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Cost-effectiveness of cardiac resynchronisation therapy for patients with moderate-to-severe heart failure: a lifetime Markov model

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To cite: Neyt M, Stroobandt S, Obyn C, *et al*. Cost-effectiveness of cardiac resynchronisation therapy for patients with moderate-to-severe heart failure: a lifetime Markov model. *BMJ Open* 2011;**1**:e000276. doi:10.1136/bmjopen-2011-000276

► Prepublication history and additional materials for this paper are available online. To view these files please visit the journal online (http://bmjopen.bmj.com).

Received 28 July 2011
Accepted 1 September 2011

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ABSTRACT

Objective: To assess the cost-effectiveness of cardiac resynchronisation therapy (CRT) both with CRT-P (biventricular pacemaker only) and with CRT-D (biventricular pacemaker with defibrillator) in patients with New York Heart Association (NYHA) functional class III/IV from a Belgian healthcare-payer perspective.

Methods: A lifetime Markov model was designed to calculate the cost–utility of both interventions. In the reference case, the treatment effect was based on the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure trial. Costs were based on real-world data. Pharmacoeconomic guidelines were applied, including probabilistic modelling and sensitivity analyses.

Results: Compared with optimal medical treatment, on average 1.31 quality-adjusted life-years (QALY) are gained with CRT-P at an additional cost of €14 700, resulting in an incremental cost-effectiveness ratio (ICER) of about €11 200/QALY. As compared with CRT-P, CRT-D treatment adds on average an additional 0.55 QALYs at an extra cost of €30 900 resulting in an ICER of €57 000/QALY. This result was very sensitive to the incremental clinical benefit of the defibrillator function on top of CRT.

Conclusions: Based on efficiency arguments, CRT-P can be recommended for NYHA class III and IV patients if there is a willingness to pay more than €11 000/QALY. Even though CRT-D may offer a survival benefit over CRT-P, the incremental clinical benefit appears to be too marginal to warrant a threefold-higher device price for CRT-D. Further clinical research should focus on the added value of CRT-D over CRT-P.

ARTICLE SUMMARY

Article focus

- To assess the cost-effectiveness of cardiac resynchronisation therapy (CRT) both with CRT-P (biventricular pacemaker only) and with CRT-D (biventricular pacemaker with defibrillator).

Key messages

- CRT-P can be recommended for reimbursement for New York Heart Association class III and IV patients if there is a willingness to pay more than €11 000/quality-adjusted life-year.
- Current evidence is insufficient to show the superiority of CRT-D over CRT-P. With a threefold-higher device cost, CRT-D's cost-effectiveness is questionable.

Strengths and limitations

- Hospital billing data of 342 Belgian CRT implantations were at our disposal for cost calculations.
- The results of the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure trial were used to model the treatment effect. This happens to be the only trial that compared CRT-P as well as CRT-D versus optimal pharmacological treatment, allowing an indirect comparison to be made between CRT-P and CRT-D.
- Following health economic theory, CRT-D is compared with CRT-P, not with optimal pharmacological treatment (ie, working on the cost-efficiency frontier).
- A direct estimate of the added value of CRT-D versus CRT-P in patients with moderate to severe heart failure is lacking. This may be an interesting topic for further research in a randomised controlled trial, especially because of the threefold higher price for a CRT-D device versus CRT-P.
- Generic utility instruments to measure quality of life are not always used in clinical trials. To support economic evaluations, it would be useful to include more systematically a generic utility instrument in the study protocol.

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome that can result from any cardiac disorder that impairs the ability of the heart to function as a pump. Patients who are clinically stable but suffer from a severely reduced contractile function (left ventricular

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ejection fraction; LVEF≤35%) remain at high risk of sudden cardiac death (SCD).[1] Approximately 50% of deaths in patients with HF are due to a sudden cardiac arrest.[2] Therefore, HF patients are potential candidates for treatment with an implantable cardioverter defibrillator (ICD). Selected patients with end-stage HF, who remain symptomatic despite optimal pharmacological treatment (OPT), could also be considered for cardiac resynchronisation therapy (CRT).[3] The scope of this manuscript is to calculate CRT's cost-effectiveness in order to provide reimbursement advice to the Belgian competent authorities.

CRT can be offered by two types of devices: biventricular pacemakers, also called CRT-P devices, and biventricular defibrillators, also known as CRT-D devices. CRT aims to improve the heart's contractile function by electrically stimulating the cardiac chambers, thus synchronising their contraction. A CRT-D device offers the additional ability to stop life-threatening ventricular arrhythmias preventing SCD.

The Belgian Health Care Knowledge Centre (KCE), an independent semigovernmental institution, conducted a health technology assessment (HTA) about the clinical effectiveness and cost-effectiveness of CRT for HF patients.

METHODS

A Markov simulation model was developed in order to evaluate the cost-effectiveness of CRT-P and CRT-D therapy. Both cost-effectiveness, expressing results in additional expenses for a life-year gained (LYG), and cost−utility analyses using quality-adjusted life-years (QALYs) gained were performed.

The analysis included direct healthcare costs from the perspective of the healthcare payer. In Belgium this constitutes payments from the government's healthcare budget as well as patients' co-payments. Dealing with a chronic disease, a lifetime horizon was also applied. Future costs and benefits were discounted at a rate of 3% and 1.5%, respectively, according to national pharmacoeconomic guidelines.[4] In scenario analyses, these rates were subsequently changed.

To capture parameter uncertainty, input variables were modelled as probabilistic values. The choice of distribution depends on the characteristics of the input variables.[5] Owing to the central limit theorem, parameters can be sampled from a normal distribution with the appropriate CI around the mean. The β distributions are used for parameters constrained to the interval 0−1 (such as quality-of-life (QoL) values). γ Distributions are used for skewed variables. One thousand Latin hypercube simulations were generated in MicroSoft Excel using the @Risk (Palisade Corporation) add-in program.

The interventions of interest, CRT-P and CRT-D, are always provided on top of OPT. Hence, OPT is the initial comparator for both CRT-P and CRT-D to determine their position on the cost-effectiveness plane (which presents the difference in effects on the x-axis and differences in costs on the y-axis). The incremental cost-effectiveness ratios (ICERs), comparing incremental costs with incremental effects, were calculated on the efficiency frontier. According to health-economic theory,[5] ICERs should be calculated on this frontier comparing an intervention with the previous most cost-effective intervention. To be able to interpret results, cost-effectiveness acceptability curves are presented, expressing the probability that an intervention is considered cost-effective (y-axis) depending on the willingness to pay (WTP) for an additional QALY (x-axis).

Model

The model simulated a hypothetical cohort of 1000 CRT-eligible patients. The type of participants considered were patients with moderate-to-severe heart failure (NYHA class III−IV) with low ejection fraction (≤35%) and delayed intraventricular conduction evidenced by a wide QRS complex. In the base case scenario, the patient population was 67 years old, and 67.4% were male, corresponding to the patients who were enrolled in the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial.[6] Baseline employment rates can safely assumed to be low in this population, and therefore indirect productivity costs were ignored.

In the literature review on effectiveness of CRT,[7] all-cause mortality and hospitalisation owing to heart failure were considered as primary endpoints. This was reflected in the Markov model with monthly cycles (figure 1). Patients receiving a CRT-P/D were subject to a procedure-related mortality risk. Furthermore, every month, patients were at risk of all-cause death. Survivors receiving OPT during that month were at risk of hospitalisation owing to heart failure and could receive an upgrade (either from OPT to ICD or from CRT-P to CRT-D).

Mortality

Randomised trials have shown that both CRT-P and CRT-D, in addition to OPT, prolong life in subsets of patients with NYHA class III/IV heart failure.[6 8] The results of the COMPANION trial[6] were used to model the treatment effect. This was the only trial that compared CRT-P+OPT as well as CRT-D+OPT versus OPT, allowing an indirect comparison to be made between CRT-P and CRT-D. Based on this trial, the monthly probability of death was 0.017 for the OPT group.[9] Applying the reduced mortality risk of 24% (p=0.059) and 36% (p=0.003) for CRT-P and CRT-D resulted in a monthly probability of 0.013 and 0.011, respectively. A normal distribution was used to account for the uncertainty around these numbers.

In the COMPANION trial, the median follow-up time was 14.8 months, 16.5 months and 16.0 months, for the OPT, CRT-P and CRT-D group, respectively.[6] In our model, extrapolation started after month 16 for the three intervention groups. The monthly probability of

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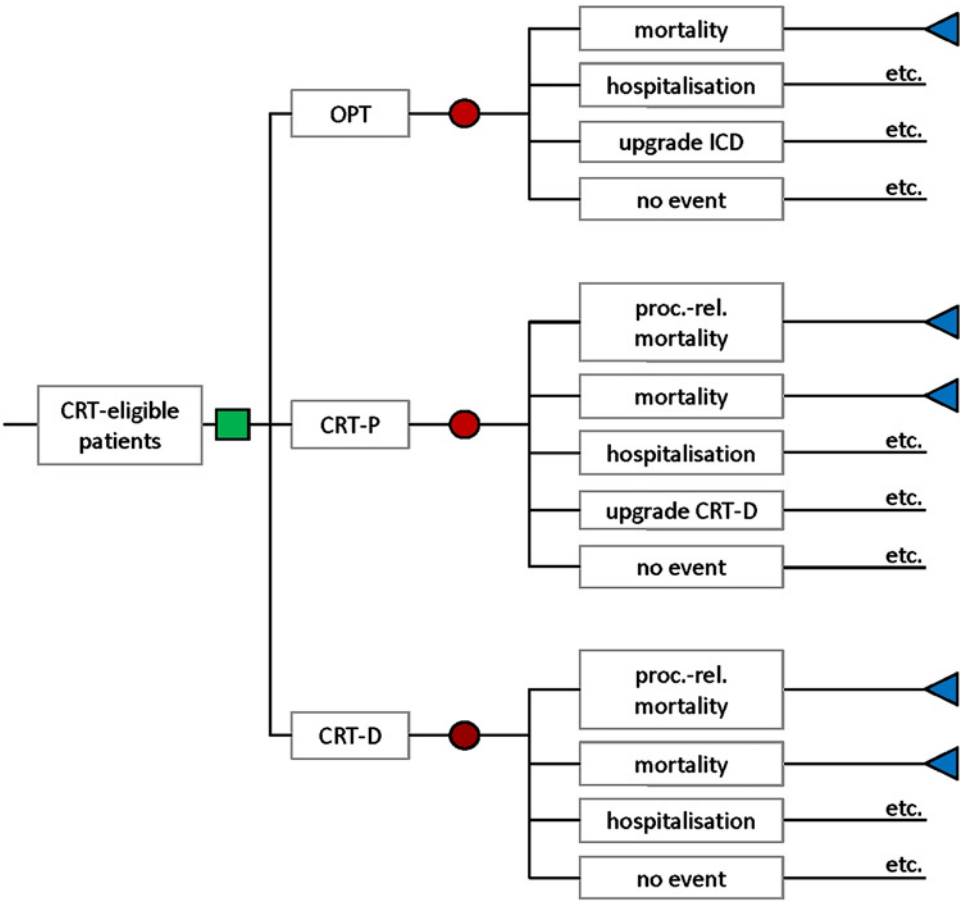

Figure 1 Decision model for cardiac resynchronisation therapy (CRT) with biventricular pacemaker only (CRT-P) and CRT with biventricular pacemaker with defibrillator (CRT-D). ICD, implantable cardioverter defibrillator; OPT, optimal pharmacological treatment; proc.-rel., procedure-related.

death was made time-dependent by adding the absolute monthly increase in mortality of the normal age- and gender-adjusted Belgian population.

In a systematic review of clinical trials on CRT,[10] 21 perioperative deaths were counted among 2757 patients (table 1). This procedure-related mortality risk of both CRT-P and CRT-D implantations was accounted for by applying a β-distribution. However, in order to avoid double counting, monthly mortalities during the first year were slightly adjusted downwards, keeping the original trial-based 1-year mortality at the same level.

Hospitalisations

Hospitalisation rates were based on the COMPANION trial as reported by Feldman *et al*.[9] The monthly probability of hospital admission was estimated to be 0.117 for the OPT group, 0.098 (p=0.172) for CRT-P and 0.097 (p=0.141) for the CRT-D group (table 1). The uncertainty around these numbers was accounted for with a normal distribution. In our reference case, the hospitalisation rates were assumed to be constant over the full time horizon. This was subsequently altered during a scenario analysis.

Costs

An average cost of €23 380 (95% CI of the mean 22 842 to 23 919) for a primo CRT-D implantation was obtained from the actual hospital billing data of 342 Belgian CRT-D primo implantations that occurred during the period 2008 until mid 2009. This cost was modelled with a normal distribution (table 1). The implantation cost of a primo CRT-P was inferred by subtracting the cost difference from the CRT-D implantation cost. Based on the reimbursement tariffs, the price for CRT-P and CRT-D, including leads, was €7187 and €21 170, respectively.[7] As such, the average cost for CRT-P implantation was €9398 (95% CI of the mean €8859 to 9936).

A similar approach was used for the cost of a device replacement. Based on Belgian data (n=121), the CRT-D replacement cost was €21 905 (95% CI of the mean €21 111 to €22 700). With a price difference between the CRT-P and CRT-D device of €12 844, this amounted to €9061 (95% CI of the mean €8267 to €9856) for CRT-P. Service life was equal to the average of expert opinion-based service lives encountered in other studies,[9 10] that is 75 months for CRT-P and 60 months for CRT-D. This assumption was altered in various scenario analyses.

Data from the Belgian Technical Cell (http://www.tct.fgov.be) served as the source for obtaining hospitalisation costs. The cost for 'APR-DRG 194 Heart Failure' was on average €5529 (90% CI 1233 to 14 132) per hospitalisation based on data from more than 19 000 hospitalisation episodes in the year 2007. This cost was included as a γ distribution and adjusted to 2008 values (Consumer Price Index of 104.5% or on average €5777) (table 1).

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Table 1 Input variables for the Markov model

	Mean	Range (95% CI)* 2.5%	97.5%	Distribution	Source
Characteristics of the population					
Start age of the cohort	67 years	/	/	/	COMPANION trial[6]
Proportion male	67%	/	/	/	
Mortality (monthly)					
OPT	0.017	/	/	/	Feldman *et al*[9]
CRT-P	0.01292	0.00868	0.01716	Normal	Feldman *et al*[9]; COMPANION
CRT-D	0.01088	0.00801	0.01375	Normal	trial[6] and own calculations
Procedure related mortality					
		α	β		
Perioperative deaths	0.76%	21	2736	β	Fox *et al*[10]
Hospitalisations (monthly probability of hospital admission)					
OPT	0.117	/	/	/	Feldman *et al*[9]
CRT-P	0.098	0.0707	0.1253	Normal	Feldman *et al*[9] and
CRT-D	0.097	0.0704	0.1236	Normal	own calculations
Length of stay					
Primo implantation	7.34	6.2	8.48	Normal	Belgian database
Replacement	4.47	3.53	5.41	Normal	
Utility weights					
OPT	0.68	0.63	0.73	β	Cleland *et al*[8]; Calvert *et al*[11];
CRT-P	0.78	0.73	0.83	β	Feldman *et al*[9] and own
CRT-D	0.78	0.73	0.83	β	assumptions
Hospitalisation primo implantation or replacement	0.46	0.41	0.51	β	
Costs†					
Primo implantation					
CRT-P	€9398	€8859	€9936	Normal	Belgian database, reimbursement
CRT-D	€23 380	€22 842	€23 919	Normal	tariffs and own adaptions
ICD	€27 261	€26 867	€27 658	γ	Belgian Health Care Knowledge Centre report implantable cardioverter defibrillators[12]
Replacement					
CRT-P	€9061	€8267	€9856	Normal	Belgian database, reimbursement
CRT-D	€21 905	€21 111	€22 700	Normal	tariffs and own adaptions
Hospitalisation	€5777	€1129	€17 807	γ	Technical Cell (All Patient Refined Diagnosis Related Groups 194 'heart failure')
Follow-up medication (monthly cost)	€30.88	€29.85	€31.82	β for volumes	Belgian database (volumes) and Belgian Centre for Pharmacotherapeutic Information (prices)
Follow-up visits (average monthly cost)	OPT	CRT-P	CRT-D		
GP, cardiologist (ECG, echo, integrity check)	€52.98	€71.87	€90.77	β for volumes	Expert opinion
Crossover/upgrade					
OPT—ICD	0.0015	−50%	+50%	Uniform	Bond *et al*[13]
CRT-P—CRT-D	0.0005	−50%	+50%	Uniform	

*95% CI, unless otherwise mentioned.
†Unless otherwise stated in the text, the year of costs reflects 2008 values.
/, fixed value in the model; COMPANION, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT-P/D, cardiac resynchronisation therapy (CRT) both with pacemaker (CRT-P) and additionally including a defibrillator (CRT-D); ECG, electrocardiogram; GP, general practitioner; ICD, implantable cardioverter defibrillator; OPT, optimal pharmacological treatment.

Prescription medication use was taken from the available data on the Belgian CRT population, right before implantation.[7] The amount and type of drugs were assumed to remain the same after implantation on a per patient base. Prescription medication costs were based on the cheapest formulation as indicated by the Belgian Centre for Pharmacotherapeutic Information (http://www.bcfi.be accessed November 2010). The percentage

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of users was included as a β distribution with parameters reflecting the values of the Belgian CRT sample. The average monthly medication cost was €30.88 per patient (95% CI 29.85 to 31.82) (table 1). Details are presented as a data supplement (www.jamia.org).

Based on expert opinion, we assumed that patients consulted their cardiologist four times a year at €34.02 per consultation, and received GP visits at €19.37 per visit for the remaining 8 months of the year. This was modelled applying a β distribution with the minimum and maximum ±50% above/under the average. For every consultation an ECG (€16.94) and echocardiographic examination (€69.24) were billed as well. A CRT integrity check was also counted at €56.68 for CRT-P and €113.36 for CRT-D systems. As such, the monthly visit costs for OPT, CRT-P and CRT-D were respectively €52.98, €71.87 and €90.77 (table 1).

Finally, the model also included a possibility for crossover or upgrade. Patients in the OPT group could receive an ICD, whereas patients in the CRT-P group could be upgraded to CRT-D. Medical therapy and CRT recipients received an ICD in the model of Bond *et al*[13]/Fox *et al*[10] as soon as they survived a serious arrhythmic event. Based on their model, we included upgrade probabilities of 0.0015 and 0.0005 per month for the OPT and CRT-P group, respectively (table 1). These probabilities were multiplied with a uniform distribution (0.5−1.5) to reflect the large uncertainty around these numbers. The cost of an ICD implantation was based on another Belgian ICD study and amounts to €27 261 (95% CI 26 867 to 27 658).[12] We preferred not to index this cost, since the reimbursement price for the device has decreased since then. For an upgrade from CRT-P to CRT-D, the cost of a CRT-D replacement was taken into account. Crossover- or upgrade-related procedural deaths were not explicitly accounted for, since we assumed these to be reflected in the initial intention-to-treat mortalities.

Utilities

Utility values were based on the studies of Cleland *et al*,[8] Calvert *et al*[11] and Feldman *et al*[9] The baseline out-of-hospital utility was set to 0.68 (table 1).[9] The utility improvement in the CRT-P/D groups was estimated to amount to 0.1,[8 9 11] resulting in a utility weight of 0.78. An average utility weight of 0.46 was incorporated during the hospital stay of the initial and replacement implantations, which averaged 7.34 days and 4.47 days respectively in the Belgian CRT sample (table 1). Details of the studies that support these utility values are briefly outlined in the data supplement on utilities (www.jamia.org).

Sensitivity and scenario analyses

Results of the probabilistic model are presented on the cost-effectiveness plane and as cost-effectiveness acceptability curves. Several scenario analyses are performed for mortalities, hospitalisations, discount rates and device service life.

RESULTS

According to the model, the undiscounted life expectancy is 4.6 years for the OPT group. CRT-P increases life expectancy with 1.31 years (95% CI −0.04 to 3.21). CRT-D adds another 0.8 years (95% CI −1.40 to 2.95) on top of CRT-P. If QoL changes are taken into account, this becomes 1.47 QALYs (95% CI 0.39 to 3.00) and 0.63 QALYs (95% CI −1.18 to 2.38), respectively. This results in a discounted incremental effect adjusted for quality of life of 1.31 QALYs (95% CI 0.36 to 2.64) and 0.55 QALYs (95% CI −1.02 to 2.07), respectively.

The average incremental cost is <€15 000 for CRT-P versus OPT. In combination with the discounted gain in life expectancy, this results in an average ICER of about €12 800/LYG. If QoL adjustments are taken into account, this becomes €11 200/QALY gained. The ICER of CRT-D versus OPT is higher than that of CRT-P versus OPT; thus calculating the ICER on the efficiency frontier, CRT-P becomes its economic justified comparator. The total incremental cost of CRT-D versus CRT-P is on average more than €30 000. The ICER becomes on average €44 100/LYG or €56 600/QALY gained. More details and CIs are available in the data supplements (www.jamia.org).

Figure 2 shows the cost-effectiveness plane; on top both CRT-P and CRT-D versus OPT (incremental effects on the x-axis expressed as QALYs gained), while at the bottom CRT-P becomes the comparator for CRT-D. The scatter plot clearly shows the impact of considering CRT-P as the comparator for CRT-D. If we compare CRT-D with OPT, then the simulations are completely in the first quadrant. In contrast, if we compare CRT-D with CRT-P, about 23% of the simulations are situated in the dominated quadrant (being more costly and less effective).

For each of the 1000 simulations, ICERs are calculated, allowing the results to be expressed as the probability that the three alternatives are considered cost-effective depending on the WTP for a QALY. Figure 3 shows these cost-effectiveness acceptability (CEA) curves. OPT is the preferred option if the WTP for a QALY gained is <€11 000. Above this threshold, CRT-P is most probably the best alternative with a probability of about 90% at a threshold of about €21 000 per QALY gained. If this willingness is more than €30 000, the probability that OPT is chosen is almost nil. This WTP has to increase to more than €56 000 per QALY gained for CRT-D to have a probability of more than 50% for being considered a cost-effective alternative. The fact that there is still a probability that CRT-P is cost-effective at this high WTP threshold illustrates the uncertainty around the incremental benefit of CRT-D versus CRT-P.

Scenario analyses on mortality, hospitalisation and discount rates revealed that the results for CRT-P versus OPT can be considered robust. The difference in cost-effectiveness between CRT-P and CRT-D is mainly determined by the threefold-higher device price for a CRT-D versus CRT-P. Furthermore, at current price differences between CRT-P and CRT-D, small

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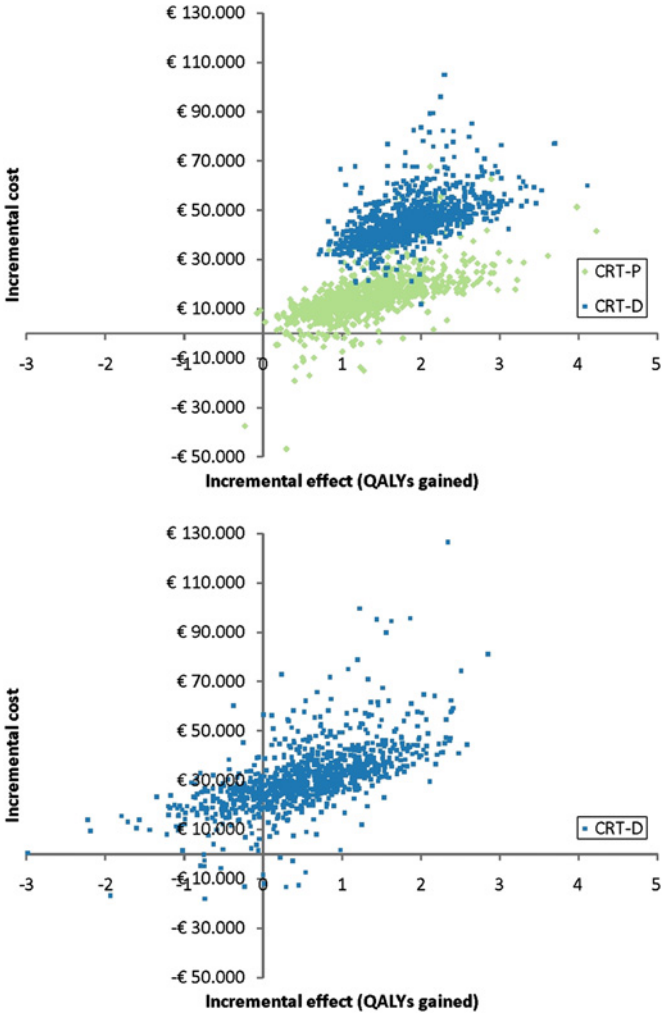

Figure 2 Cost-effectiveness planes for cardiac resynchronisation therapy with biventricular pacemaker only (CRT-P)/cardiac resynchronisation therapy with biventricular pacemaker with defibrillator (CRT-D) versus optimal pharmacological treatment (top) and CRT-D versus CRT-P (bottom). QALYs, quality-adjusted life-years.

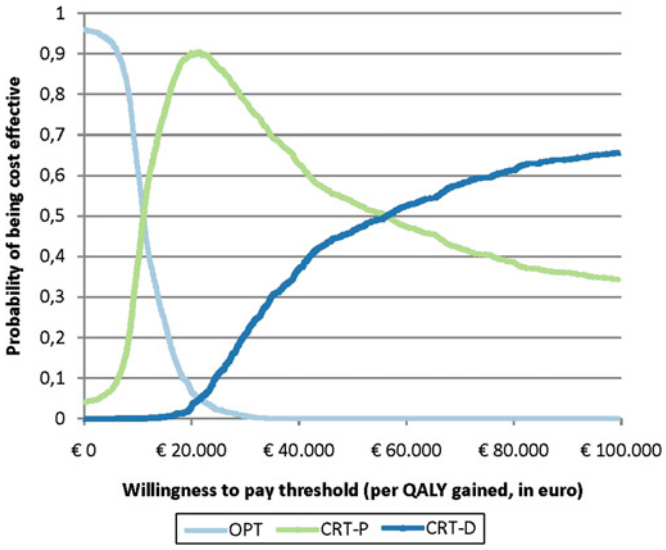

Figure 3 Cost-effectiveness acceptability curves for the three alternative treatment options: optimal pharmacological treatment (OPT), cardiac resynchronisation therapy with biventricular pacemaker only (CRT-P) and cardiac resynchronisation therapy with biventricular pacemaker with defibrillator (CRT-D). QALY, quality-adjusted life-year.

incremental benefits of CRT-D versus CRT-P result in relatively unfavourable cost-effectiveness ratios for CRT-D. For the results of these scenario analyses, we refer to the data supplements and the full HTA report (www.jamia.org).[7]

DISCUSSION

In previously published health economic evaluations of CRT, ICERs vary considerably, both for CRT-P versus OPT (from €3600[14] to $108 000[15] per QALY gained) and for CRT-D versus CRT-P (from £40 200[13] to $172 300[9] per QALY gained). A detailed overview of these evaluations is available in the full HTA report.[7] Since costs and resource use may widely vary across countries and because of methodological considerations, results might not be applicable to Belgian practice, and thus it was decided to perform a health-economic evaluation of CRT from a Belgian healthcare-payer perspective.

Compared with OPT, on average 1.31 QALYs are gained with CRT-P at an additional cost of €14 700, resulting in a relatively robust ICER of about €11 200/QALY. Reimbursing CRT-P can thus be considered as efficient use of limited sources if the WTP is higher than €11 000 for a QALY gained. Compared with CRT-P, CRT-D provides on average 0.55 QALYs at an extra cost of €30 900 or an average ICER of €57 000/QALY. This result largely depends on the added value of CRT-D versus CRT-P. Based on our indirect comparison, CRT-D was dominated by CRT-P in about 23% of the simulations. Current evidence is insufficient to show the superiority of CRT-D over CRT-P. With a threefold-higher device cost, CRT-D's cost-effectiveness is questionable.

All economic evaluations, including our own model, are subject to a number of common limitations. First, there is the short-term follow-up of the trials necessitating extrapolation assumptions. Second, the economic evaluations are limited by the external validity of the trial results. The technical skills of providers, patient selection and differences in the optimal treatment regimen may vary in real-world practice and affect the clinical effectiveness of the therapy. For example, only experienced providers participated in the trials. Therefore, it is possible that the complication rates are not generalisable to other, less experienced, provider settings, and results of the economic models may be biased in favour of CRT.

Furthermore, economic evaluations are limited by the way in which QoL was included. Generic utility instruments to measure QoL are not systematically used in trials. In contrast to this economic evaluation, several studies include utility values by NYHA class rather than for the different treatment groups. The validity of this approach depends on a double link: first, the link

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between the treatment and the outcome (in terms of NYHA class, which is a subjective measure for functional disability); second, the link between NYHA class and QoL. Such indirect determination bears an increased risk of inaccuracy. Since NYHA class utility estimates vary substantially between publications,[7] and results can be somewhat manipulated. It would be useful to include more systematically a generic utility instrument to measure QoL in trials. Calvert *et al*[11] showed that the EQ-5D appears to be an acceptable valid measure for use in patients with HF. Nevertheless, a minority of studies include such an instrument in addition to disease-specific instruments in their research protocol.

In our assessment of the cost−utility of CRT, we found that, compared with OPT, CRT-P has a better cost-effectiveness ratio than CRT-D. Therefore, the relevant comparator for assessing the cost-effectiveness of CRT-D, which is marginally and non-significantly more efficacious regarding mortality than CRT-P, is therefore CRT-P. The chosen comparator obviously may have a large impact on the resulting ICER. Feldman *et al*,[9] for instance, compared both CRT-P and CRT-D with OPT, but did not compare CRT-D with CRT-P. The ICER of CRT-D compared with OPT as reported by Feldman *et al* was $43 000 per QALY, whereas the ICER compared with CRT-P would have resulted in $172 300 per QALY. Economic evaluations should be performed on the so-called 'efficiency frontier,' and choosing an inappropriate comparator may influence results in a misleading way and alter conclusions.

A direct comparison of the performance of CRT-P versus CRT-D has not yet been performed. A Bayesian network meta-analysis of randomised controlled trials indicated that evidence is insufficient to show the superiority of CRT-D over CRT-P in these patients.[16] The added value of CRT-D versus CRT-P in patients with moderate to severe HF is unknown and may be an interesting topic for further research in a randomised controlled trial, especially because of the threefold-higher price for a CRT-D device versus CRT-P.

Correction notice The "To cite: …" information and running footer in this article have been updated with the correct volume number (volume 1).

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None.

Contributors MN carried out the economic analysis and drafted the paper. SS and CO performed an economic literature review to collect relevant data. SD prepared the demand for the Belgian commission for the protection of personal data. CC and SD analysed the Belgian data. CDL and HV provided medical advice and performed a medical literature review in search for relevant data. All authors participated in revising the draft paper and approved the version to be published. MN is guarantor for the paper.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Individual patient data are not available. Aggregated data are published in "Van Brabandt H, Camberlin C, Neyt M, *et al*. Cardiac Resynchronisation Therapy. a Health Technology Assessment. Brussels: Belgian Health Care Knowledge Centre (KCE), 2010" which is publicly available at http://kce.fgov.be/index_en.aspx?SGREF=5223&CREF=18664.

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APPENDICES

Costs for medical treatment

Prescription medication use was taken from the available data on the Belgian CRT population, right before implantation.[7] The amount and type of drugs are assumed to remain the same after implantation on a per patient base. Prescription medication costs are based on the cheapest formulation as indicated by the Belgian Centre for Pharmacotherapeutic Information, www.bcfi.be (accessed November 2010) (table A1). The percentage of users is included as a beta distribution with parameters reflecting the values of the Belgian CRT sample. This provides an average monthly medication cost of €30.88 per patient (95%CI 29.85 - 31.82).

Table A1: Costs for medical treatment

Drug	Units/ pkg	Price/ pkg	Non-refund.	DDD	Price/ DDD	Use*	Beta distribution**	
							alpha	beta
ACE-inhibitors								
captopril 50 mg (oral)	60	€9.04	€1.70	50mg	€0.15	65.1%	507	272
Angiotensin II antagonists								
losartan 50 mg (oral)	98	€30.09	€8.14	50mg	€0.31	20.7%	161	618
Beta-blocking agents								
carvedilol 6.25 mg (oral)	56	€7.56	€1.19	37.5mg	€0.81	68.5%	534	245
Spironolacton 25 mg (oral)	50	€7.90	€1.30	75mg	€0.47	34.0%	265	514
Loop diuretics						61.0%	475	304
furosemide 40 mg (oral)	100	€8.86	€1.64	40mg	€0.09	30.5%		
bumetanide 1 mg (oral)	30	€8.12	€1.38	1mg	€0.27	30.5%		
Digoxine 0.25 mg (oral)	120	€7.09	€1.03	0.25mg	€0.06	10.4%	81	698
Amiodaron 200 mg (oral)	60	€9.24	€1.77	200mg	€0.15	23.2%	181	598

*Source: Belgian CRT patients; **: Beta distribution applied for the percentage of users.
Antithrombotic agents were not included in this cost since they are not considered being part of optimal pharmacologic treatment of HF. For loop diuretics we assumed furosemide and bumetanide were taken in 50/50% of cases.
DDD: defined daily dose; non-refund.: non-refundable part; pkg: package

Utilities

Utility values are based on the studies of Cleland et al.,[8] Calvert et al.[11] and Feldman et al.[9] which are briefly outlined here.

In the CARE-HF publication, Quality of Life (QoL) was assessed at 90 days using the generic EQ-5D instrument. Patients in the CRT group had a better QoL compared to patients in the OPT group. The EQ-5D scores were 0.63 (SD 0.29) in the OPT group and 0.70 (SD 0.28) in the CRT group. The difference of 0.08 (95%CI 0.04 to 0.12) was statistically significant ($p<0.001$).[8] Unfortunately, no measurement of QoL at baseline was reported. As a result, it remains uncertain whether this difference is causally related to the resynchronization therapy.

Calvert et al.[11] presumed a potential 0.1 increase to the EQ-5D index score due to CRT. This assertion was based on the observed 13 point decrease (indicating an improvement) in the

Minnesota Living with Heart Failure (MLWHF) score of the MUSTIC trial[17] and the observed relationship between the EQ-5D index and MLWHF scores. On the other hand, Feldman et al.[9] employed data from the COMPANION trial. The participants of this trial completed the MLWHF questionnaire at baseline before implantation and after three and six months. Although this survey was not specifically designed to measure utility, a previously published algorithm[18] was used to convert MLWHF scores to utility preference weights. This resulted in utility weights at the baseline, third month, and sixth month of respectively, 0.62, 0.68, and 0.70 for the OPT group; 0.62, 0.78, and 0.79 for the CRT-P group; and 0.60, 0.77, and 0.77 for the CRT-D group.[9] Thus, also this study arrives at an indirectly measured QoL improvement of about 0.1.

All this lead to the following assertions for our model: 1) The baseline out-of-hospital utility was set to 0.68 (Table 1), i.e. the level after three months of OPT treatment in the COMPANION study, according to Feldman et al. Any lower baseline level would have implied that not all our modelled patients were already receiving optimal treatment at implantation. 2) We assumed that the utility improvement in the CRT-P/D groups amounts to 0.1, resulting in a utility weight of 0.78. In order to allow us to model a significant utility differences, these values were inserted into the model as symmetric beta distributions with an assumed minimum and maximum value of 0.05 below and above the mean value.

Finally, a utility weight for hospitalization due to heart failure was derived from the study of McAlister et al.[19] In that study, four health states were considered: NYHA functional class II, III, and IV, as well as heart failure severe enough to require hospitalization. People were presented a number of hypothetical scenarios, each illustrating what patients would typically feel and experience whilst living in one of these health states. The standard gamble technique for eliciting preferences was used. Based on the answers of 90 respondents, mean utilities for NYHA class II, III and IV were, respectively, 0.74, 0.84, and 0.94. Hospitalization corresponded to a mean utility of 0.57. These reported weight differences between NYHA class III or IV and heart failure hospitalization lead us to put the QoL weight for hospitalization an amount of 0.17 to 0.27 below that of baseline, resulting in an average utility weight of 0.46 for hospitalization. In absence of any better generic QoL estimates despite our literature search, we resented having to resort to this very crude estimate. Eventually, this lower utility was attributed only to the hospital stay of the initial and replacement implantations, which averaged respectively, 7.34 days and 4.47 days in the Belgian CRT sample (Table 1). For other hospitalizations, we assume that the impact of hospitalization on QoL was already implied in the QoL values of 0.68 for OPT and 0.78 for CRT-P and -D.

Results (base case)

According to the model, the undiscounted life expectancy is 4.6 years for the OPT group. CRT-P increases life expectancy with 1.31 years (95%CI -0.04 – 3.21). CRT-D adds another 0.8 years (95%CI -1.40 – 2.95) on top of CRT-P. If quality of life changes are taken into account, this becomes 1.47 QALYs (95%CI 0.39 – 3.00) and 0.63 QALYs (95%CI -1.18 – 2.38), respectively. This results in a discounted incremental effect adjusted for quality of life of 1.31 QALYs (95%CI 0.36 – 2.64) and 0.55 QALYs (95%CI -1.02 – 2.07), respectively (Table A2).

The average incremental cost is less than €15,000 for CRT-P versus OPT. In combination with the discounted gain in life expectancy, this results in an average ICER of about €12,800/LYG. If QoL-adjustments are taken into account, this becomes €11,200/QALY gained (Table A2). The ICER of CRT-D versus OPT (in red in table A2) is higher than that of CRT-P versus OPT, thus calculating the ICER on the efficiency frontier, CRT-P becomes its economic justified comparator. The total incremental cost of CRT-D versus CRT-P is on average more than €30,000. The ICER becomes on average €44,100/LYG or €56,600/QALY gained. More details and confidence intervals are available in Table A2.

Table A2: IC, IE, and ICERs for CRT-P/D, depending on the modelled mortality scenario

		Base case scenario
CRT-P vs OPT	**IC***	€14,745 -€1,935 €36,008
	IE (LYG)	1.15 -0.04 2.80
	IE (QALY gained)	1.31 0.36 2.64
CRT-D vs OPT	**IC**	€45,624 €29,821 €68,108
	IE (LYG)	1.85 0.81 3.17
	IE (QALY gained)	1.86 0.99 2.95
CRT-D vs CRT-P	**IC**	€30,879 €7,183 €60,263
	IE (LYG)	0.70 -1.21 2.54
	IE (QALY gained)	0.55 -1.02 2.07
ICER (€/LYG)	**CRT-P vs OPT**	*€12,834***
	CRT-D vs OPT**	€26,638 €16,531 €46,931
	CRT-D vs CRT-P	*€44,080*
ICER (€/QALY gained)	**CRT-P vs OPT**	*€11,219*
	CRT-D vs OPT	€25,639 €16,920 €41,385
	CRT-D vs CRT-P	*€56,615*

*: mean and 95%CI are mentioned;

** Results comparing CRT-D versus OPT were calculated and are shown to situate CRT-D versus OPT on the cost-

effectiveness plane. Results are shown in red since this comparison is not situated on the efficiency frontier.
*** The probabilistic average and 95%CI are mentioned where appropriate. This approach is not reliable in case the simulated ICERs are spread over several quadrants of the cost-effectiveness plane. As an alternative (in italics), in these cases, the presented ICERs are calculated by dividing the mean incremental cost by the mean incremental effect.
CRT-P/D: cardiac resynchronization therapy (CRT) both with pacemaker (CRT-P) and additionally including a defibrillator (CRT-D); IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LYG: life-year gained; OPT: optimal pharmacologic treatment; QALY: quality-adjusted life year.

Scenario analyses

In the base case scenario, mortality was inferred from the COMPANION trial data, for it being the only trial looking separately at both CRT-P and CRT-D versus OPT. In a different scenario, based on the meta-analysis of Lam et al.,[16] the odds ratio for all cause mortality was 0.67 (95%CI 0.5 to 0.9) for CRT-P versus OPT (based on the CARE-HF, COMPANION, MUSTIC, and MIRACLE trials) and 0.64 (95%CI 0.46 to 0.9) for CRT-D versus OPT (based on COMPANION). Both ratios were modelled using a log-normal distribution and this treatment effect was applied to the age-dependent survival of the OPT group. Results of this scenario are presented in table A3.

Out of all the modelled scenarios, this scenario has a relatively large influence on results. The survival gain of CRT-P versus OPT improves and becomes significant when results of the meta-analysis are used. The ICER of CRT-P versus OPT remains about the same, i.e. €11,200/QALY gained. For the comparison of CRT-D versus CRT-P, the result is much less favourable (€187,500/ QALY gained). However, for this comparison, this scenario is less reliable since the results of the meta-analysis are based on four studies for CRT-P (CARE-HF, COMPANION, MUSTIC, MIRACLE), whereas there is only the COMPANION study for CRT-D. As a result, this indirect comparison may be based on different populations which might lead to an important bias on the reliability of such an indirect comparison between CRT-P and CRT-D. Nevertheless, the analysis shows that at current price differences between CRT-P and CRT-D, small incremental benefits of CRT-D versus CRT-P result in unfavourable cost-effectiveness ratios for CRT-D.

Table A3: IC, IE, and ICERs for CRT-P/D, depending on the modelled mortality scenario

		Base case scenario		Alternative mortality scenario	
CRT-P vs OPT	**IC***	€14,745		€18,691	
		-€1,935	€36,008	€3,066	€43,148
	IE (LYG)	1.15		1.61	
		-0.04	2.80	0.40	2.90
	IE (QALY gained)	1.31		1.67	
		0.36	2.64	0.68	2.69
CRT-D vs OPT	**IC**	€45,624		€45,237	
		€29,821	€68,108	€27,209	€70,048
	IE (LYG)	1.85		1.79	
		0.81	3.17	0.40	3.28
	IE (QALY gained)	1.86		1.81	
		0.99	2.95	0.68	2.96
CRT-D vs CRT-P	**IC**	€30,879		€26,547	
		€7,183	€60,263	-€600	€57,607
	IE (LYG)	0.70		0.18	
		-1.21	2.54	-1.64	2.03

	IE (QALY gained)	0.55 -1.02	2.07	0.14 -1.37	1.66
ICER (€/LYG)	**CRT-P vs OPT**	*€12,834****		*€11,623*	
	CRT-D vs OPT**	€26,638 €16,531	€46,931	*€25,249*	
	CRT-D vs CRT-P	*€44,080*		*€144,628*	
ICER (€/QALY gained)	**CRT-P vs OPT**	*€11,219*		*€11,180*	
	CRT-D vs OPT	€25,639 €16,920	€41,385	*€26,905* €16,875	€48,954
	CRT-D vs CRT-P	*€56,615*		*€187,479*	

*: mean and 95%CI are mentioned;
** Results comparing CRT-D versus OPT were calculated and are shown to situate CRT-D versus OPT on the cost-effectiveness plane. Results are shown in red since this comparison is not situated on the efficiency frontier.
*** The probabilistic average and 95%CI are mentioned where appropriate. This approach is not reliable in case the simulated ICERs are spread over several quadrants of the cost-effectiveness plane. As an alternative (in italics), in these cases, the presented ICERs are calculated by dividing the mean incremental cost by the mean incremental effect.
CRT-P/D: cardiac resynchronization therapy (CRT) both with pacemaker (CRT-P) and additionally including a defibrillator (CRT-D); IC: incremental cost; ICER: incremental cost-effectiveness ratio; IE: incremental effect; LYG: life-year gained; OPT: optimal pharmacologic treatment; QALY: quality-adjusted life year.

For hospitalizations, two alternative scenarios were modelled. In a first scenario, the overall hospitalization rate was 0.089 after 24 months, as in the study of Feldman et al.[9] This corresponds to the monthly admission rate during months 19 to 24, averaged across the three study groups according to the COMPANION trial data. The other hospitalization scenario was based on Bond et al.[13]/Fox et al.[10] Here, a monthly probability of hospitalization due to heart failure was set to 0.0381 for the OPT group. The relative risk of heart failure hospitalization was 0.65 (95%CI: 0.45 to 0.94) for both CRT-P and -D groups, modelled as a log-normal distribution. Both scenarios assumed hospitalization rates to remain constant over the full time horizon.

A scenario with an equal service life of 5 years for CRT-P and CRT-D alike was also included. In a final set of scenarios, discounting was changed in a number of ways, considering either equal discounting for both costs and effects (at respectively 0%, 3% and 5%) or only discounting of costs (at respectively 3% and 5%).

For the results of these and other scenario analyses, we refer to the full HTA report.[7] The most important conclusion of these scenario analyses is that the calculated ICER for CRT-P versus OPT seems to be robust, while the ICER of CRT-D versus CRT-P is very dependent on the incremental clinical benefit of CRT-D in comparison to CRT-P. A Bayesian network meta-analysis[16] of randomized controlled trials indicated that evidence is insufficient to show the superiority of CRT-D over CRT-P. Further research could focus on the added value of CRT-D versus CRT-P in patients with moderate to severe heart failure, especially because of the threefold higher price for the CRT-D device.