to optimal medical therapy (OMT) compared with OMT alone in a cohort of European patients from the REVERSE trial.

Methods

Overview of REVERSE

The design and results of this international, multicentre, double-blind randomized controlled clinical trial have been reported in detail.22–24 Briefly, in the main study,23 610 adults with QRS duration >120 ms and left ventricular ejection fraction (LVEF) ≤ 40% were implanted with a CRT device and randomly assigned (2:1) to active CRT or control for 12 months. All patients were NYHA III, had stable HF for at least 3 months prior to entry and were treated with OMT in accordance with HF guidelines.25 CRT-D devices were implanted at the discretion of the investigator. The primary endpoint was the percentage of patients with a worse HF clinical composite response, which scores patients as improved, unchanged, or worsened. The prospectively powered secondary endpoint was LV end-systolic volume index (LVESVI). Other secondary endpoints were hospitalization for worsening HF and mortality. The primary endpoint—the proportion of patients worsened at 12 months—did not differ between CRT-ON and CRT-OFF groups (P = 0.10) but significant reverse ventricular remodelling in the CRT-ON group was achieved, as well as a reduced need for HF related hospitalizations.23 Mortality did not differ significantly between assignments.

For the purpose of the European health economics study,22 a total of 287 European patients (‘REVERSE-EU’) were enrolled at 35 centres and received a CRT-P or CRT-D device. Successfully implanted patients (n = 262) were randomly assigned (2:1) to have CRT switched on (CRT-ON) or not (CRT-OFF) and followed in the randomized assignment for 24 months. Thereafter, all devices were advised to be programmed to CRT-ON and all patients followed for a total of 5 years in accordance with the study protocol.22

Model description

We examined the cost-effectiveness of CRT compared with OMT (i.e. no CRT). Data on healthcare resource use were restricted to the REVERSE-EU cohort, and in order to retain internal consistency, all analyses were carried on this dataset with 24 months randomized follow-up.

Owing to the international nature of REVERSE, and the modest sample size, it was not possible to stratify resource use by country. We therefore used the overall resource use data in the REVERSE-EU cohort in combination with unit costs from one country—the UK—for all cost estimates in this analysis. Our analysis took a third party payer perspective.

We constructed a proportion in state model with Monte Carlo simulation to describe the underlying disease process of patients with mildly asymptomatic HF. Health states were defined by NYHA class (I–III) and death. NYHA class IV was not included in the model since no patient was classified as being in NYHA IV at any follow-up visit. Costs and utilities were attached to each health state and patients in each treatment arm accrued costs and benefits as they passed through these states. Time was measured in discrete units of one month and a ten year time horizon was used.

The model was implemented in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) using a three stage process. First, at any given time point, the proportion of the original cohort still alive was derived. Secondly, for the same time point the distribution across three NYHA classes was derived for all patients still alive. Finally, the derived proportions in each health were multiplied by the relevant cost and utility estimates to derive monthly values. All totals were summed over the time horizon to generate total intervention values.

The methods used to model key parameters are summarized below. Fuller detail is provided in the supplementary technical appendix.

Estimating mortality

Mortality was low in the REVERSE-EU cohort. Therefore, in order to maximize the amount of information available to inform parameterization, all follow-up data for European patients initially randomized to CRT-ON arm were used. For patients in the CRT-OFF arm only data for the first 2 years post-randomization were available to inform model parameters.

A range of parametric survival functions were fitted to time-to-event data with treatment used as a covariate. On the basis of estimated log-likelihood values, a Weibull proportional hazard model was used.

Estimating NYHA mix

Multinomial logistic regression was used to estimate NYHA mix over time. NYHA class was the dependant variable in all analyses and in addition to a constant term, analyses were carried out using different predictor variables—time, time squared, exp(time), log(time). All analyses were clustered by patient. On the basis of a visual inspection of goodness-of-fit to the within-trial data, and the opinion of the project steering committee concerning the plausibility of long-term predicted state occupancy, log(time) was used in the final models.

Estimating resource use by NYHA class

Insufficient data were available to directly estimate NYHA class-specific event rates for specific cardiovascular-related adverse events (stroke, MI etc.). Thus, we undertook a hospitalization event and length of stay (LOS)-based analysis and estimated the expected number of days per month individuals in each NYHA class would
The composition of background OMT was assumed to be the same of all subsequent device replacements was included in the model. CRT-D device were allocated the cost of an ICD implant. The cost to 2008 values. Individuals in the CRT-OFF arm who received a weights for use in a series of sensitivity analyses.

The algorithm was used to convert this information into EQ-5D preference weights for use in a series of sensitivity analyses. Separate models were used for overall, GW and ICU LOS.

In order to be consistent with previous economic evaluations of CRT, battery upgrade (CRT-D) 14 250 14 203 14 326 NHS Reference Costs Lognormal, battery upgrade (CRT-D) 14 250 14 203 14 326 NHS Reference Costs Lognormal, battery upgrade (ICD) 14 250 14 203 14 326 NHS Reference Costs Lognormal.

Costs and utilities

Health related quality of life (HRQoL) was included in the model through the use of the utilities. The values applied to each of the three NYHA classes were taken from a previous model of CRT and derived using the EQ-SD instrument (Table 1). HRQoL data captured using the Minnesota Living With Heart Failure (MLWHF) questionnaire was available for the REVERSE-EU cohort and a published mapping algorithm was used to convert this information into EQ-SD preference weights for use in a series of sensitivity analyses.

Device costs were taken from a recent NICE appraisal and inflated to 2008 values. Individuals in the CRT-OFF arm who received a CRT-D device were allocated the cost of an ICD implant. The cost of all subsequent device replacements was included in the model. The composition of background OMT was assumed to be the same as in Fox et al. and current drug prices were taken from the most recent version of the British National Formulary at the time of analysis. The values used in the model are summarized in Table 1.

Device longevity

In order to be consistent with previous economic evaluations of CRT, we assumed that CRT devices were replaced every 6.5 years, CRT-D devices every 5.5 years and ICD devices every 6 years. These values were altered in sensitivity analyses.

Table 1  Utility values and non-drug costs used in the economic model

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>95% LCI</th>
<th>95% UCI</th>
<th>Source</th>
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<td>Utility scores</td>
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<td>Kirsch et al.</td>
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<td>NYHA II</td>
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<td>0.72</td>
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<td></td>
<td>NYHA III</td>
<td>0.61</td>
<td>0.59</td>
<td>0.63</td>
<td>Calvert et al.</td>
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<td>Non-drug costs (Euros)</td>
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<td>1569</td>
<td>1262</td>
<td>1875</td>
<td>NHS Reference Costs</td>
</tr>
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<td></td>
<td>Day on GW</td>
<td>162</td>
<td>130*</td>
<td>195*</td>
<td>Walsh et al.</td>
</tr>
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<td></td>
<td>Outpatient visit</td>
<td>79</td>
<td>54</td>
<td>102</td>
<td>Curtis</td>
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<td></td>
<td>Initial implant (CRT)</td>
<td>6235b</td>
<td>6140b</td>
<td>6386b</td>
<td>Fox et al.</td>
</tr>
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<td>Initial Implant (CRT-D)</td>
<td>21 218</td>
<td>21 123</td>
<td>21 369</td>
<td>Fox et al.</td>
</tr>
<tr>
<td></td>
<td>Initial Implant (ICD)</td>
<td>14 250</td>
<td>14 203</td>
<td>14 326</td>
<td>NHS Reference Costs</td>
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<td></td>
<td>Battery upgrade (CRT)</td>
<td>5054b</td>
<td>5054b</td>
<td>5054b</td>
<td>Fox et al.</td>
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<tr>
<td></td>
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<td>20 336b</td>
<td>20 336b</td>
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</tr>
<tr>
<td></td>
<td>Battery upgrade (ICD)</td>
<td>14 250</td>
<td>14 203</td>
<td>14 326</td>
<td>NHS Reference Costs</td>
</tr>
</tbody>
</table>

*Assumed range of ± 20%.

Published value inflated to 2008 equivalent using the HCHS pay and prices index.

Discounting an exchange rate

We applied a discount rate of 3.5% annually for costs and benefits. An exchange rate of £1 = €1.11 (correct as of 22 April 2009) was used in all cost conversions.

Sensitivity analyses

We conducted a probabilistic sensitivity analysis (PSA) whereby individual sets of parameter values were drawn from appropriate statistical distributions, with results generated for 1000 simulation runs. Cost-effectiveness acceptability curves were generated to illustrate uncertainty. A range of deterministic analyses were performed to explore the impact of alternative parameter values and modelling assumption on model results.

Statistical analyses

The analysis of time to event data was undertaken in SAS v9.1 (SAS Institute Inc., Cary, NC, USA). In order to undertake the analysis of NYHA class and resource use data, it was necessary to create additional data sets using SAS v9.1. The analyses of these data sets were carried out in Stata v10.1 (StataCorp, College Station, TX, USA).

Results

REVERSE clinical trial

Most REVERSE-EU patients were randomized in Denmark (n = 65), France (n = 49), Sweden (n = 24), and the UK (n = 15). The baseline age of patients was 61.7 ± 10.0 years in CRT-ON and 60.4 ± 11.2 years in CRT-OFF. The majority of patients randomized received a concomitant ICD (CRT-ON: 66%, CRT-OFF: 72%). Ischaemic HF aetiology was present in 44% of patients in CRT-ON and 41% in CRT-OFF. More information on patient characteristics has been previously published.

At 24 months of follow-up, a worsening of the HF clinical composite response was observed in 19% assigned to CRT-ON.
Figure 1  Number of hospitalizations (A) and total days in hospital (B) for REVERSE patients. Information relating to CRT-OFF drawn from 82 patients over a 24 month time period and information relating to CRT-ON drawn from 160 patients over a 36 month time period. Hence, absolute numbers are not comparable.

Figure 2  Comparison of observed and predicted NYHA mix.
compared with 34% assigned to CRT-OFF ($P < 0.01$). Left ventricular end-systolic volume index decreased by a mean of $27.5 \pm 31.8$ in the CRT-ON, versus $2.7 \pm 25.8 \text{mL/m}^2$ in the CRT-OFF group ($P < 0.0001$). The time to first HF hospital stay was significantly longer in the CRT-ON (7.8% hospitalized) than in the CRT-OFF (18.4%) group [hazard ratio (HR): 0.39, $P < 0.01$]; however, the mortality was not significantly affected (CRT-ON 5.7%, CRT-OFF 8.6%, HR: 0.40, $P = 0.09$).

Information on the total number of recorded hospitalizations and total days in hospital over the total follow-up period is presented in Figure 1A and B, respectively. The majority of patients in both arms did not experience any hospitalizations and consequently the average number of days spent in hospital was low (CRT-ON: 3.6 days, CRT-OFF: 4.4 days).

A comparison of the observed and predicted NYHA mix for each treatment arm is presented in Figure 2.

### Cost-effectiveness results

The lifetime costs and benefits generated when the model was run probabilistically are presented in Table 2. In comparison with CRT-OFF, individuals in the CRT-ON incurred an additional cost of €11 455 over the 10 year period post-implantation. However, treatment conferred an additional 0.94 years, or 0.80 QALYs, over this time period. Thus, the base case ICERs were €12 172 per life year gained (LYG) and €14 278 per QALY gained. The number needed to treat (NNT) to avoid one death is 4.9 at 10 years.

The cost-effectiveness acceptability curves for CRT-OFF and CRT-ON are presented in Figure 3. Assuming a willingness-to-pay (WTP) threshold of €22 200 (£20 000) per QALY gained, for patients with mildly asymptomatic HF there is a 66.8% chance that CRT is a cost-effective intervention. At a threshold value of €33 300 (£30 000) per QALY gained, this probability increases to 79.6%.

### Truncation of time horizon

The initial cost of CRT is relatively high, with or without an ICD, and benefits develop gradually over future years. We explored the impact of reducing the period of time over which the REVERSE data were extrapolated. The longest follow in the trial was 3.5 years. At a WTP threshold of €33 300 per QALY gained, CRT becomes cost effective after approximately four-and-a-half years (Figure 4). Minimal extrapolation of follow-up time was therefore needed to demonstrate cost-effectiveness.

### Reducing the impact of cardiac resynchronization therapy on overall survival

The impact on the cost-effectiveness of CRT of varying the all-cause mortality HR is shown in Figure 5. In REVERSE, mortality was not significantly reduced for the CRT-ON group compared with the CRT-OFF group. However, as noted above, the overall mortality rate was low and the sample size rather small.

Figure 5 indicates that holding other factors constant, a threshold relative mortality hazard for a CRT of 0.82 (compared with the

<table>
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<th>Table 2</th>
<th>Cost-effectiveness results (mean, 95% CI) for base case assumptions</th>
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<td>Arm</td>
<td>Costs (Euros)</td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
</tr>
<tr>
<td>CRT-OFF</td>
<td>16 626 (11 325, 17 995)</td>
</tr>
<tr>
<td>CRT-ON</td>
<td>28 081 (20 559, 29 408)</td>
</tr>
<tr>
<td>Difference</td>
<td>11 455 0.94</td>
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</table>

Figure 3 Cost-effectiveness acceptability curves.
0.40 estimate obtained in REVERSE$^{24}$) would be sufficient for CRT to be cost-effective in patients with mildly asymptomatic HF.

**Additional sensitivity analyses**

A number of alternative approaches to modelling the REVERSE trial data were explored, with none resulting in an ICER above €33 300 per QALY gained (Table 3). In addition, we explored the impact of varying individual parameter values on model results. Whereas the model was sensitive to changes in the proportions receiving an ICD and the associated cost of implantation, no realistic values for these parameters resulted in an ICER above €33 300 per QALY gained. The model was insensitive to changes in device service lifetime or choice of utility values for each NYHA class.

**Discussion**

The clinical efficacy of CRT in patients with moderate to severe HF has been established in a number of trials.$^{11–13}$ In contrast, for patients with asymptomatic or mildly symptomatic HF, CRT represents a potentially novel treatment option. Evidence on the clinical efficacy of CRT in this patient group has recently emerged with the publication of the REVERSE and MADIT-CRT trials.

Daubert et al.$^{24}$ reported that CRT decreased disease progression as measured in terms of the proportion of patients with worse scores on a clinical composite endpoint.$^{26}$ Significant and progressive improvement of left ventricular systolic function was also observed in terms of impact on LVEF as well as left ventricular end systolic and diastolic volume index. Time to first HF hospital stay or death was significantly delayed by CRT.
Importantly, MADIT-CRT, dimensioned as a morbidity and mortality trial, showed a significant reduction in the risk of death or HF events (HR: 0.66, P = 0.003) mainly driven by a 41% reduction in HF hospitalizations. Significant improvements in LV function were also demonstrated.

In both trials, mortality rates were low and no significant reduction of all-cause mortality was found during the observation periods, indicating that longer follow-up periods are needed to demonstrate an effect on mortality in patients with early stage HF. Longer follow-up periods have been reported in randomized trials of pharmacological treatments, but only one device trial (SCD-HeFT) that included 70% patients in NYHA III and 30% in NYHA II.28

The model presented here represents the first attempt at assessing the cost-effectiveness of CRT in this patient group. The cost-effectiveness ratio generated in the base case analysis was €14 278 per QALY.
per QALY gained and as such CRT is highly likely to be deemed as cost-effective at WTP thresholds used in Europe.

Previous analyses of the COMPANION20 and CARE-HF17,18 trials indicated that both CRT-P and CRT-D devices are cost-effective in patients with NYHA class III/IV (Table 4). In addition, when the extrapolated REVERSE data are used to calculate the NNT to avoid one death, the value generated (4.9) at 10 years is similar to those for studies in patients with moderate to severe HF (CARE-HF: 5.6, COMPANION 6.3). Further, our results are similar to those derived for other cardiovascular interventions (Table 4). Therefore, an important finding in this study was that CRT in mildly symptomatic patients is similarly cost-effective as in more severely ill patients.

The ICERs presented in this paper are higher than those derived from the CARE-HF study.17 This is likely to be a result of a 10 year rather than lifetime time horizon. If the model were run for a lifetime the increased benefits associated with delayed progression to NYHA III/IV would become more apparent. However, further work is required to test this hypothesis.

<table>
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<th>Intervention</th>
<th>Patient group</th>
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<tr>
<td>CRT</td>
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<td>REVERSE</td>
<td>€14 278</td>
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<tr>
<td>CRT-P</td>
<td>NYHA III/IV</td>
<td>CARE-HF17</td>
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<td>NYHA III/IV</td>
<td>EUROPA13</td>
<td>€35 210–€62 339</td>
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<td>Stable CAD</td>
<td>IDEAL34</td>
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<td>Kupersmith et al.35</td>
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<tr>
<td>CABG</td>
<td>Angina Pectoris</td>
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*aCompared with OMT; CAD, Coronary Artery Disease; AMI, Acute Myocardial Infarction; PCS, Primary Coronary Stenting; CABG, Coronary Artery Bypass Graft.*

**Table 4** Comparison of results from REVERSE analysis with those for other cardiovascular interventions

Limitations

In constructing and parameterizing the model, we selected commonly applied measures of HRQoL. However, we were limited by the modest number of individuals recruited into European centres, the low frequency of adverse events and the need to extrapolate over a long-term time horizon. The latter point is particularly important since the principal cost associated with CRT is the initial implant, while benefits accrue over time.

In order to assess the impact of these limitations, a number of alternative approaches to extrapolating trial data were identified and the effect of each explored in sensitivity analysis. A range of different parametric survival functions were fitted to the all-cause mortality data and alternative regression approaches were used to extrapolate NYHA data. We also looked to use MLWHF data collected in REVERSE rather than using the published EQ-5D values and to using non-REVERSE data to capture the cost associated with severe HF. Regardless of approach, CRT remained a cost-effective treatment option.

At the time of analysis, trial data were available for up to three-and-a-half years in patients in the CRT-ON arm. The analysis of alternative time horizons showed that CRT was cost-effective after approximately four-and-a-half years. Thus the positive cost-effectiveness result has a limited dependency on our methods of extrapolation. Long-term data are not available in the patient group at this time and as such quantitative model validation was not possible. However, we made extensive use of clinical opinion on the plausibility of all long-term predictions. In addition, we compared the predicted 10 year survival estimates in each arm with the values reported for patients with moderate to severe HF. The rationale for this approach is that the mathematical functions used should not predict a worse prognosis than the observed data in more severe patient groups.

In addition, due to the number of patients recruited into the REVERSE trial it was not possible to generate cost-effectiveness estimates relating to the use of CRT-D devices in this patient group (i.e. for CRT-D vs. ICD and CRT-D vs. CRT-P).

Despite these limitations our analysis is robust and the results represent the best estimate of cost-effectiveness to date of CRT in this patient group.

**Conclusion**

Results from the European cohort of the REVERSE study indicate that CRT in mildly symptomatic HF has a similar cost-effectiveness ratio as in moderate to severe HF and other commonly used interventions for HF. At commonly used European WTP thresholds, CRT represents a cost-effective treatment option for patients with mildly symptomatic HF and for asymptomatic patients with left ventricular dysfunction and previous HF symptoms.

**Supplementary material**

Supplementary material is available at *European Heart Journal* online.

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