

# Economic Assessment of Cardiac Resynchronization Therapy

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**Introduction and objectives.** Cardiac resynchronization devices have been shown to be effective in treating heart failure. They reduce overall mortality, heart failure mortality and hospitalizations due to heart failure. The aim of this study was to compare the cost effectiveness of cardiac resynchronization therapy (CRT) with that of optimal drug therapy (ODT) by carrying out an economic assessment in the Spanish healthcare setting.

**Methods.** An existing model was adapted for use in the Spanish healthcare setting. The effectiveness of cardiac resynchronization therapy was determined from published systematic reviews. The costs of the various interventions were determined using a range of Spanish data sources. The model adopted the perspective of the public health system and the time horizon considered was the remainder of the patient's life. The outcome variables were life-years gained and quality-adjusted life-years (QALYs) gained.

**Results.** Overall, ODT, CRT and CRT with a defibrillator resulted in gains of 2.11, 2.8 and 3.19 QALYs, respectively, at a cost of €11,722, €31,629 and €52,592, respectively. Consequently, each QALY gained with CRT relative to ODT involved the consumption of €28,612 of additional resources. Similarly, the use of CRT with a defibrillator cost an additional €53,547 per QALY relative to CRT without a defibrillator.

**Conclusions.** The use of CRT without a defibrillator could be a cost-effective alternative to ODT for treating heart failure in a carefully selected group of patients. The study results were sensitive to uncertainties in many of the variables used in the model.

**Key words:** *Pacemakers. Heart failure. Cardiac resynchronization. Cost-benefit analysis. Electrophysiology. Defibrillator.*

## Evaluación económica de la terapia de resincronización cardiaca

**Introducción y objetivos.** La terapia de resincronización cardiaca es un tratamiento de eficacia demostrada para la insuficiencia cardiaca y reduce el número de hospitalizaciones y la mortalidad por progresión de la insuficiencia y total. El objetivo de nuestro trabajo es determinar la eficiencia de la terapia de resincronización cardiaca comparada con la terapia farmacológica mediante una evaluación económica adaptada a nuestro entorno sanitario.

**Métodos.** Se realiza la adaptación al ámbito sanitario español de un modelo previamente existente. Las fuentes de efectividad utilizadas son revisiones sistemáticas de la literatura publicadas. Los costes de las distintas intervenciones se determinan de acuerdo con diversas fuentes de datos españolas. Se utiliza la perspectiva del sistema sanitario; como horizonte temporal, el resto de vida de los pacientes, y como variables de resultado, años de vida y años de vida ajustados por calidad (AVAC).

**Resultados.** El tratamiento farmacológico, la resincronización y resincronización + desfibrilador alcanzaron 2,11, 2,8 y 3,19 AVAC, a un coste de 11.722, 31.629 y 52.592 euros, respectivamente. Cada AVAC obtenido con resincronización frente a medicación requiere el uso de 28.612 euros de recursos adicionales. De modo análogo, la resincronización con desfibrilador cuesta 53.547 euros/AVAC respecto a la resincronización sin desfibrilador.

**Conclusiones.** La terapia de resincronización cardiaca sin desfibrilador puede ser una opción de tratamiento coste-efectiva para el grupo de pacientes adecuadamente seleccionados, comparada con la terapia farmacológica óptima. Este resultado es sensible por la incertidumbre en numerosas variables del modelo.

**Palabras clave:** *Marcapasos. Insuficiencia cardiaca. Resincronización cardiaca. Análisis coste-beneficio. Electrofisiología. Desfibrilador.*

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## ABBREVIATIONS

CRT: cardiac resynchronization therapy  
CRT-ICD: cardiac resynchronization therapy with implantable cardioverter defibrillator  
HF: heart failure  
ICD: implantable cardioverter defibrillator  
ICER: incremental cost-effectiveness ratio  
NYHA: New York Heart Association  
ODT: optimal drug therapy

## INTRODUCTION

Heart failure (HF) is one of the most prevalent and fatal disorders, with one of the highest resource consumption rates in healthcare systems. In Spain, at least 2% of the population over 40 years old and between 6% and 10% of the population over 60 suffer from HF.<sup>1</sup> It is the leading cause of hospitalization among those over 65 years old, with 74 000 hospitalizations per year. As such, it consumes between 1.8% and 3.1% of the healthcare budget.<sup>2,3</sup> It is a progressive and fatal disorder for which prognosis is unsatisfactory, even with proper treatment. The mortality rate at 4 years is 50%, while the rate in people suffering from severe HF is about 1 year,<sup>4</sup> similar to more aggressive cancer types.

To ascertain the severity of HF<sup>5</sup> we usually examine the symptoms, limitations in physical activity<sup>6</sup> and the structural changes produced in the heart.<sup>7</sup>

The optimal drug therapy (ODT) for HF has made use of multiple strategies which included and combined the following: ACE inhibitors or angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, aldosterone antagonists, and beta-blockers. However, a large number of patients continued to suffer from a lower quality of life and have a high mortality rate. These are non-responder patients, who continued suffering despite receiving proper drug treatment.

Cardiac resynchronization therapy (CRT) is a technology that offers a new treatment option for patients with HF. As a mechanical device, it aims to improve the effectiveness of blood pumping by coordinating the various segments of the heart, which previously functioned without synchronization.<sup>8</sup> The performance mechanism of CRT corrects the electromechanical asynchrony by acting on the atrioventricular, interventricular, intraventricular, and intramural delay. It therefore improves the haemodynamic parameters and the cardiac function

without increasing oxygen consumption.<sup>9</sup> It can be used together with an implantable cardioverter-defibrillator (CRT-ICD). It is estimated that between 20% and 30% of patients with symptomatic HF and 10% of unselected HF patients suffer from intraventricular conduction disorders, and these patients could benefit from CRT.<sup>10</sup> At present, to reduce morbidity and mortality,<sup>5,7</sup> CRT is recommended in clinical practice guidelines for the treatment of patients in functional class III and IV of the New York Heart Association (NYHA) who remain symptomatic despite ODT and have a decreased ejection fraction and prolonged QRS.

The continuing emergence of new healthcare technologies requires the assessment of additional benefits provided by these technologies in relation to the increasing healthcare expenditure involved.

In this context, this paper will carry out an economic evaluation of CRT by comparing it with ODT for the treatment of patients with HF in NYHA functional class III and IV, within the Spanish healthcare setting.

## METHOD

A cost-benefit analysis was performed in patients with HF in NYHA functional class III and IV and with a decreased ejection fraction and prolonged QRS. The analysis included 4 treatment alternatives. The first consisted of CRT. The second included CRT without defibrillation capability, in addition to optimal drug therapy (CRT + ODT), and the third also incorporated defibrillation capability (CRT – ICD + ODT). Quality-adjusted life years (QALYs) were used as the main measure of effectiveness. The evaluation was developed from the perspective of the financial backer (National Healthcare System), and both the costs and effects that would occur in the future were discontinued at a rate of 3%.<sup>11</sup>

### Baseline Characteristics of the HF Population

Four Spanish registers of patients with HF were used<sup>12-15</sup> to determine the age characteristics of the reference population. Thus, based on 7939 patients included in the abovementioned records, our cohort was composed of 39.5% women and the mean age was 69.3 years.

### Non-Cardiac Mortality

It is assumed that the value in this variable is not affected by the treatment received.

This variable was calculated with data on mortality by cause that were available from the Spanish National Statistics Institute, according

to the International Statistical Classification of Diseases and Related Health Problems (ICD) 10 (<http://www.ine.es/jaxi/tabla.do?path=/t15/p417/a2007/10/&file=01000.px&type=pcaxis&L=0>) for 2007, adjusted by sex and age group.

Any mortality related to heart disease, codes I44 to I50 of the ICD-10, was deducted from the overall mortality variable for each age group and sex. The probability of dying from other causes, age and sex weighted, was calculated with these figures and those of the population, also by age and sex.

## Effectiveness Data

Following the criteria of evidence-based medicine, a meta-analysis of previously published randomized clinical trials was used<sup>16,17</sup> as the best source to determine the relative clinical effectiveness of the alternatives studied (Table 1). The relative risks among the various treatment options were obtained from the study of McAlister et al,<sup>17</sup> which introduced an independent analysis for the subgroup of patients in functional class III and IV.

**TABLE 1. Parameters Used in the Model**

Parameter	Value (95% CI)	Source
Progression of death probability for HF with ODT	Weibull distribution ( $\lambda = 0.0027 / \gamma = 1.31$ )	16, 27
RR interval of HF progression	CRT and CRT-ICD 0.56 (0.38 to 0.82)	17
	ICD: 0.99 (0.70 to 1.38)	17
Sudden death probability for ODT	Weibull distribution ( $\lambda = 0.0015 / \gamma = 1.4$ )	16, 27
RR interval for sudden death	CRT: 0.91 (0.60 to 1.38)	17
	CRT-ICD and ICD: 0.46 (0.37 to 0.57)	17
Hospitalization probability <sup>a</sup> for HF with ODT	0.0412 (0.0318 to 0.0572)	16
RR interval of hospitalization for HF	CRT and CRT-ICD: 0.51 (0.41 to 0.64)	17
Arrhythmia probability <sup>a</sup> requiring hospitalization	ODT and CRT: 0.0083	16
	CRT-ICD and ICD: 0	Assumption
Complications probability <sup>a</sup> of CRT-ICD implant	0.1063	16
Death probability <sup>a</sup> for CRT or ICD surgery	0.0076 (0.005 to 0.012)	16
Infection probability <sup>a</sup> for CRT or ICD	0.0022 (0.00 to 0.0062)	16
Migration probability <sup>a</sup> of CRT electrode cable	0.006	16
Duration of battery	CRT: 78 months	Assumption
	CRT-ICD: 66 months	
	ICD: 60 months	
<b>Costs</b>		
Item	Cost, €	Source
Hospitalization due to HF	3076.26	21
Hospitalization due to arrhythmia	1558.37	21
First visit	141.5	23
Next visit	84.69	23
Discharge visit	210.11	23
CRT device	4257	EUCOMED
RV cable for CRT-ICD	400	
RA cable for CRT-ICD	400	
LV cable for CRT-ICD	832	
CRT-ICD device	20 294	
Defibrillation cable	1318	
Defibrillator implant	12 066.03	21
Hourly cost / operating theatre	989.98	CM Cost accounting
Daily stay at nursing unit	493.99	CM Cost accounting
DT / month	22.09	22
<b>Scale of values</b>		
NYHA I	0.69±0.16	18 and AstraZeneca Data on file
NYHA II	0.60±0.14	18 and AstraZeneca Data on file
NYHA III	0.49±0.15	18 and AstraZeneca Data on file
NYHA IV	0.35±0.20	18 and AstraZeneca Data on file

Abbreviations: CM: Community of Madrid; CRT / CRT – ICD, cardiac resynchronization therapy / cardiac resynchronization therapy with defibrillator; ODT, drug therapy; GRD, diagnosis-related group; HF, heart failure; ICD, implantable cardioverter-defibrillator; RA, right atrium; RV / LV, right ventricle / left ventricle.

<sup>a</sup>Probability by monthly cycle

Utility values associated with the stages of the NYHA scale were obtained from measurements taken from 2709 patients from the Spanish INCA study.<sup>18</sup>

The patient cohort included in the model began in functional class III and IV. The temporal evolution of the functional class depended on the treatment followed. Therefore, the information of the clinical trial CARE-HF<sup>19,20</sup> was used, since it was the study with the longest follow-up period that included Spanish patients. After 18 months, ie, the follow-up period of the abovementioned trial, we assumed that the patients remained in the functional class achieved.

### Cost Data

Various sources were used to determine unit costs. Official sources were preferred, whenever possible, as they were considered less subject to bias. In this way, those procedures collected by diagnosis-related groups (DRGs) were taken from the Spanish Ministry of Health and Social Policy,<sup>21</sup> as were the medicine prices that constitute the ODT costs.<sup>22</sup> The prices for visits were obtained from the official prices of the Community of Madrid.<sup>23</sup>

Since the cost of CRT and CRT-ICD devices exceeded the cost of the procedure as reported by DRGs already be collected, we referred to the information submitted by the manufacturer. We used the average purchase price of the resynchronization devices in the public tenders in the first quarter of 2009. The cost of the surgery and hospital stay was added to the cost of the device, which was calculated using cost data taken from the cost accounting of the Community of Madrid.

The cost data were updated through the general index of consumer prices at constant 2009 prices, whenever necessary.

### Analytical Model of Economic Evaluation

The economic evaluation was performed by adapting a previously published Markov model of the Spanish healthcare setting.<sup>16</sup> The Markov models are representations of reality through a finite number of healthcare states, which must be comprehensive and exclusive, ie, each individual must match only one of those states. Events that may happen to each individual included in the model are modeled as steps or transitions between states, which occur at fixed-time intervals called "cycles." The likelihood that these steps occur between states is defined by the transition probabilities between states.<sup>24,25</sup> For the patients on the CRT and CRT-ICD options, the model began with the surgery to implant the device. These

patients could suffer complications leading to death or the complications were finally overcome. Subsequently, the patients went through one of the health states associated with the device implanted. These 4 states were as follows: stable, worsening of HF requiring hospitalization, local infection caused by the device, or migration of the electrode cable. In the case of the CRT device without a defibrillator and ODT, the patients, who suffered an arrhythmia that required hospitalization underwent surgery to install a CRT-ICD or an implantable cardioverter-defibrillator (ICD), respectively. At any moment, and from all health states considered, death could occur due to the following 3 reasons: worsening of HF, sudden death or other causes (Figure 1).

The duration of the cycle in our model was 1 month, which we consider adequate to reflect the possible evolution of the disorder.

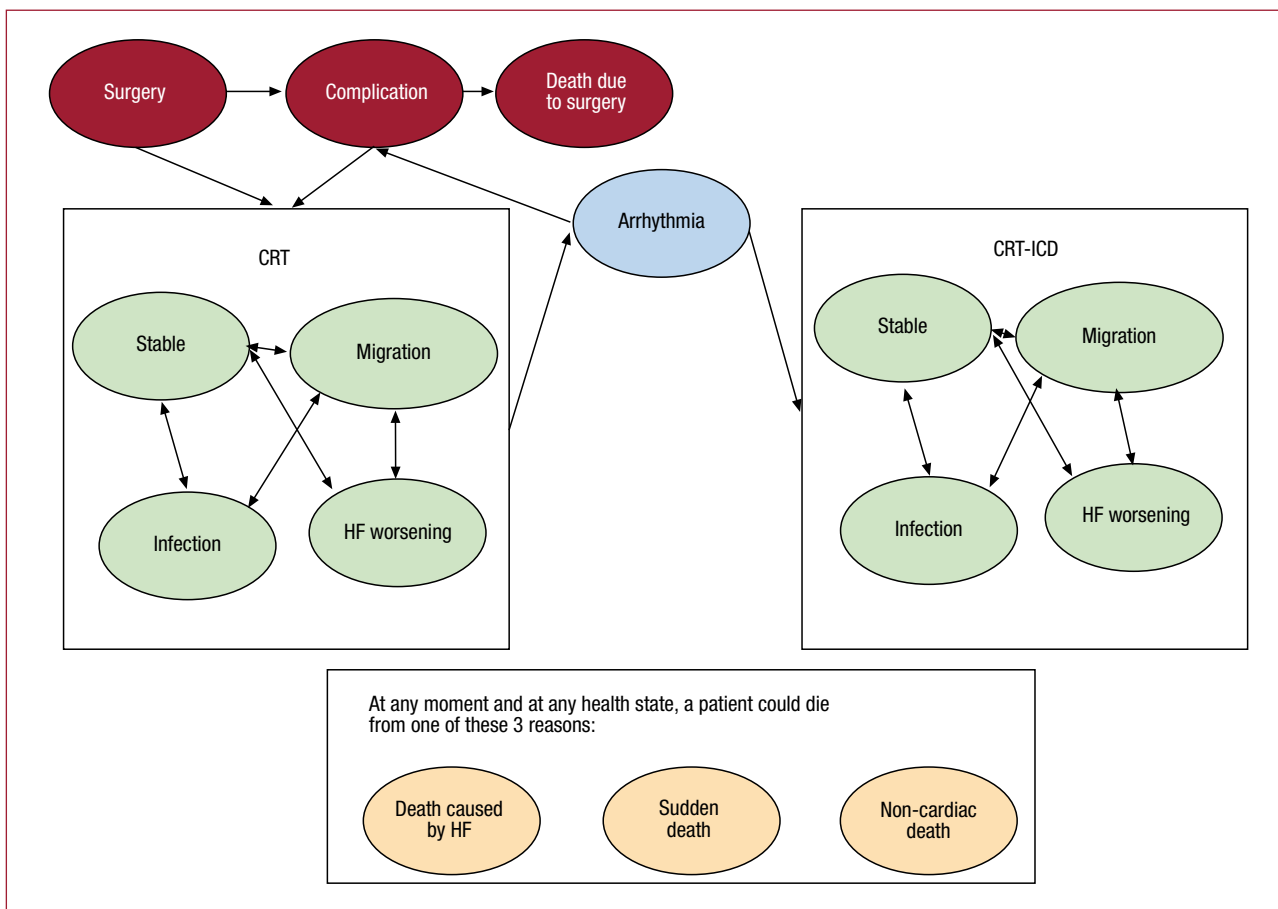
We performed a univariate sensitivity analysis on all the parameters of the model to confirm the ones that had a greater influence on the results obtained. The results of the sensitivity analysis are presented through tornado diagrams that show the degree to which the variation of the values of the different variables affects the model's results. The ranges of variation set for each variable were the confidence intervals estimated at 95%.

The model and the calculations were created using the Microsoft Excel 2003 application.

## RESULTS

The results for the baseline case of our economic evaluation (Table 2), that is, a cohort of patients with an average age of 69 years and 3 months, made up of 39.5% women, were:

1. The patients treated with ODT had a discounted half-life of 3.86 years, 2.11 QALYs and the average cost of treatment was €11 722.
2. The patients treated with CRT + ODT lived for 4.71 years, 2.80 QALYs, with a cost of treatment of €31 629. Regarding the ODT, CRT improves discounted life expectancy in this group of patients by 0.85 years and 0.70 QALYs, with an incremental cost of approximately €20 000. This means that with this option each QALY year would cost €28 612, compared with treatment with ODT.
3. In patients treated with CRT-ICD + ODT, life expectancy was 5.36 years, 3.19 QALYs, with a cost of treatment of €52 593. These results entailed an improvement of 1.50 years of life in the prognosis of patients compared to ODT and 0.65 years in comparison to resynchronization without an associated defibrillator. The QALYs increased by



**Figure 1.** Model for the CRT alternative option. A patient with HF is implanted with the CRT. The surgery can involve complications and even death. With the device implanted, the patient may remain stable or suffer deterioration of the HF that requires hospitalization, device-related infection, or migration of the electrode cable. He may also suffer from arrhythmia that requires the updating of the CRT-ICD device. The patient can die from any of the abovementioned causes because of HF, sudden death or other causes.

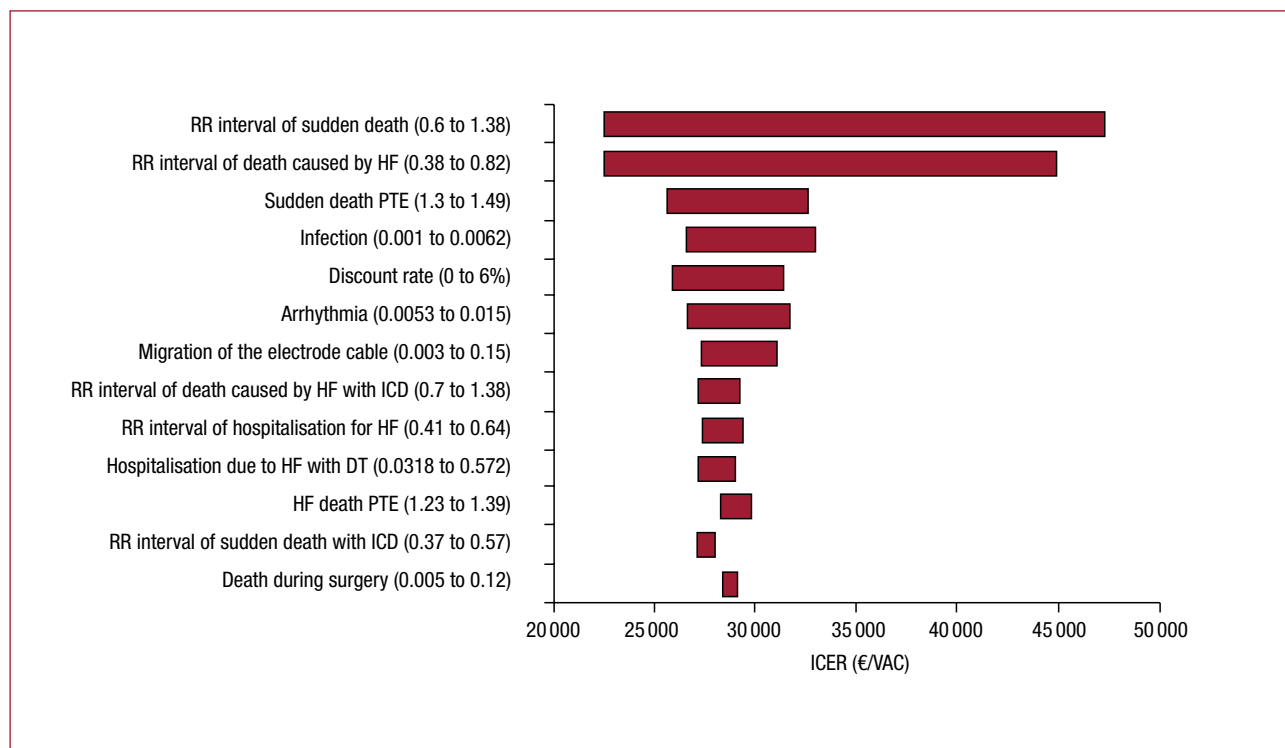
**TABLE 2. Results of the Baseline Case**

	Cost, €	Δ Cost	Life Years	Δ Life Years	QALY	Δ QALY	€/life year gained	€/QALY
<b>Mixed cohort</b>								
ODT	11 722		3.86		2.11			
CRT+ODT	31 629	19 906	4.71	0.85	2.80	0.69	23 419	28 612
CRT-ICD +ODT	52 593	20 963	5.36	0.65	3.19	0.39	32 250	53 547
<b>Men</b>								
ODT	11 505		3.78		2.07			
CRT+ODT	31 082	19 576	4.59	0.81	2.73	0.66	24 167	29 339
CRT-ICD +ODT	51 625	20 543	5.21	0.62	3.1	0.37	33 133	55 478
<b>Women</b>								
ODT	12 054		3.98		2.17			
CRT+ODT	32 467	20 413	4.89	0.91	2.91	0.74	22 432	27 608
CRT-ICD +ODT	54 076	21 608	5.59	0.7	3.33	0.42	30 869	50 964

Δ: indicates increase; CRT/CRT-ICD, cardiac resynchronization therapy/cardiac resynchronization therapy with defibrillator; DT, drug therapy; QALY, quality-adjusted life years.

1.09 and 0.39 years, respectively. These improvements were achieved with an incremental cost of €40 870 for ODT and €20 964 for CRT without a defibrillator.

Therefore, the incremental cost-effectiveness ratio (ICER) was €37 591 per QALY versus ODT and €53 547 per QALY versus CRT + ODT.



**Figure 2.** CRT versus ODT sensitivity analysis. The tornado diagram shows how the individual variations of the parameters affect, within its limitations, the result of the incremental cost-effectiveness ratio (€/QALY) calculated by our model.

## Sensitivity Analysis

The results obtained in our baseline case were sensitive to individual variations in the values of the key effectiveness parameters used in the model, depending on the alternative options compared.

If we compare CRT and ODT (Figure 2), we can see that the 2 most influential parameters on the end result were the relative risks of death from HF and sudden death with CRT versus ODT. In the lowest value of the confidence interval of 95%, these risks decreased the ICER approximately to €22 500 per QALY. By contrast, when placed in the highest value of the confidence interval, the ICER reached €45 000 and €47 000 per QALY, respectively. In addition, other parameters that would boost the result of our evaluation beyond the value of €30 000 per QALY are as follows: the likelihood of arrhythmia, the migration and infection of the device, the slope of the survival curve for sudden death and the discount rate.

If the comparison analyzed was for CRT-ICD versus CRT, the result, in terms of ICER, remained constant between €48 000 and €70 000 per QALY, as shown in Figure 3. The only parameter that moved the results outside this range was the relative risk of sudden death between the systems with CRT and those with ODT. The result, therefore, varied between €33 000 and €147 000 per QALY.

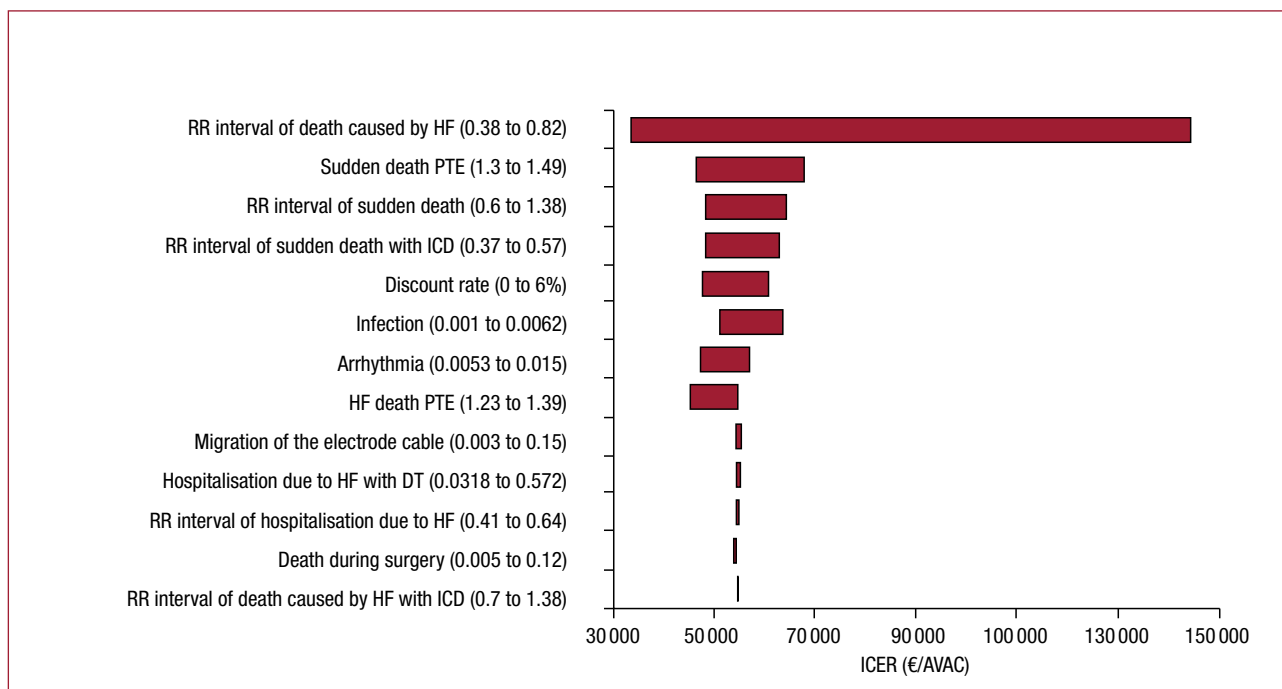
## DISCUSSION

The economic evaluation of healthcare technologies aims to provide information during the decision-making process on the introduction of technologies within the healthcare service portfolio. It does not seek to replace the judgment of medical professionals who have made a decision for an individual patient.

We have developed an economic evaluation model that uses the meta-analysis of randomized controlled trials (RCTs) as a source of effectiveness, which is considered the highest level of scientific evidence. The results will be valid to the extent that similar results can be achieved in routine clinical practice.

The results of the economic evaluation made for our healthcare setting are within the range of previously published studies<sup>16,26-31</sup> for other geographical areas.

The following limitations of our economic evaluation should be noted: first, it is a developing technology, thus it is expected that the results will be further improved as the technology evolves. By including data from the first published RCTs, we are possibly skewing the results of our evaluation against CRT. Secondly, by including only randomized studies, it is possible that the results are more favorable for surgery than those achieved in the routine clinical practice.



**Figure 3.** CRT-ICD versus CRT sensitivity analysis. The tornado diagram shows how the individual variations of the parameters affect, within its limitations, the result of the incremental cost-effectiveness ratio (€/QALY) calculated by our model.

Our model is based on published studies, the majority of which have a short follow-up period. It seems clear that the longer the follow-up period, the greater the incremental effect achieved with CRT.<sup>32</sup> In fact, only one study has an average follow-up period of over 2 years (CARE HF),<sup>26,27</sup> which would mean that the benefits of CRT were under-considered.

The results obtained by visual analog scale were used as quality-of-life scores, although it would have been desirable to use those obtained from the EQ-5D questionnaire. Nevertheless, they constitute the scores available in a sufficiently representative sample of Spanish patients with HF.<sup>18</sup>

It should be noted that two systematic reviews were used to determine the clinical effectiveness of CRT.<sup>16,17</sup> The review by McAlister et al<sup>17</sup> performed an analysis of a subgroup of patients in NYHA functional class III and IV, which is currently indicated for recourse to this procedure. We used this analysis in our evaluation to estimate the effectiveness of CRT. The sense in which this decision affects the results of our evaluation is unclear, since on the one hand the effect of CRT will be greater when this group of selected patients is independently analyzed. On the other hand, it will mean that, except for ODT, the control group includes other treatments.

The cost data were obtained from various official sources, whenever possible. The Spanish Ministry of Health publishes both the hospital procedures of the DRGs<sup>21</sup> and the medicines on the Name Index.<sup>22</sup> Concerning visits, we used information published by the Community of Madrid<sup>23</sup> in the Official Gazette, since such information is unavailable at a national level. All these sources can be considered highly representative of our scenario, although using different sources may affect the calculation methodology. The price of resynchronization devices, and therefore of related procedures, was the only datum that could not be obtained from any official source. The DRG procedures published by the Ministry, which would include the implant procedure for resynchronization systems, has a lower cost than the CRT-ICD generator. We therefore decided to calculate the costs incurred by these procedures from the information on the price for the award of public tenders in the first quarter of 2009, which was compiled by the consultancy EUCOMED for the Spanish industry. We added a price for the cost of the surgery and hospital stay in these prices, which was obtained from the analytical accounts of the Community of Madrid.

The life expectancy of patients who were implanted with the device affects the effectiveness of the device, since the greater the effectiveness is, the longer the patients will benefit from an improvement in their

quality of life, and the greater the prevention of a number of events requiring hospitalization for HF. It may therefore be a factor to consider when deciding on the implant. The price of the device is a factor that greatly affects the effectiveness of the technology. If, as it appears from the technology diffusion curve, the price decreases with time, together with the actual progress and continuous improvement in the devices, it will lead to an improvement in the effectiveness of the technology.

The use of CRT-ICD features better clinical effectiveness in terms of survival and a QALY of approximately 1.5 times that achieved with CRT without a defibrillator. However, the cost increase is more than 2 times that of CRT without a defibrillator. Future research should focus on identifying the group of patients that may obtain a greater benefit from the addition of the defibrillator to the cardiac resynchronization therapy.

## CONCLUSIONS

Our economic evaluation indicates that cardiac resynchronization therapy can be an effective treatment option for patients with HF and NYHA functional class III and IV, compared to the ODT option. CRT achieves a significant improvement in the median survival rate and in the QALYs. It achieves this effectiveness through an increase in the cost of just under €30 000 per QALY, which is acceptable for Spanish healthcare technologies,<sup>33</sup> even though the result is influenced by the existing uncertainty in many parameters of the model that place the comparative effectiveness of the technology over the abovementioned limit.

CRT-ICD also achieves an improvement in the expected survival rate and in the expected QALYs, when compared to CRT without an associated defibrillator. However, this increase in effectiveness is achieved with an increase in the cost of about €60 000 per QALY. This discourages its widespread use for the patients who are the subject of our evaluation, requiring the correct selection of patients for the joint use of resynchronization and defibrillator. Further research should be undertaken to try to clarify the abovementioned group of patients.

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