Cardiac resynchronisation therapy
A Health technology Assessment

KCE reports 145C

Belgian Health Care Knowledge Centre
Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
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FOREWORD

Every year, more than 15,000 Belgians are diagnosed with heart failure for the first time. The number of patients suffering from heart failure is constantly growing due to ageing of the population and the fact that people increasingly survive an acute cardiac problem.

Until ten years ago the only treatment for heart failure was medication and dietary measures. Only a small number of patients were eligible for a heart transplantation. For the past ten years or so, a new technique that can bring relief to certain heart failure subjects has been available: cardiac resynchronisation therapy. This technique involves implanting a specially designed pacemaker that optimises the contraction of the heart. Large-scale international studies have demonstrated the efficacy of this treatment, but implantation of such a device remains a very expensive and sophisticated technique.

This report extends and complements the previous KCE reports on conventional pacemakers (report no. 137) and implantable defibrillators (report no. 58). As usual, we assess to what extent the published studies support this treatment modality and we document how it is currently used in Belgium. This report is intended to assist the public authorities to implement these technologies in Belgian healthcare, while taking into account the limited availability of resources.

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Summary

INTRODUCTION

Cardiac resynchronisation therapy (CRT) is a treatment modality that makes use of a special pacemaker that stimulates the ventricles of the heart (so-called biventricular pacing) with the aim of improving the heart's pumping action. This technique has been in use since 2000 for certain patients suffering from heart failure in whom a standard treatment with a combination of drugs and diet is not adequate.

Heart failure can result from various cardiac pathologies, in particular myocardial infarction, arterial hypertension, cardiac muscle disorders and valve problems.

The effectiveness of cardiac muscle contraction is represented by the left ventricular ejection fraction, which is the percentage of blood present in the heart that is ejected with each contraction. This fraction is normally greater than 50%.

Heart failure patients suffer mainly from shortness of breath. Nevertheless, the symptoms vary considerably and are expressed on a scale of I to IV in the New York Heart Association classification (NYHA). A NYHA class I patient is not affected during normal daily activities. Class II patients find that ordinary daily activities cause them problems. Class III patients are affected by the least effort and class IV patients are even affected when at rest.

The prognosis for heart failure patients is bleak. A recent Belgian study on new heart failure cases indicates that 20% of such patients die within a period of six months, mainly those in NYHA class III or IV.

This report highlights the following aspects of cardiac resynchronisation therapy:

- The efficacy and effectiveness of CRT according to the medical literature.
- Current CRT practice in Belgium, based on administrative data from Belgian patients.
- Health economic evaluation of CRT, based on the same data sources.

It also attempts to answer a series of policy questions:

- What is the cost of CRT?
- How many patients are eligible for such treatment?
- How can this technology be optimally used in Belgium with a view to providing superior healthcare yet taking into account the available resources?

CRT TECHNOLOGY

In its basic form, the biventricular pacemaker used for cardiac resynchronisation is called CRT-P ("P" for pacemaker). There is a version that also has a defibrillator function which is known as the CRT-D ("D" for defibrillator).

CRT-P

A conventional bradycardia pacemaker stimulates the heart to induce contraction when it beats too slowly (bradycardia). A CRT-P differs from a conventional pacemaker in that, in addition to stimulating the right atrium and the right ventricle, it also stimulates the left ventricle via an additional electrode. The contractions of the different heart cavities are therefore better synchronised and the heart, under certain conditions, provides a better pumping action.

In some heart failure patients, a lack of synchronisation of the contraction of the cardiac chambers constitutes the underlying mechanism of defective pumping. This is usually revealed by the electrocardiogram. On the trace, widening of the QRS complex – which reflects the electrical activity of the ventricles during contraction – suggests poor synchronisation.

As a general rule cardiac resynchronisation therapy is used in patients with a significantly reduced ejection fraction and very pronounced widening of the QRS complex.

The table below summarises the different modalities of cardiac stimulation.

	Conventional devices		Cardiac resynchronisation therapy	
	Bradycardia pacemaker	Implantable defibrillator (ICD)	CRT-P	CRT-D
Stimulation of the heart to make it pump faster in case of bradycardia	√	√	√	√
Administration of a shock in the event of a life threatening tachy-arrhythmia		√		√
Stimulation of the heart to make it pump stronger			√	√

CRT-D

Patients with heart failure not only suffer from shortness of breath but they are also at an increased risk for sudden cardiac arrest. For this reason, some of them are treated with an implantable cardioverter defibrillator (ICD), a device that for many years has been used in cardiologic practice. In the event of cardiac arrest, the ICD generates a shock to the heart thus restoring normal beating. In a previous KCE report, we concluded that ICD treatment for primary prevention is clinically effective for certain patients with symptomatic cardiac failure not exceeding NYHA class III. In the economic assessment of that report however, we found that, given the reimbursement rates in force, ICD treatment for the primary prevention of sudden death was not cost-effective.

The fact that patients suffering from heart failure can face two clinical problems, namely symptoms of shortness of breath and the risk of sudden death, led to the development of a device that combines the cardiac resynchronisation function with that of an ICD. This device is known as a CRT-D.

IMPLANTATION

From a technical standpoint, the implantation of a CRT-P or a CRT-D is far from simple. The difficulty lies mainly in correctly positioning the electrode that connects the device to the left ventricle. In 10% of cases, several implantation sessions are required to place this electrode correctly, and sometimes this proves to be quite impossible. In addition, subsequent problems can occur in patients where the implantation initially went well, such as haemorrhage or dislocation of the electrode. A study of CRT-D implantations carried out by experienced doctors reveals that there complications occurred in 20% of patients over a period of 3.5 years.

For these reasons, the European Society for Cardiology recommends a minimum of 20 implantations a year per centre.

CLINICAL EFFECTIVENESS

PATIENTS IN NYHA CLASSES III/IV

In recent years the results of several randomised clinical trials have highlighted the effectiveness of cardiac resynchronisation therapy. These studies compared the use of CRT-P and CRT-D with an optimal standard treatment for heart failure. They initially focused on patients with the most severe symptoms (NYHA classes III/IV) for whom a standard medical treatment was inadequate. Moreover, the patients that were included in those studies had additional clinical signs: their ejection fraction was lower than 30-35%, they had a regular heart rhythm and their electrocardiogram showed a marked widening of the QRS complex.

These clinical trials demonstrated that cardiac resynchronisation therapy resulted in a reduced mortality, as well as in a reduction of the number of hospitalisations due to heart failure. However, the trials did not make clear whether the total number of hospitalisations declined as well. This is because problems associated with the device itself could also result in additional hospital admissions.

One study compared both CRT-P and CRT-D with optimal standard treatment. On the basis of its results and Belgian demographic data, modelling of the life expectancy for this type of patients in an optimistic scenario shows an average extension of life with CRT-P of 1.31 years (95% CI -0.04 to 3.21). The implantation of a CRT-D in those patients could result in an additional extension of life of 0.8 years (95% CI -1.40 to 2.95). The meta-analyses that we have used in other modelling scenarios show that the life extension obtained by the CRT-P is statistically significant (1.83 years, 95% CI 0.45 to 3.33).

PATIENTS IN NYHA CLASSES I/II

Later studies also examined cardiac resynchronisation therapy in patients with relatively lesser symptoms (NYHA classes I/II). However, these studies only enrolled patients in whom it had already been decided to implant a conventional defibrillator. Hence, these studies looked at the supplementary effect of cardiac resynchronisation therapy, over and above that of a conventional ICD.

The most recently published study (the RAFT trial) showed that cardiac resynchronisation therapy with a CRT-D in comparison with an ICD reduces both mortality and the number of hospitalisations for heart failure. However, this study clearly included NYHA class II patients with a much less favourable prognosis than the earlier studies in NYHA class II patients which did not show a survival benefit.

In NYHA class I/II patients, it has never been studied directly whether the same treatment effect could have been obtained from a simpler CRT-P device instead of an ICD or a CRT-D.

RESYNCHRONISATION THERAPY IN BELGIUM

REGULATORY FRAMEWORK

At the present time, Belgian doctors have to comply with the rules governing the implantation of conventional pacemakers and conventional defibrillators for cardiac resynchronisation therapy. In principle, a CRT-P can be implanted in practically all general hospitals, provided that the cardiologist who performs the implant requests the advice of an electrophysiologist affiliated to an "E" cardiac care programme ("E" for electrophysiology). To implant a CRT-D, a hospital must have an ICD accreditation, which means that the hospital has a special agreement with the RIZIV/INAMI allowing for the reimbursement of ICDs.

A request for reimbursement must be submitted individually for each patient by the hospital concerned. The above-mentioned agreement also stipulates that in Belgium, a maximum of 1,300 defibrillators (ICD + CRT-D) can be reimbursed. In addition, a maximum of 40% of these can be implanted for primary prevention, i.e. in patients where the risk of cardiac arrest is considered to be high but has never occurred. The RIZIV/INAMI is currently re-considering these quota (1300/40%). At the moment, 23 Belgian hospitals have an ICE accreditation and are therefore licensed to implant both CRT-D and CRT-P devices.

The regulatory effect of the accreditation concept used by the RIZIV/INAMI was highlighted in our previous report on the use of implantable defibrillators. It has resulted in the fact that the number of defibrillator implantations has never been inexplicably high in Belgium compared with neighbouring countries, which is not the case for conventional pacemakers.

Cardiac resynchronisation therapy is currently already reimbursed to a large degree under the above-mentioned conditions. Only reimbursement of the left ventricular electrode is still under discussion. For the moment, this electrode is only reimbursed in association with a CRT-D. To date, when it is associated with a CRT-P, it is reportedly supplied free of charge by the manufacturer.

Reimbursement of a CRT-P with its electrodes costs around €7,000, while the amount for a CRT-D with electrodes is three times as high (€21,000).

USE OF THE CRT

Via Belgian insurance companies, we had access to certain administrative data on patients that had received cardiac resynchronisation therapy. In 2008, around 530 patients were treated in this way for the first time (228 CRT-Ds and 302 CRT-Ps) and some 190 had a replacement of a previously implanted device. Of all these interventions, 80% took place in a hospital with ICD accreditation. Of these 23 ICD hospitals, 8 had carried out less than 20 CRT implantations in 2008. None of the 48 other hospitals carrying out implants performed 20 or more implantations per year.

PATIENTS

The median age of Belgian CRT-D patients was 67 years – significantly lower than that of CRT-P patients, whose median age was 74 years. The average life expectancy of patients receiving CRT treatment remains limited. Mortality at one year for Belgian patients in 2008 was 16.3% for those implanted with CRT-P devices and 7.2% for those with a CRT-D (these mortality figures cannot be compared with each other because they refer to different populations of patients). The mortality figures recorded are at least six times higher than for subjects of the same age in the general population.

COMPARISON WITH OTHER COUNTRIES

Compared with other countries, the use of cardiac resynchronisation therapy is average. Based on figures supplied by EUCOMED, an organisation for manufacturers and distributors of medical equipment, Belgium and France are in 7th place out of 16 European countries for the CRT implantation rate per million inhabitants. In this respect, Belgium has a high score for the number of CRT-P devices and a rather low number for CRT-Ds. The use of cardiac resynchronisation therapy in Belgium has probably been held back by the restriction on the number of centres authorised to perform CRT-D implants and the non-reimbursement of the left ventricular electrode for CRT-Ps. The statutory limit on the number of defibrillators reimbursed for primary prevention has no doubt also encouraged a move away from CRT-D towards CRT-P.

PROJECTIONS FOR THE FUTURE

Using two recent Belgian studies on patients suffering from heart failure, we made an assessment of the number of those that would be eligible in the future for cardiac resynchronisation therapy. We arrived at a figure of 3,000 to 3,800 new subjects that would meet the inclusion criteria used in clinical studies (NYHA classes II, III and IV). Of those, 680 to 850 would subsequently receive the treatment. The latter figure depends largely on the general condition of the patients, on their clinical response to standard treatment, and to the propensity of the patient and the attending physician towards invasive treatment.

COST-EFFECTIVENESS

Based on medical data, we performed a cost-benefit analysis from the standpoint of healthcare payers, including the costs paid by the medical insurance and the user charges paid by the patient. Administrative data, data from the literature and the advice of experts were used to determine the cost of interventions, hospitalisations, follow-up medical treatment and consultations.

For the therapeutic effect, we used the results of the COMPANION trial. This is the only study that compares both CRT-P and CRT-D with optimal medical treatment (OMT) (thereby allowing indirect comparison). The study included mainly patients in NYHA class III and, to a lesser extent, patients in NYHA class IV.

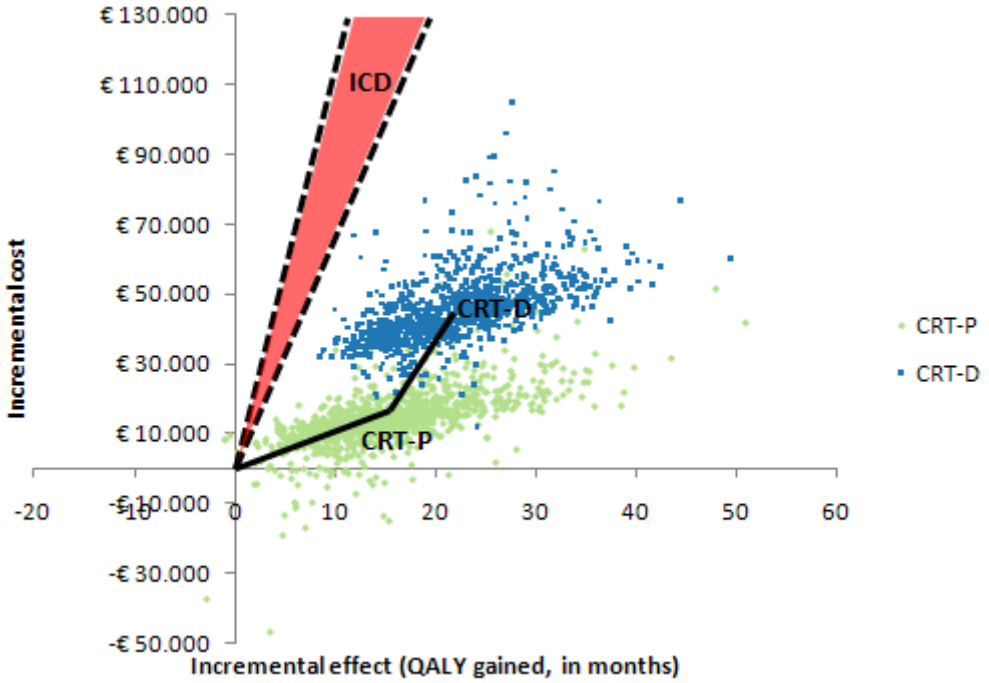
Based on the result of the COMPANION study and an optimistic extrapolation of life expectancy, a fall in mortality in the order of 24% (p=0.059) for CRT-P compared with OMT results in an expected gain in survival adjusted for the quality of life (QALYs gained) of 16 months (4 – 32). For CRT-D compared with OMT the gain is 22 months (12 – 35), with a reduction in mortality of 36% (p=0.003). From the above, it transpires from the model that CRT-D compared with CRT-P results in an additional quality adjusted gain in survival of 6 months (-12 to 25). This difference is however not statistically significant. The results for CRT-P compared with OMT improve and become statistically significant when the effect of the treatment is modelled on the basis of the results of a meta-analysis.

The discounted additional costs over the entire period for CRT-P compared with OMT have been calculated at €14,700 (-1,900 to 36,000). For CRT-D compared with CRT-P, the amount was €30,900 (7,200 to 60,300). Because the results of the simulation were distributed between the quadrants of the cost-effectiveness plan (Figure 1), the incremental cost-effectiveness ratio (ICER) was determined by dividing the average incremental cost by the average incremental effects. In this way we obtain an ICER of around €11,200 per QALY gained for CRT-P vs OMT and around €57,000 per QALY gained for CRT-D vs CRT-P. Such a gap in cost-effectiveness is due mainly to the three times higher cost of a CRT-D compared with a CRT-P. Note also that the cost-effectiveness clearly deteriorates when we consider a period of 10 years.

Based on medical arguments, we can consider an ICD as a rational comparator for a CRT-D. However, from an economic point of view an ICD in this population cannot be considered as cost-effective (as shown in the figure, based on a previous KCE report), and it is therefore not relevant to assess the degree of efficiency of alternatives based on an inefficient use of these alternatives. This implies that the economically rational comparator for CRT-D is CRT-P and not ICD.

Finally, for NYHA classes I/II, there is no study available that compares CRT-P and CRT-D with optimal medical treatment and that provides hard endpoint information. Consequently, for this population it is not possible to make a reliable cost-effectiveness ratio calculation.

Figure 1: Cost-effectiveness plane for CRT-P, CRT-D (and ICD)



DISCUSSION AND CONCLUSIONS

Cardiac resynchronisation therapy provides an added value compared with standard conventional treatment for heart failure patients with a severely reduced left ventricular ejection fraction and a marked prolongation of their QRS complex. It prolongs life and reduces the number of hospitalisations for heart failure. This beneficial effect is most evident in patients belonging to NYHA class III. Based on the RAFT study, it seems that this finding is equally valid for the more serious NYHA class II cases.

The application of cardiac resynchronisation therapy requires special skills from the implanting physician. Even in the hands of experts, the intervention fails in a number of patients. In addition, serious complications may occur.

In 2008, some 720 resynchronisation devices were implanted in Belgium: 530 new devices and 190 replacements. Of these implantations, 80% were carried out in a hospital with ICD accreditation. We estimate that in the near future, 680 to 850 persons a year will be eligible for a first CRT.

In Belgium, implantable defibrillators used for primary prevention (ICD and CRT-D) are currently reimbursed for patients suffering from heart failure with a severe left ventricular systolic dysfunction. In a prior KCE study, the use of ICDs for primary prevention appeared clinically effective but not cost-effective. Subsequently, public authorities opted for a limit on the yearly number of reimbursed ICDs.

Randomised studies in combination with long-term modelling show that resynchronisation therapy using a CRT-P prolongs survival of patients in NYHA class III by around 1.3 years compared with optimal standard treatment. In such cases, the cost-effectiveness of this type of treatment is relatively favourable. In addition, there is limited evidence that resynchronisation coupled with a defibrillator (CRT-D) can prolong survival somewhat longer than a CRT-P. However, from a statistical standpoint, the gap is not significant, while the price of a CRT-D is three times higher than that of a CRT-P, and CRT-Ds are associated with a number of additional potential problems.

In spite of the fact that, from a medical point of view, the CRT-D might seem more beneficial than the CRT-P in patients suffering from heart failure, for the moment there is little conclusive data to confirm that this is really the case. This raises the question of whether the disproportionate cost difference between the two CRT modalities can be justified from the point of view of health insurance. Even if robust conclusive data were to confirm that treatment with a CRT-D would procure survival for an additional period of 6 months compared with a CRT-P, we still do not know whether society is ready to pay an additional €57,000 on average for each QALY gained. The reimbursement conditions for ICDs in Belgium show that, for the time being, the cost-effectiveness considerations are not always decisive.

RECOMMENDATIONS[a]

- **Scientific studies show that cardiac resynchronisation therapy provides added value compared with standard treatment in specific subgroups of patients with heart failure. An economic analysis shows that treatment with a CRT-P can also be considered as sufficiently cost-effective. As a result, reimbursement for CRT-P (including the electrodes) appears to be justified; the total price requested should nevertheless be discussed.**
- **Scientific studies reveal a non-significant trend suggesting that CRT-D could further prolong survival of these patients compared with CRT-P. However the associated additional expense is excessive.**
- **Based on the specific technical requirements and skills required for a CRT implantation, we recommend a minimum threshold of 20 CRT implantations a year per centre. As the concept of ICD accreditation has proved its worth in Belgium and the threshold of 20 implants a year was not achieved by any non-ICD hospital in 2008, we recommend henceforth restricting the performance of cardiac resynchronisation therapy (for both CRT-P and CRT-D) to hospitals that have an ICD accreditation.**
- **Implanting doctors should be encouraged for prior discussion of the advantages and drawbacks associated with cardiac resynchronisation therapy with their patients. In reality, it is a therapy that can only partially remedy the problems of heart failure and is frequently accompanied by (sometimes serious) complications.**
- **The existing ICD register should be broadened to include the parameters that apply specifically to cardiac resynchronisation therapy. In collaboration with the College of Physicians, the register should also be extended to include CRT-P as well. Moreover, the registration should allow for recording late complications from the treatment.**
- **If the public authorities wish to modify the reimbursement procedures for one of the implants concerned, it would be desirable to study how additional conclusive data could be better collected to support future decisions (for example, the added value of CRT-D compared with CRT-P).**

a KCE has sole responsibility for recommendations to the public authorities

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Glossary

ACC American College of Cardiology
ACE-inhibitor Angiotensin Converting Enzyme inhibitor
AF Atrial Fibrillation
AHA American Heart Association
AMI Acute Myocardial Infarction
AR Absolute Risk
ARB Angiotensin II antagonists
ARR Absolute Risk Reduction
AVB Atrioventricular Block
BeHRA Belgian Heart Rhythm Association
BNP Brain Natriuretic Peptide
CAD Coronary Artery Disease
CARE-HF CArdiac REsynchronization-Heart Failure
CCP Cardiac Care Program
CCP-A Cardiac Care Program accreditation relating to basic clinical cardiology
CCP-E Cardiac Care Program accreditation relating to Electrophysiology
CCP-P Cardiac Care Program accreditation relating to Pacemaker therapy
CCU Critical Care Unit
CE-plane Cost-Effectiveness plane
CEA-curve Cost-Effectiveness Acceptability curve
COMPANION Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure
CI Confidence Interval
CRT Cardiac Resynchronisation Therapy
CRT-D Cardiac Resynchronisation Therapy, combined with ICD
CRT-P Cardiac Resynchronisation Therapy, combined with Pacing
CVD Cardiovascular Disease
DDD Defined Daily Dose
ECG Electrocardiogram
EF Ejection Fraction
EQ-5D European Quality of Life 5 Dimensions
ESC European Society of Cardiology
GP General Practitioner
HF Heart Failure
HR Hazard Rate
HTA Health Technology Assessment
IC Incremental cost
ICD Implantable Cardioverter-Defibrillator
ICER Incremental Cost-Effectiveness ratio
ICU Intensive Care Unit
IE Incremental Effectiveness
IMA Intermutualistic Agency
IQR Interquartile range

ITT Intention-to-treat

LOS Length of Stay

LV Left Ventricular

LVEF Left Ventricular Ejection Fraction

LVSD Left Ventricular Systolic Dysfunction

LYG Life Years Gained

MADIT Multicenter Automatic Defibrillator Implantation Trial

MCD Minimal Clinical Data

MI Myocardial Infarction

MIRACLE Multicenter InSync Randomized Clinical Evaluation

MLHFQ Minnesota Living with Heart Failure Questionnaire

NNT Number Needed to Treat

NYHA New York Heart Association

OPT Optimal Pharmaceutical Therapy

peak VO2 Peak oxygen uptake

PH Proportional Hazards

PSA Probabilistic Sensitivity Analysis

QoL Quality of Life

QRS complex The QRS complex represents the electrical activity that gives rise to the contraction of the heart

RAFT Resynchronisation/ Debrillation for Ambulatory Heart Failure Trial

REVERSE Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction

RIZIV/INAMI Rijksinstituut voor ziekte- en invaliditeitsverzekering/Institut national d'assurance maladie-invalidité

RCT Randomized Controlled Trial

RR Relative Risk

RRR Relative Risk Reduction

SCD Sudden Cardiac Death

SD Standard Deviation

SP Specialist

SSS Sick Sinus Syndrome

SR Systematic Review

Part I.

Scope

This Health Technology Assessment (HTA) report provides a systematic review of the clinical effectiveness and the cost-effectiveness of cardiac resynchronisation therapy (CRT) for patients with chronic heart failure that are receiving optimal medical treatment. Two different types of CRT devices are available: one in combination with a conventional pacemaker, known as CRT-P, and one in combination with a conventional implantable defibrillator, known as CRT-D. The effectiveness of both CRT types will be studied in this report.

The use of these devices will be considered from a patient and from a public health payer perspective. Furthermore, a description will be provided of the current use of CRT therapy in Belgium. Real world Belgian data will be used to feed a health economic model.

Based on the present report, the following decision problems should find an answer:

1. Is CRT safe and clinically effective? What is the comparative effectiveness of CRT-P versus CRT-D?
2. Is CRT cost-effective and consequently, should this mode of therapy be reimbursed in eligible patients?
3. What is the yearly number of eligible patients for CRT in Belgium? Should the implantation of CRT devices be restricted to specialised centres?

Part II.

Clinical aspects of cardiac resynchronisation therapy

1 Clinical background: heart failure

1.1 Clinical picture

Heart failure (HF) is a complex syndrome that can result from any cardiac disorder that impairs the ability of the heart to function as a pump. The most common underlying conditions are coronary artery disease, arterial hypertension, malfunctions of heart valves and primary cardiac muscle diseases. HF is clinically characterised by breathlessness and fatigue and signs such as fluid retention. There is no single diagnostic test for HF, and diagnosis largely relies on clinical judgement based on a combination of history and physical examination completed with appropriate investigations, a.o. electrocardiogram (ECG), brain natriuretic peptide (BNP) and echocardiography. HF is a common disease, especially in the elderly. In an incidence study by general practitioners across Belgium, the median age of patients at diagnosis was 79 years: 82 years for women and 76 years for men.[7]

The pumping function of the heart can be deficient due to an inadequate contraction of the heart's muscle or to an impeded filling of the heart with blood. An impairment of the contraction capacity of the heart leads to an insufficient ejection of blood and is known as "HF with a reduced ejection fraction". The heart's function can also be disabled because of an impaired relaxation of the heart muscle which leads to an impeded filling with blood. In this case HF is known as "HF with a preserved ejection fraction". Among patients under the age of 75 years, HF is most often due to coronary artery disease, causing a predominantly systolic dysfunction. Among elderly patients arterial hypertension and cardiac hypertrophy, as well as fibrosis may be more important causes of HF. These abnormalities predominantly manifest as diastolic dysfunction.[9] HF can present itself both acutely and chronically. Acute HF can present itself de novo in a patient without previously known cardiac dysfunction or as an acute decompensation of chronic HF. Acute HF in its most typical presentation is manifested as pulmonary oedema. Cardiac resynchronisation therapy, the topic of the present reports, currently addresses only a subgroup of patients with chronic systolic HF.

The prognosis associated with HF is worse than that of most cancers. Half of patients carrying a diagnosis of HF will die within 4 years, and in patients with severe HF more than 50% will die within a year.[9] HF is the most frequent cause of hospitalisation among people older than 65 years of age. In the year 2004, the Belgian register of Minimal Clinical Data reported 61632 hospital admissions related to 48932 patients with a principal or a secondary diagnosis of HF.

1.2 Definitions and concepts

1.2.1 Heart rhythm

Normally, the heart rate is dictated by a natural pacemaker, the so-called sinus node, a structure residing within the right atrium. The ensuing physiological rhythm is known as "normal sinus rhythm". In atrial fibrillation (AF), the normal sinus node activity is suppressed by a pathological electrical hyperactivity within the atria, leading to an irregular and inappropriately fast heart rhythm. The condition can occur intermittently or remain chronic. It is the most common arrhythmia in clinical practice. The prevalence of AF is age-dependent and is present in 10% of octogenarians.[10]

In almost all trials on CRT, normal sinus rhythm was a prerequisite for enrolment, since patients in AF cannot benefit from the atrial component of resynchronisation.[1]

1.2.2 New York Heart Association functional class

The functional status of patients with HF is traditionally encoded by means of the New York Heart Association (NYHA) classification. Subjective symptoms are used to rank patients according to their functional capacity into four classes as shown in Table 1.1.

Table 1.1.: Ranking of functional status according to NYHA class

NYHA	Patient Symptoms
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnoea.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

An additional NYHA class has recently been introduced, "ambulatory NYHA class IV", which is referred to in clinical guidelines related to CRT. This notation was first used in the 2008 US guideline.[11] It has been adopted and defined in the ESC most recent update on device therapy for HF as follows: "NYHA class IV patients that have had no scheduled or unscheduled admission for HF during the month preceding the CRT implantation and who have a life expectancy of at least 6 months".[12]

Although the NYHA class is a very subjective measure, it is very often used in clinical trials to evaluate symptoms in HF patients. A literature survey showed that 99% of research papers do not reference or describe their methods for assigning NYHA classes and an interoperator comparison on NYHA class II and III patients gave a result that was little better than chance.[13,14] The fact that inclusion of patients in CRT trials essentially was based on the NYHA class of the patients may compromise the external validity of the trials.

1.2.3 Left ventricular ejection fraction

The left ventricular ejection fraction (LVEF) refers to the percentage of blood the filled heart ejects during contraction. It is used to quantify the systolic function of the heart (i.e. the pump function) and its normal value lies above 50%. It can be estimated by various invasive and non-invasive imaging techniques such as left ventricular angiography, echocardiography, MRI- or CT-scanning and nuclear imaging. The determination of LVEF however lacks a "gold standard" and there can be considerable variation among observers and clinical techniques. A reduction in the systolic function of the heart does not necessarily lead to symptoms. Half of patients with a significantly reduced LVEF seem to be symptom-free.[15]

Most trials that studied CRT, which is the topic of this report, addressed symptomatic patients with a severely reduced LVEF of less than 35%.

1.2.4 Remodelling

Chronic myocardial disease is frequently associated with a progressive enlargement and dilatation of the left ventricular chambers and a concomitant reduction in LVEF. This unfavourable change in shape of the heart is known as cardiac remodelling. Certain drugs as

well as device therapy, have shown to reverse the dilatory process that became known as reverse remodelling.

1.2.5 Intraventricular conduction delay

The electrocardiogram (ECG) is a graphical representation of the electrical activity of the heart as it can be derived from the surface of the body by means of electrodes. The sequence of electrical events related to a single heart beat is shown in Figure 1.1. The QRS complex represents the electrical activity that gives rise to the contraction of the heart, and normally lasts 120 ms or less. In the diseased heart, the conduction of the electrical impulse through the heart can be delayed which can be recognised from the ECG by a prolonged QRS interval. The conduction delay can be predominantly located in the right or to the left side of the heart, and is then known as right or as left bundle branch block. The intraventricular conduction delay leads to a dyssynchronous contraction of the heart and in patients with a poor contractile function makes a bad situation even worse.[16] By stimulating areas of the heart that would otherwise contract (too) late, the pumping function of the heart is improved by cardiac resynchronisation therapy, at least in patients with symptomatic HF. Echocardiographic studies suggest that resynchronisation of the heart's contraction also prevents remodelling.

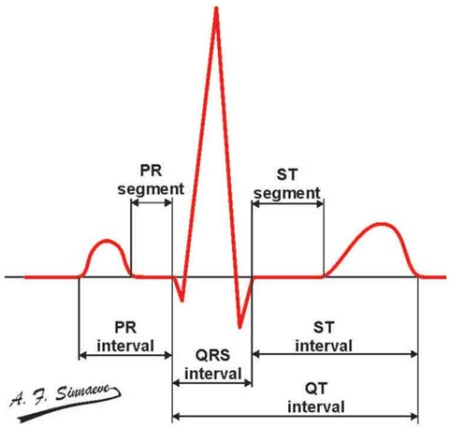


Figure 1.1.: Normal electrocardiographic QRS complex
Source: R. Stroobandt, Dienst Cardiologie, UZ Gent

Accordingly, biventricular stimulation of the heart results in a narrowing of the QRS-complex as shown in Figure 1.2 The presence of an intraventricular conduction delay (QRS width >120 ms) is a requirement for CRT. In the European CRT survey, the mean QRS duration of 157±32 ms before CRT was reduced to 133±27 ms during biventricular pacing.[17]

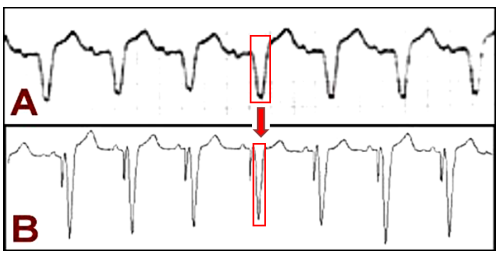


Figure 1.2.: Impact of biventricular pacing on QRS complex width
Source: adapted from: http://www.washingtonhra.com/22.html. Panel A shows an ECG strip with a broadened QRS complex. After implantation of a CRT system, Panel B shows narrowing of the QRS-complex.

1.3 Epidemiology

Because of widely varying definitions, the epidemiology of HF is difficult to interpret. European estimates of the prevalence of HF in the general population range from 0.4 to 2%.[18] The prevalence of HF increases rapidly with age and in people 70 to 80 years of age, HF is estimated to be present in 10 to 20% of the population.[19] The crude incidence of HF in the general population ranges from 1 to 5 cases per 1000 population per year. There is a steep increase in the incidence with advancing age. In Belgium, in 2005 there were 68 032 admissions of 53003 patients with a (principal or secondary) diagnosis of Heart Failure (ICD-9-CM Diagnosis Code 428).

1.4 Management of heart failure

The management of HF is aimed at a reduction of symptoms and an increase of survival. Next to dietary measures, standard treatment includes drug therapy: diuretics, an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, a beta-blocker and an aldosterone antagonist.[19] In some patients, physical exercise training is advocated.

Patients who are clinically stable but have a severely reduced contractile function (LVEF<35%) remain at high risk of sudden death (SCD).[19] Approximately 50% of deaths in patients with HF are due to a sudden cardiac arrest.[20] Therefore, they are potential candidates for treatment with an ICD. Selected patients with end stage HF, who remain symptomatic despite optimal medical treatment, can be considered for cardiac transplantation. In others, device therapy with CRT, constituting the topic of the present HTA report, can be indicated.

2 Cardiac resynchronisation technology (CRT)

2.1 Conventional pacemakers

Pacemaker (PM) therapy is related to the prevention of symptoms induced by an inappropriately slow heart rate or "bradycardia". The PM is able to continuously monitor the heart rate of an individual in whom such a device has been implanted. If a predefined low heart rate is detected, it sends an impulse to the heart stimulating its contraction. This impulse is repetitively delivered at a given frequency as long as the patient's own heart rhythm has not regained the lower limit. PM therapy is the only known effective treatment for chronic symptomatic bradycardia. PMs intended to treat bradycardia are denoted as "conventional" or "bradycardia" PMs, to distinguish them from a new type of PMs, used for the treatment of heart failure. The latter pacing mode is known as cardiac resynchronisation therapy (CRT) and is the subject of the present report. Conventional pacing practice in Belgium was the topic of a KCE report, issued in September 2010.[10]

A pacemaker is an electronic device, powered from an internal battery, that is connected to the heart with one or more insulated electric wires, denoted leads or electrodes. The device is implanted subcutaneously, generally under local anaesthesia, usually below the right or left clavicle. The lead(s) are advanced through a vein to the inner surface of the heart's right atrium and/or right ventricle, using fluoroscopic guiding. The technique has been developed in the 1950s, and since 1959 transvenous pacing, requiring only minor surgery, has become the standard procedure. Pacemakers may be either "single-chamber" or "dual-chamber" depending on whether or not both the right atrium and/or the right ventricle are involved. The PM is able to detect ("sense") the heart rate and is programmed to stimulate ("pace") the heart through the leads when the patient's heart rate falls below a pre-specified rate. The choice of the type of PM depends on the exact nature of the bradycardia. Once a PM has been implanted, several parameters can be changed noninvasively by using an external programmer that communicates with the PM by means of magnetic coupling via a wand placed on the patient's skin above the device or more recently also remotely.

2.2 Conventional implantable cardioverter defibrillators (ICD)

ICDs are battery-powered implantable devices capable of monitoring heart rhythm and delivering an electric shock to restore normal rhythm when a life-threatening arrhythmia is detected. It is used in survivors of cardiac arrest (secondary prevention) and in patients at high risk for it (primary prevention). In contrast to conventional PMs that address extremely slow heart rates (bradycardia), an ICD aims at treating abnormally fast heart rhythms that result in a functional cardiac standstill (ventricular fibrillation, ventricular tachycardia). An ICD consists of two main parts: the defibrillator and the leads. The defibrillator can have one or more leads. Early devices required open chest surgery to be implanted but current ICDs are placed under the skin in the pectoral region with the leads into the heart inserted via a vein.

The latest devices offer graded responses (so called "tiered therapy") to a sensed ventricular arrhythmia. Antitachycardia pacing, low-energy synchronised cardioversion and high-energy defibrillation shocks can be delivered successively via a transvenous lead, terminating the arrhythmia. Any ICD nowadays incorporates an antibradycardia pacemaker as well, for back-up pacing following a shock.

A health technology assessment on the use of ICD therapy in primary prevention has been issued by the KCE in 2007.[21]

2.3 CRT technology

A cardiac resynchronisation therapy (CRT) pacemaker or CRT-P, in its basic configuration is a pacemaker that is specially designed for the treatment of HF. Basically, it is a conventional pacemaker connected to the right atrium and the right ventricle that can also stimulate the left ventricle via a third electrode. CRT, also known as biventricular pacing, improves cardiac output by synchronising the pumping action of the heart's chambers (upper chambers=atria, lower chambers=ventricles). The first clinical trials studying CRT were published at the beginning of the 21st century.

The CRT system includes the stimulating device and 3 cables, denoted "leads" or "electrodes". Two of these connect the device with the right atrium and the right ventricle of the heart respectively. A third electrode is connected to the left ventricle and is needed to stimulate the left ventricle. The connection with the left ventricle can be established via the venous system of the heart (coronary sinus), or it can also be stitched on the outer side of the heart ("epicardial") via thoracoscopy, involving an additional surgical incision through the chest wall.

The CRT technology can also incorporate an implantable cardioverter defibrillator (ICD) resulting in a device that can (1) perform resynchronisation therapy and (2) deliver a shock in case cardiac arrest occurs. In this configuration, the system is known as CRT-D. The electrode that is positioned in the right ventricle of the heart fulfils a dual role: it stimulates the right ventricle to contract and it is used to deliver a shock to the heart in case a cardiac arrest occurs. The rationale to combine CRT and ICD therapy in one patient is related to the fact that HF patients are at high risk for sudden cardiac death. Approximately 50% of deaths in patients with HF are due to a sudden cardiac arrest.[20] Apart from beta-blockers, anti-arrhythmic drugs have not shown to be effective to prevent sudden cardiac arrest and therefore, patients with HF are potential candidates for both CRT and ICD therapy. Combined CRT-D devices have been developed and Figure 2.1 shows a chest X-ray of a patient who has been implanted a CRT-D, with the three leads connecting the device with the heart.

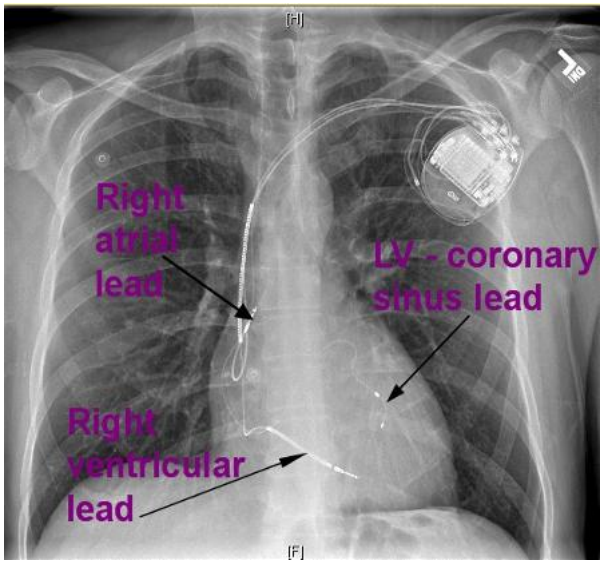


Figure 2.1.: Chest X-ray of a patient with a CRT-D
Source: http://www.washingtonhra.com/22.html. Arrows indicate location of the 3 leads.

European and US clinical guidelines, along with clinical reimbursement conditions imposed by the Belgian government (RIZIV/INAMI) are presented in the appendix to this chapter.

The basic functionalities of the cardiac devices described above are summarised in Table 14.2.

Table 2.1.: Basic functionalities of cardiac stimulatory devices

	CONVENTIONAL DEVICES		CARDIAC RESYNCHRONISATION THERAPY	
	BRADYCARDIA PACEMAKER	IMPLANTABLE DEFIBRILLATOR (ICD)	CRT-P	CRT-D
INCREASES HEART RATE IN CASE OF BRADYCARDIA	√	√	√	√
DELIVERS SHOCK IN CASE OF FATAL ARRHYTHMIA		√		√
AIMED AT IMPROVING CONTRACTILE FUNCTION			√	√

3 Current Belgian legislation

3.1 Cardiac Care Programs

In 1999, so-called "care programs" ("zorgprogramma's", "programmes de soins") have been installed by the Belgian federal government. They are related to a variety of hospital services such as geriatrics, paediatrics, oncology, reproductive health and cardiology. Further in this report, the latter will be referred to as "cardiac care program (CCP)". Several distinct CCPs have been defined: A, B, P, E, T, and C (Table 3.1). CCP "T", relating to heart- and lung transplantation, and CCP "C" relating to congenital heart disease, are beyond the scope of the present report. Virtually all acute hospitals can have a CCP "A" certification allowing for clinical cardiology without limitations as far as non-invasive diagnosis or non-invasive treatment is concerned. To obtain a higher level of CCP a hospital needs to adhere to a number of qualitative and quantitative criteria. CCP "B" relates to the license to perform invasive coronary diagnosis (B1), percutaneous treatment of coronary disease (B2) and cardiac surgery (B3). Hospitals with a CCP "P" (P=pacemaker) are accredited to provide PM therapy. In order to obtain a CCP "E" (electrophysiology) qualification, a hospital must have a CCP "B" and a CCP "P" accreditation in addition to a number of quantitative requirements, amongst others subject to a minimum number of electrophysiology procedures and the number of cardiologists affiliated with the hospital.

Table 3.1.: Cardiac Care Programs

A		basic clinical cardiology
B	B1	invasive coronary diagnosis
	B2	percutaneous treatment of coronary disease
	B3	cardiac surgery
P		PM therapy
E		electrophysiology
T		heart- and lung transplantation
C		congenital heart disease

Most if not all Belgian hospitals providing standard cardiac care (CCP "A") are also qualified as CCP "P". It is mandatory for a hospital with a CCP "P" to have a formal cooperation statement with a hospital that has both CCP "B" and "E" qualifications. The legislation related to CCP "P" also mentions a number of quality standards to be fulfilled. For PM implants with indications other than complete heart block or slow atrial fibrillation with pauses longer than 2.5 seconds, expert advice from an electrophysiologist affiliated with a CCP "E" has to be obtained and registered. By Royal Decree, all care programs must be submitted to an internal and an external quality appraisal, the latter to be organised and controlled by the College of Physicians. More specifically, the responsibility for the quality control of the CCP "P" lies with the College of Physicians – Cardiac Pathology - Section Pacing and Electrophysiology. In practice however, this obligation has never been enforced, and hospitals have only been encouraged to contribute data to the Belgian Heart Rhythm Association (BeHRA) pacemaker register, whose register data are copied within the activity reports of the College of Physicians.

3.2 ICD accreditation

A particularity of ICD therapy in Belgium is that, in contrast to PM therapy, it is strictly regulated, both in terms of the authorisation of centres delivering this kind of therapy, as in terms of the application of an upper limit of reimbursable devices per year per centre. These regulations originally were instituted for conventional ICDs but they currently apply to CRT-Ds as well, the latter being part of overall ICD practice.

Hospitals have to comply with certain prerequisites in order to receive accreditation for ICD implantation. Ever since 1987 ICD reimbursement is based on a model convention between the implant centre, called "centre for implantable heart defibrillators", and the RIZIV/INAMI. A hospital is eligible for ICD-accreditation if it has an accredited heart centre (interventional cardiology, cardiac surgery and electrophysiology), 6 FTE cardiologists, 2 FTE electrophysiologists and performs on average at least 15 ICD procedures per year. As of May 2010, 23 Belgian centres received accreditation. The convention between the RIZIV/INAMI and the accredited centres includes a list of accepted indications for ICD implantation, based on international guidelines. Yearly reports of the total number of ICD implants to the RIZIV/INAMI as well as peer review submission are mandatory. In order to control a justifiable volume of reimbursable devices and to establish the indications for an intervention, a consultative body, the so-called Agreement Council ("Akkoordraad", "Conseil d'accord"), was created from the start as an essential element of the model convention with the participating centres. This council consists of electrophysiologists of the accredited centres and of members of the Board of Senior Medical Officers. The chairmanship is filled by the Chairman of the Board of Senior Medical Officers. The agreement council convenes for instance each time when the Board of Senior Medical Officers established that the annually fixed quotum of expected first implants will be exceeded. Also for the execution of the peer review tasks of the agreement council, the Board of Senior Medical Officers will transmit to the other members-cardiologists the anonymised essential data of each first implant for which an intervention was granted.

On July 1st, 2009 a revised contract of the model convention became effective. It introduced an upper limit of 1300 reimbursable ICD primo implants per year in Belgium. A maximum of 40% (520) of these are accepted for primary prevention. If an individual centre exceeds the 40% limit of primo implants for primary prevention, reimbursement for that centre is discontinued for as long as its percentage of primo implants exceeds 40%. In this case, the patient can be referred to a centre that meets the 40% rule. On October 4, 2010, 4 of 23 ICD centres were (temporarily) blocked because of violation of the 40% rule.[a] Currently, RIZIV/INAMI in deliberation with other stakeholders, is discussing whether these quota should be adapted.

The July 12, 2010 meeting of the Agreement Council ("Akkoordraad", "Conseil d'accord") confirmed an agreement on the clinical conditions in both primary and secondary prevention for which reimbursement of an ICD was agreed upon.[b] In this meeting, it was also decided to await the KCE reports on cardiac pacemakers and on CRT (i.e. the present report), to make further reimbursement decisions for CRT-P and CRT-D. Later this year, negotiations within the Agreement Council have been initiated to adapt the existing quotas, mentioned above.

3.3 Current CRT reimbursement

The reimbursement tariffs of PM devices and leads that are applicable in Belgium are described in art.35 of the RIZIV/INAMI reimbursement nomenclature. It lists a number of additional requirements needed to obtain a reimbursement of the PM and its accessories.

a. http://inami.fgov.be/care/nl/revalidatie/convention/defibrillator/index.htm#4
b. http://www.riziv.be/care/nl/revalidatie/convention/defibrillator/pdf/agreement20090701.pdf

They refer to the need of the hospital to have a CCP "P" accreditation and a number of formal prescription rules. Reimbursement requires a standardised prescription form representing details of the PM and the leads that have been implanted, together with coded information on clinical and electrocardiographic characteristics of the patient justifying the implantation. The prescription form has to be signed by 2 cardiologists (or 1 cardiologist and 1 internist) and sent to the patient's health insurer. Each hospital must also proclaim to the RIZIV/INAMI the cardiologist that is responsible for the clinical PM activity. Under these conditions, cardiologists working in a CCP A hospital are entitled to perform PM implants in patients presenting with strictly described clinical indications: "(1) complete heart block and (2) sick sinus syndrome and/or slow atrial fibrillation with symptoms of syncope, and/or bradycardia with a heart rate lower than 30 beats per minute". In other conditions, the CCP-A cardiologists are legally obliged to ask and register the advice of an electrophysiologist who is connected to a CCP-E hospital. Accordingly, the latter condition applies to patients with HF but no bradycardia, in whom a CCP-A cardiologist considers the implantation of a CRT-P pacemaker.

The 2010 tariffs are listed in Table 3.2. The left ventricular electrode is reimbursed since July 1, 2007 in ICD accredited centres only, when it is used in combination with a CRT-D device. In some cases, an implanting physician may decide to implant a CRT-D device without implanting a left ventricular lead and hence without implementing the resynchronisation feature of the system. In these instances, the left ventricular port of the device is plugged, hence the label "CRT-D plugged" in the table. In this configuration, the device will function as a standard ICD and therefore, reimbursement will be lower than for a CRT-D. If the physician decides to add the left ventricular lead in a second procedure, within 2 months following the first, an additional fee can be claimed.

It can be inferred from the table that the reimbursement of a typical CRT-P system amounts to €5,686.30 (or €7,187.00 if the cost of left ventricular lead is taken into consideration). In these instances, the LV lead is not reimbursed. A typical CRT-D system is reimbursed €20,031.00, obviously applicable to ICD accredited centres only. (A conventional dual chamber PM is currently reimbursed €5,246.30 and a conventional dual chamber ICD €17,598.00; data not shown in Table 3.2).

Table 3.2.: Device reimbursement tariffs - 2010 (Tariff A/B refers to more/less recent marketed devices).

	Hospitals with Cardiac Care Program P (mandatory advice from CCP-E hospital).		23 centres accredited for ICD therapy	
	NOMENCLATURE CODE	€	NOMENCLATURE CODE	€
PM lead - unipolar	685731/685742	571,15	685731/685742	571,15
PM lead - bipolar	685753/685764	571,15	685753/685764	571,15
PM lead - myocardial	685775/685786	571,15	685775/685786	571,15
PM lead - single-pass	685790/685801	777,72	685790/685801	777,72
CRT-P	684530/684541 684375/684386 684555/684666	4544,00	684530/684541 684375/684386 691670/691681	4544,00
Pacing electrode (endo- or myocardial, uni- or bipolar)	NOT APPLICABLE		691795/691806	571,15
Single pass electrode			691810/691821	777,72
ICD electrode 1 coil, shock only			691692/691703	663,07
ICD electrode 1 coil			691714/691725	1320,98
ICD electrode 2 coils			691736/691740	2098,70
Subcutaneous patch			691751/691762	676,50
Subcutaneous electrode			691773/691784	1064,84
Left ventricular lead - percutaneous			691832/691843	1500,70
Left ventricular lead - epicardial			691854/691865	500,92
CRT-D plugged			691633/691644 691655/691666	Tarif A: 15318,00 Tarif B: 13786,20
CRT-D full feature				Tarif A: 17388,00 Tarif B: 15649,00
Upgrade of a plugged CRT-D within 2 months			691670/691681 691670/691681	Tarif A: 2070,00 Tarif B: 1863,00
ICD stand alone - single chamber			691633/691644 691655/691666	Tarif A: 14652,00 Tarif B: 13186,60
ICD stand alone - dual chamber				Tarif A: 15318,00 Tarif B: 13786,20

KEY POINTS

- **Any Belgian general hospital is licensed to implant a CRT-P.**
- **Regulations originally addressing the reimbursement of conventional ICDs also apply to CRT-Ds. Implantation of these devices is limited to 23 hospitals. An upper limit of 1300 reimbursable defibrillator primo implants per year is currently applicable, with a primary prevention indication in no more than 40% (520) of them.**
- **Except for the left ventricular lead if used in combination with a CRT-P, cardiac resynchronisation therapy is fully reimbursed in Belgium. The device cost, including the leads, amounts to about €7000 for a CRT-P and €21 000 for a CRT-D.**

4 Clinical effectiveness of CRT in NYHA class III/IV patients

4.1 Literature search and references

The review of the evidence on clinical effectiveness in this chapter is mainly based on the evidence identified in the recently updated guideline from the European Society of Cardiology (ESC) as that updated guideline was considered by both the authors of this HTA report and the consulted external experts as being sufficiently comprehensive and up-to-date (see also the appendix to this chapter for a more thorough description of that updated guideline).[12]

We further searched for more recent health technology assessments (HTA) and systematic reviews (SR) using Medline and the databases from the Centre for Reviews and Dissemination (CRD: databases DARE, NHS EED and HTA). Since this was a rapid assessment of effectiveness we relied mainly on the relevant MeSH terms: *"Pacemaker, Artificial" OR "Defibrillators, Implantable" and limited to systematic reviews*. In addition, a more specific search for meta-analyses of CRT was conducted in Medline using the search terms *("CRT" OR "cardiac resynchronisation therapy" OR "cardiac resynchronization therapy") AND systematic[sb] Limits: Meta-Analysis*.

Relevant articles were selected based on title and abstract and subsequently retrieved in full. In the following description and unless otherwise specified all results are presented as CRT vs. optimal medical treatment. When comparing the two CRT modalities, the comparison is CRT-D vs. CRT-P. All confidence intervals (CI) shown are two-sided 95% CI.

4.2 Description of the most relevant clinical trials

The ESC guidelines and the two considered meta-analyses considered several studies. We will describe in more detail the largest (n > 300) of those trials that were considering patient in NYHA Class III/IV (see Table 4.1). They were all taken into account in both the ESC guidelines and in the meta-analyses described further. However, for the CARE-HF trial different references were used in different reviews (either the original or the extension study). Full data extraction forms are available from the HTA report from Fox,[6] and were therefore not reproduced for this report.

4.2.1 MIRACLE, 2002

Trial description The MIRACLE trial (Multicenter InSync Randomized Clinical Evaluation) is a *double-blind trial* intended to evaluate the efficacy of CRT-P in patients with moderate to severe heart failure and a prolonged QRS interval but without an indication for pacing or defibrillator therapy.[22] Patients were eligible for the study if they had moderate or severe (NYHA class III or IV) chronic heart failure due to either ischaemic or nonischaemic cardiomyopathy. All patients had a LVEF $\leq$ 35% or less, end-diastolic dimension of 55 mm or more, a QRS interval $\geq$ 130 ms or more, and a six-minute walking distance of 450 m or less. Patients received all appropriate treatments for heart failure, which included a diuretic, an angiotensin-converting–enzyme inhibitor or an angiotensin-receptor blocker, and (usually) digitalis and a beta-blocker. Patients were excluded if they had a pacemaker or ICD or had an indication for or a contraindication to cardiac pacing. There were also several other exclusion criteria.

In the MIRACLE trial, eligible patients underwent a series of baseline evaluations including NYHA classification, six minute walking test, and quality-of-life evaluation. After the initial evaluation *all selected patients underwent implantation* of a CRT-P. The *453 patients* who had undergone successful implantation were subsequently randomly assigned to CRT (the intervention group, n=228) or to a control group (no pacing, with CRT switched off, n=225) for *six months*, during which time medications for heart failure were to be kept constant. At each site, an electrophysiologist, who was otherwise uninvolved with clinical care, opened a sealed envelope at the time of randomisation, programmed the device, and performed all tests that could reveal the identity of the assigned pacing mode. Neither the patients nor the physicians treating them for heart failure and performing the study evaluations were aware of the treatment assignment.

The primary end points were the NYHA functional class, Quality of Life (QoL), and the distance walked in six minutes. Quality of Life was assessed using the Minnesota Living with Heart Failure Questionnaire (MLWHF).[23] Additionally, several secondary end points (peak oxygen consumption, time on a treadmill, left ventricular ejection fraction and end-diastolic dimension, severity of mitral regurgitation, duration of QRS interval, and a clinical composite response, which assigns patients to one of three response groups — improved, worsened, or unchanged) were the major efficacy variables for the study. In addition, the protocol specified an analysis of death or worsening heart failure (as safety variables), as well as the number of days spent in the hospital. All analyses were according to the intention-to-treat principle (ITT).

Recruitment ran from November 1998 till December 2000 and was *sponsored by Medtronic*. It was designed as a multi-centre trial in the USA and Canada.

Main results The authors report that the two groups were similar with respect to all base-line characteristics. They report several clinical improvements in the patients randomised to CRT-P. Regarding the primary endpoint, patients in the CRT-P group compared to the control group experienced an improvement in the distance walked in six minutes (+39 vs. +10 m, p=0.005), NYHA functional class (p<0.001), Quality of Live (-18.0 vs. -9.0 points, p= 0.001), time on the treadmill during exercise testing (+81 vs. +19 sec, p=0.001), and ejection fraction (+4.6% vs. -0.2%, p<0.001).

Differences in favour of CRT were apparent as early as one month after the initiation of treatment, and the magnitude of improvement was maintained without attenuation for the entire study period. The magnitude of the effect on the three primary end points was not influenced by the use of a beta-blocker, the cause of heart failure (ischaemic or nonischaemic), the configuration of the QRS complex (left or right bundle branch block), or the base-line duration of the QRS interval (analysed as a continuous variable, p>0.10 for all interactions).

Patients in the CRT group had an improvement in the two measures of maximal exercise performance: peak oxygen consumption (p=0.009) and total exercise time (p=0.001). Furthermore, the left ventricular ejection fraction increased and the end diastolic dimension, the area of the mitral regurgitant jet, and the duration of the QRS interval all decreased in the resynchronisation group (all p< 0.001 for the comparison with the control group). Finally, CRT had a favourable effect on the clinical composite heart-failure score. At the end of six months, the condition of more patients in the group assigned to CRT was considered to have improved (67% vs. 39% in the control group) and that the condition of fewer patients was considered to have worsened (16% vs. 27%) (p<0.001).

There were 12 deaths (5%) in the CRT vs. 16 deaths (8%) in the control group. In an analysis of time to a first event, 28 patients (12 %) in the CRT group died or were hospitalised for worsening heart failure vs. 44 patients (19%) in the control group.

Fewer patients in the group assigned to CRT than control patients required a *first* hospitalisation (8 % vs. 15 %) or intravenous medications (7 % vs. 15 %) for the treatment of heart failure (p<0.05 for both comparisons). The combined risk of a major clinical event (death or

hospitalisation for heart failure) was 40% lower in the resynchronisation group than in the control group (p=0.03).

The number of hospitalisations in this six months period and the total number of hospital days was lower in the CRT-P group compared to controls: 25 hospitalisations for heart failure in 18 patients (a total of 83 hospital days) vs. 50 in 34 patients (a total of 363 days) respectively (p=0.02). However, the two treatment groups were similar with respect to hospitalisations unrelated to HF or to left ventricular lead functioning: 37 (16 %) and 33 (15%) hospitalisations in the CRT and control groups respectively. Patients in the CRT-P group also required less use of intravenous medication for worsening heart failure (p=0.004).

Adverse events Implantation and maintenance of a resynchronisation device were associated with risks that were greater than those of conventional pacing devices. Implantation of the device was unsuccessful in 8% of eligible patients and was complicated by refractory hypotension, bradycardia, or asystole in four patients (two of whom died) and by perforation of the coronary sinus requiring pericardiocentesis in two others.

Of the 225 patients assigned to the control group, 16 died, 2 received a heart transplant, 1 had complications related to the device,. Of the 228 patients assigned to CRT, 12 died and 1 had complications related to the device. No patient was lost to follow-up for the analysis of death or worsening heart failure.

As compared with the control group, patients in the CRT group were more likely to be re-hospitalised for repositioning or replacement of the left ventricular lead (11 and 3 patients in the CRT and control groups, respectively).

However, those data only include the 453 patients who were ultimately randomised for the six- months study and also include patients in a pilot 3 month scheme. When all possible reasons for technical failure were considered, about *8 % of the 571 participating patients were unable to receive and be maintained on CRT* for the planned duration of treatment. Of those, 4 did not undergo randomisation because of adverse clinical events during the implantation procedure. Complete heart block that required permanent cardiac pacing developed in two patients, progressive hypotension developed in one patient who died later the same day and one patient had asystole and required cardiopulmonary resuscitation, did not recover neurologically, and died one month later. In addition, during the procedure, 23 patients (4%) had a coronary-sinus dissection, and 12 patients (2%) had a cardiac-vein or coronary-sinus perforation. Of these, three required intravenous catecholamines, pericardiocentesis, or both for a presumed or confirmed diagnosis of hemopericardium but recovered without sequels and continued in the study.

Of the 528 patients who underwent successful implantation, the median duration of the procedure was 2.7 hours (range, 0.9 to 7.3). After implantation, 20 patients required repositioning of the left ventricular lead and 10 required its replacement; 7 patients reported a pacemaker-related infection that required explantation, 4 of whom had the device re-implanted uneventfully. The frequency of adverse events unrelated to the device or to heart failure did not differ significantly between the two treatment groups.

Conclusions The authors of this study concluded that in these patients with advanced heart failure (NYHA class III or IV) and a prolonged QRS interval CRT results in significant clinical improvement.

In contrast with the two largest studies (COMPANION and CARE-HF described below) this smaller study offers the benefit of being double blinded. Also in contrast with those larger studies, not only the first occurrence of composite end points was described but also the effect on the number of hospitalisations and the total number of hospital days, making this study more helpful for the economic evaluation of CRT.

A drawback is the short duration of this study, and the outcomes, both beneficial outcomes and adverse effects reported in a study of 500 patients evaluated for six months may not reflect the effects seen in thousands of patients treated for years.

4.2.2 MIRACLE ICD, 2003

Trial description The MIRACLE ICD trial (Multicenter InSync ICD Randomized Clinical Evaluation) is also a *double-blind trial* intended to evaluate the efficacy of CRT-D vs. ICD alone in patients with moderate-to-severe heart failure a prolonged QRS interval and at high risk of life-threatening ventricular arrhythmia's.[24] The hypothesis was that patients with moderate to severe HF symptoms and an established indication for an ICD would not only benefit from the ICD (reduced HF mortality) but also symptomatically benefit from the CRT, and that the CRT would not be proarrhythmic or compromise the ICD therapy.

Patients were eligible for the study if they had moderate or severe (NYHA class III or IV) chronic heart failure due to either ischaemic or nonischaemic cardiomyopathy, a LVEF of $\leq$ 35% or less, left ventricular end-diastolic dimension of 55 mm or more, a QRS interval $\geq$ 130 ms or more *and previous cardiac arrest due to ventricular fibrillation or ventricular tachyarrhythmia, or spontaneously sustained ventricular tachyarrhythmia, or inducible ventricular fibrillation or sustained ventricular tachyarrhythmia*. Patients needed to be on a stable drug regimen for more than a month.

In the MIRACLE ICD trial, eligible patients underwent a series of baseline evaluations including estimation of NYHA functional class, six-minute walking test and Quality of Live evaluation using the Minnesota Living with Heart Failure Questionnaire (MLWHF).[23] After the initial evaluation, *all selected patients underwent implantation of a CRT-D*. The *369 patients* who had undergone successful implantation were subsequently randomly assigned to CRT-D (the intervention group, n=187) or to the control group (CRT switched off but ICD activated, n=182) *with a follow-up duration of six months.* Patients and physicians from the HF team, continued to follow patients after implantation of the CRT-D system but were not involved in the programming of the device and remained unaware of the randomisation assignment until after the six month visit. After six months, the CRT function was additionally activated in all patients.

The primary double-blind trial end points were changes between baseline and six months in Quality of Live, functional NYHA class, and six-minute walking distance. Additional outcome measures included changes in exercise capacity, plasma neurohormones, left ventricular function, and a clinical composite response, which assigns patients to one of three response groups (improved, worsened, or unchanged). Survival, incidence of ventricular arrhythmias, and rates of hospitalisation were also compared. All analyses were according to the intention-to-treat principle (ITT).

The MIRACLE ICD recruitment ran from October 1999 to August 2001 and was *sponsored by Medtronic*.

Main results Except for a higher percentage of patients with ischaemic heart disease in the control group, the baseline clinical characteristics of the two groups were similar. In the control group, 14 patients (8%) crossed over to CRT before the end of the randomised phase of the study. In the CRT group, ten patients (5%) crossed over from active bi-ventricular pacing to no pacing before the end of the randomised phase.

Regarding the primary endpoints (ITT analysis), the Quality of Live at six months improved more in patients assigned to CRT that in controls, with a median Quality of Live score –17.5 (95% CI –21 to –14) vs. –11.0 (–16 to –7), respectively (p=0.02). The median functional class improved with –1 (–1 to –1) vs. 0 (–1 to 0), respectively (p=0.007) but there was no difference in the change in the six minute walking distance: 55 m (95% CI 44 to 79) vs. 53 m (43 to 75), respectively (p=0.36).

The treatment effect on Quality of Live score and NYHA functional class was not influenced by the use of a β-blocker, underlying heart disease (ischaemic vs. nonischaemic), morphology of the QRS complex (left vs. right bundle branch block), or the baseline duration of the QRS interval (p>0.10 for all interactions with randomisation assignment).

Patients in the CRT group had an improvement of the parameters of maximal exercise performed: peak oxygen consumption increased by 1.1 ml/kg per minute (0.7 to 1.6) in the CRT group vs. 0.1 ml/kg per minute (–0.1 to 0.8) in controls (p=0.04), while treadmill exercise duration increased by 56 seconds (30 to 79) and decreased by 11 seconds (–55 to 12) respectively (p<0.001). No significant differences were observed in changes in left ventricular size or function.

Using the overall composite clinical HF status endpoint there was only a statistical trend toward more improvement in the CRT group but no significant difference (p=0.07), which is remarkable since the NYHA functional class measurement significantly improved more in the CRT group. There were also no significant differences between the treatment groups for survival and rates of hospitalisation. No proarrhythmia was observed and arrhythmia termination capabilities were not impaired.

During the six-month randomisation period, 47 patients (26%) in the control group and 42 patients (22%) in the CRT group experienced at least one spontaneous episode of ventricular tachycardia or fibrillation (p=0.47). Four episodes (1.7%) were not successfully terminated within the interval determined by device criteria in the control group vs. 1 episode (0.1%) in the CRT group. These five episodes all eventually terminated spontaneously. There was no difference between the study groups in the detection times of ventricular fibrillation episodes. Furthermore, there was no difference in the number of patients receiving either appropriate or inappropriate ICD treatment, when comparisons are made by ITT or whether through on-protocol analysis.

A total of 15 patients in the control group and 14 patients in the CRT group died during the six-month follow-up (8% in both groups). In each group, three of these deaths were characterised as sudden deaths. Cumulative survival at six months was 92.2% in the control group (87.2 to 95.3) vs. 92.4% (87.5 to 95.4) in the CRT group (log rank p=0.96). Of the 429 enrolled patients with at least one implant attempt, five (1.2%) died within 30 days of their latest implant attempt.

Between randomisation and the six-month visit, 78 patients in the control group (42.9%) and 85 patients in the CRT group (45.5%) were hospitalised. The mean (SD) length of hospital stay was 5.4 days (4.7) in the control group vs. 4.8 days (4.9) in the CRT group (p=0.06). During the six-month follow-up, the probability of hospitalisation for worsening HF or death from any cause was 25.9% (19.8 to 32.5) for the control group vs. 25.7% (19.6 to 32.3) for the CRT group (p=0.69). The risk of the composite end point of death or all-cause hospitalisation was 48.3% (40.6 to 55.6) for the control group vs. 47.4% (40.0 to-54.4) for the CRT group (p=0.88).

Adverse events Of the 429 enrolled patients with at least one implant attempt, five (1.2%) died within 30 days of their latest implant attempt. Of these 429 patients, 120 patients (28%) experienced 159 complications from implant to hospital discharge. Of these 159 complications, 37 (23%) were related to the LV lead, including 15 coronary sinus dissections and four cardiac perforations. Other peri-operative complications included HF decompensation in six patients, all treated with intravenous medications; heart block in three patients, all requiring bradycardia pacing support; muscle stimulation in four patients, treated by either a lead repositioning or lead replacement; pericardial effusion in two patients treated with a pericardiocentesis; pericarditis in one patient treated with intravenous medications; haemo/pneumothorax in three patients treated with the placement of a chest tube; ventricular tachycardia and ventricular fibrillation in five patients, in which three patients were treated with external defibrillation and two patients were treated with intravenous medications; and elevated pacing thresholds or loss of capture in seven patients, in which six patients

were treated with a lead repositioning or lead replacement and one patient had a set screw tightened in the connector block.

Fifty patients had an unsuccessful CRT system implant but a successful placement of an ICD-only system. Of those 50 patients, 20 experienced a total of 35 complications from the time of hospital discharge through six months. Heart failure decompensation was the most common complication, accounting for 19 events.

From hospital discharge to the end of the six-month randomisation period, 175 (46%) of the 379 patients with successful implants experienced 398 complications. The rate of device-related events was substantially lower than the rates anticipated in the pre-specified criteria of the original study protocol. The frequency of adverse events unrelated to the device or to HF did not differ significantly between the two groups.

Conclusions The authors of this study concluded that in these patients CRT in addition of ICD functionality improved Quality of Live, functional status, and exercise capacity compared to appropriate medical management only, and without proarrhythmia or compromised ICD function.

Although the improvements in Quality of Live and NYHA functional class in those patients were similar to those observed in comparable patient populations without indications for ICDs, the absence of a positive treatment effect on the six-minute walking test contrasts with other trials and with the improvements observed in this study with the measurements of peak VO_2 and treadmill exercise duration. The reasons for these discrepancies remain uncertain.

Overall, the findings in this trial are less compelling than those in the original MIRACLE study. However, also this double blind RCT delivers some useful information for the clinical effectiveness, since it gives useful information on outcomes, Quality of Live, adverse effects of implantations and hospitalisations. However, the scope of this study is on ICDs with or without CRT whereas the scope of our report is mainly on optimal medical therapy with or without CRT-D or CRT-P. Therefore, this study is less useful for our purposes.

4.2.3 COMPANION, 2004

Trial description The COMPANION trial (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) is a *non-blinded trial* that tested the hypothesis that prophylactic CRT with or without a defibrillator would reduce the risk of death and hospitalisation among patients with advanced chronic heart failure and intra-ventricular conduction delays from either ischaemic or nonischaemic cardiomyopathy, with sinus rhythm, no clinical indication for a pacemaker or implantable defibrillator, and a hospitalisation for the treatment of heart failure or the equivalent in the preceding 12 months.[25] Patients, physicians, independent statisticians, and members of the data-management group and the data safety and monitoring board were *not blinded* to the treatment assignments, whereas the steering committee, the end points committee, and the sponsor were unaware of the treatment assignments.

In the COMPANION trial, *1520 patients* with advanced heart failure (NYHA class III or IV), a QRS $\geq$ 120 ms and an LVEF $\leq$ 35% were randomly assigned in a 1:2:2 ratio (308 optimal medical treatment, 617 CRT-P, 595 CRT-D) to receive either optimal medical treatment (diuretics, angiotensin-converting–enzyme inhibitors, beta-blockers, and spironolactone) alone or in combination with CRT-P or CRT-D.

The primary composite end point was *time to death from or hospitalisation for any cause*, while a secondary end point was *death from any cause*. In addition, the outcomes of death from or hospitalisation for cardiovascular causes and death from or hospitalisation for heart failure were reported upon, although they had not been pre-defined as outcomes in the initial protocol.

Adverse events were defined as any undesirable clinical outcome and included device-related events as well as events related to the patients' general condition. All analyses were conducted according to the intention to treat principle. Efficacy analyses were based on the time to a first event unless for some secondary endpoints such as death from any cause.

The trial ran from January 2000 and follow-up was stopped on December 1st 2002 and *was sponsored by Guidant.* It was designed as a multi-centre trial in the USA. Participants were randomised before implantation and followed-up for a mean time of 14.6 months. The study was stopped early after 1638 patients were enrolled after predictions that the targets for primary and secondary end points had been met. The effective follow-up duration was depending upon the endpoint measured, ranging from 11.9 to 16.5 months.

Main results Although the authors report no clinically significant differences in baseline variables or mandated background therapy among the three groups, there were some remaining imbalances between patients after randomisation: overall only 14% of patients where in NYHA class IV, while in the control group this was 18% (see table 1 in the original publication,[25]). Also the six minute walking distance was somewhat shorter in the control group. Overall the rate of successful implantation was approximately 90%.

During the course of the study, a substantial number of patients withdrew from the optimal medical treatment group (26% vs. 6% and 7% in the CRT-P and CRT-D groups respectively) to receive commercially available implants because of arrhythmia or heart failure. This large number of withdrawals could possibly at least partly be attributed to the non-blinded nature of this study. Therefore the steering committee implemented a policy of asking patients who had withdrawn before December 1st 2002, to consent to the collection of data on vital status and hospitalisations for the duration of the study to allow for a further intention to treat analysis.

CRT-P decreased the risk of the *primary end point (time to death from or hospitalisation for any cause)*, HR, 0.81 (p=0.014) compared to the control group, but these events were mainly driven by hospitalisations. CRT-D decreased the risk of the primary end point similarly, HR, 0.80 (p=0.01). Overall there was almost no difference between the groups receiving CRT-P or CRT-D.

CRT-P reduced the risk of the *secondary end point (death from any cause)* by 24% (p=0.059, NS) while a CRT-D reduced the risk by 36% (p=0.003), both compared to the control group. The risk of the *combined end point of death from, or hospitalisation for heart failure* was reduced by 34% in the CRT-P (p<0.002) and by 40% in the CRT-D group (p<0.001) compared with the control group, but again this endpoint was mainly driven by hospitalisations rather than by death.

Subgroup analyses according to baseline characteristics resulted in hazard ratios for the primary and secondary end points that were consistently below 1, indicating consistent efficacy for each device across those subgroups.

Quality of life (QoL) was assessed by the Minnesota Living with Heart Failure questionnaire,[23] with higher scores indicating a poorer Quality of Live. The reduction of this score (improvement of QoL) was significantly larger in both treatment groups at month 3 and month 6 (p<0.001 for all comparisons). Also the NYHA class and the distance walked in six minutes improved significantly more in the treatment groups (p<0.001 for all comparisons).

Adverse events A total of 61% of patients in the control group had a moderate or severe adverse event from any cause, as compared with 66% of patients in the CRT-P group (p=0.15) and 69% of patients in the CRT-D group (p=0.03). There was no significant difference between CRT groups in the proportion of patients with moderate or severe device-related adverse events (p=0.42).

Moderate or severe adverse events related to the implantation procedure occurred in 10% of patients in the CRT-P group and 8% of those in the pacemaker–defibrillator group. Included in these events were coronary venous dissection (0.3% in the pacemaker group and 0.5% in the CRT-D group), coronary venous perforation (1.1% and 0.8%, respectively), and coronary venous tamponade (0.5% and 0.3%, respectively). Five deaths (0.8% of enrolled patients) in the CRT-P group and three (0.5%) in the CRT-D group were adjudicated as related to procedural complications.

The mortality rates 30 days after randomisation were reported to be similar among the three groups: 1.0% in the CRT-P group and 1.8% in the CRT-D group, as compared with 1.2% in the optimal medical therapy group (p=0.34 and p=0.79, respectively).

Conclusions The authors of this study concluded that in patients with advanced heart failure and a prolonged QRS interval, CRT decreases the combined risk of death from any cause or first hospitalisation and, when combined with an implantable defibrillator, significantly reduces mortality.

That the primary endpoint was a *combination of death and hospitalisation for any cause* makes interpretation of this study difficult, since the results for this primary endpoint were mainly driven by the *first hospitalisation for any cause* that stopped the observations rather than by the more relevant hard end point of death. Moreover, the fact that observations for the combined primary end point were stopped at the moment of the first event makes it impossible to know whether CRT did not only delay first hospitalisation, but also the total number and duration of hospitalisations in those patients.

The secondary end point of death from any cause is easier to interpret and allows comparison with other studies.

For the purpose of economic evaluation this study offers limited added value apart from mortality, since the observations stop at the moment of first hospitalisation (or death), and offers no clue about the number nor the duration of those hospitalisations. Quality of life was measured using a disease specific instrument rather than a generic QoL instrument, again making comparisons difficult.

4.2.4 CARE HF, 2005-2006

Trial description The CARE-HF trial (CArdiac REsynchronization-Heart Failure trial) is a *non-blinded trial* that was set up to evaluate the effects of CRT-P therapy on morbidity and mortality among patients with advanced chronic heart failure due to left ventricular systolic dysfunction and cardiac dyssynchrony in addition of optimal medical therapy, and compared to optimal medical therapy only. Patients were randomly assigned to receive medical therapy alone or combined with RCT and randomisation was stratified according to the NYHA class. Eight patients assigned to undergo cardiac resynchronisation, however, ultimately had a CRT-D device implanted during the study.[1,26]

The study was *not blinded* for the patients nor for the treating physicians and patients in the control group were not scheduled to receive a device both for ethical reasons and so that the trial could assess the entire effect of CRT, including complications associated with implantation of the device. The members of the end points committee, however, were not aware of patients' treatment assignments.

In the CARE-HF trial, *813 patients* (404 in control group, 409 in intervention group) with advanced heart failure (NYHA class III or IV), a QRS $\geq$ 120 ms, a LVEF $\leq$ 35%, sinus rhythm, and a left ventricular end-diastolic dimension of at least 30 mm (indexed to height), were included. Patients with a QRS interval of 120 to 149 ms were required to meet additional criteria for dyssynchrony.

The primary composite end point was the *time to death from any cause or a first unplanned hospitalisation for a major cardiovascular event*. The principal secondary end point was *death from any cause*. Other secondary end points included a composite of *death from any cause and unplanned hospitalisation with heart failure*. *At 90 days, the NYHA class* and the *Quality of Live* were assessed by the patient with the use of the Minnesota Living with Heart Failure questionnaire (with higher scores reflecting a poorer Quality of Live),[23] and the European Quality of Life–5 Dimensions (EuroQoL EQ-5D) instrument (with lower numerical values indicating a poorer Quality of Live).[27] No baseline assessment of the Quality of Live was performed.

Reported general adverse events were blindly classified by an end points committee, but if they were procedure-related or device-related, by an independent expert who was not blinded to the study-group assignments. All analyses were conducted according to the intention to treat principle, and only the first event in each patient was included in the main analysis. Data on patients who underwent elective heart transplantation were censored seven days after the procedure, while emergency heart transplantation was counted as a death. All hospitalisations were adjudicated in a blinded fashion by the (blinded) end points committee. The first hospitalisation with documented worsening heart failure, myocardial infarction, unstable angina, arrhythmia, stroke, or other major cardiovascular event (e.g., pulmonary embolism or ruptured aortic aneurysm) or hospitalisation owing to or prolonged by a serious procedure-related event (e.g. infection, pericardial haemorrhage, or tension pneumothorax) was counted in the primary end point. Not included in the primary endpoint were admissions for symptoms without a documented major cardiac event nor readmissions for lead displacement, unless it precipitated a cardiac emergency.

The CARE-HF trial was designed as a multi-centre trial in 82 centres in 12 European countries. Participants were randomised prior to implantation and followed up initially for an average 29.4 months (interquartile range (IQR) 23.6–34.6) and afterwards in an extension study for an average 37.4 months (IQR 31.5–42.5). Trial enrolment began in January 2001 and ended in March 2003 with follow-up until September 30th 2004 (45 months maximum follow-up) *and was sponsored by Medtronic.*[1]

Afterwards, an extension phase with *death from any cause* as the primary outcome extended this follow-up until March 2005 (51 months maximum follow-up).[26] The reported main reasons for this extension phase were interim analyses showing a trend toward more cardiovascular events in the first 10 days after randomisation among patients assigned to CRT than among those assigned to medical therapy alone and a trend toward a favourable effect of RCT on long-term mortality. The board reportedly feared that they might fail to reach significance by the time of the planned closure date.[1]

Main results from the original trial[1] Baseline characteristics were similar in the two groups (see table 1 in the original manuscript,[1]). Survival status was known for all patients at the end of the main study and for all but one patient assigned to the control group at the end of the extension phase. Among the 409 patients assigned to CRT, 19 patients never received a device of whom six (31.6%) died during follow-up. One patient died while awaiting implantation, the investigator or patient decided not to proceed in four cases, and attempts at device implantation failed in 14 patients. Among the 404 patients in the control group 95 patients received a CRT device and had it activated during follow-up. There were three emergency and seven elective heart transplants in the control group and one emergency and ten elective transplants in the CRT group during follow-up. All emergency transplant patients died within seven days but none of the elective cases.

For reasons that are not totally clear, events occurring the first ten days after randomisation were excluded (12 unplanned hospitalisations for a major cardiovascular event in the CRT group and ten in the control group).

By the end of the study, the primary end point (time to death from any cause or an unplanned hospitalisation for a major cardiovascular event) had been reached in 159 patients in the CRT

group, as compared with 224 patients in the control group (39% vs. 55%), HR 0.63 (0.51 - 0.77, p<0.001). Again this primary endpoint was mainly driven by hospitalisations; death being the primary event in 74 patients (19% of primary end points), and hospitalisation in 309 patients.

Pre-specified subgroup analyses based on baseline characteristics for the primary end point revealed no heterogeneity in the effect of CRT and resulted in hazard ratios consistently below 1, indicating consistent efficacy for CRT across those subgroups.

In the CRT group, 82 patients died (secondary end point), as compared with 120 patients in the control group (20% vs. 30 %), HR, 0.64 (0.48 to 0.85, p<0.002) and 83% of those deaths were classified as cardiovascular death. The cause of death was attributed to worsening heart failure in 47% of deaths in the control group and in 40% in the CRT group.

CRT reduced the risk of the secondary composite end point of death from any cause or hospitalisation for worsening heart failure: HR, 0.54 (0.43 to 0.68, p<0.001). Patients in the intervention group had less severe symptoms: average NYHA class at 90 days was 2.7±0.9 in the control group and 2.1±1.0 in the CRT group, a difference of 0.6 (0.4 to 0.7, p<0.001).

CRT-P lowered the proportion of unplanned hospitalisations for worsening HF, HR 0.48 (0.36 to 0.64, p<0.001) and the number of unplanned hospitalisations for major cardiovascular events, HR 0.61 (0.49 to 0.77, p<0.001).

Quality of life (QoL) at 90 days was better in the intervention group: the average Minnesota Living with Heart Failure scores were 40±22 and 31±22 respectively (difference -10 (-8 to -12) p<0.001). The average EQ-5D scores were 0.63±0.29 and 0.70±0.28 respectively (difference 0.08 (0.04 to 0.12, p<0.001). However, the interpretation of these data is difficult since there were no baseline measurements of QoL

Main results from the extension phase The primary outcome of the extension phase of the CARE-HF trial was *all-cause mortality* from the time of randomisation to completion of the extension phase while a *secondary outcome was mode of death*.[26]

The findings on mortality mainly confirm the original findings from the study. There were 154 deaths (38.1% or 12.2% per year) in the control group and 101 (24.7% or 7.9% per year) in the intervention group: HR 0.60 (0.47-0.77, p<0.0001). No evidence of heterogeneity in pre-specified subgroups was detected. It was reported that the proportional hazards of both sudden death and death from worsening heart failure were constant throughout the CARE-HF trial and the extension phase.

For the secondary end points, the risk of death due to heart failure was 5.1 vs. 3.0% per year for control vs. intervention, and for sudden death 4.3 vs. 2.5% per year, with HR = 0.55 (0.37–0.82, p=0.003) and 0.54 (0.35–0.84, p= 0.005) respectively, both in favour for the intervention group.

Subgroup analyses basically confirmed the findings from the original trial

Adverse events from the original trial There was one device-related death in each group: one patient in the CRT group died of heart failure aggravated by lead displacement and one patient in the control group died of septicaemia after receiving a device. The most common adverse device- or procedure-related events in the CRT group were lead displacement (24 patients), coronary-sinus dissection (ten patients), pocket erosion (eight patients), pneumothorax (six patients), and device-related infection (three patients).

Worsening heart failure was more common in the control group (affecting 263 patients, as compared with 191 patients in the CRT group, p<0.001), whereas atrial arrhythmia's or ectopy was more common in the CRT group (affecting 64 patients in that group, as compared

with 41 in the medical-therapy group, p=0.02). The frequencies of respiratory tract infections, hypotension, falls or syncope, acute coronary syndromes, renal dysfunction, ventricular arrhythmia's or ectopy, and neurologic events were similar in the two groups.

Adverse events from the extension phase No further adverse events were discussed in the report on the extension phase of CARE-HF.[26]

Conclusions The authors of this study concluded that in patients with heart failure and cardiac dyssynchrony, CRT improves symptoms and the Quality of Live and reduces complications and the risk of death. They stress that these benefits are in addition to those afforded by standard medical therapy and that the implantation of a CRT device should therefore routinely be considered in such patients. From the extension phase they concluded that the benefits of CRT observed in the main trial persisted or increased with longer follow-up. Reduction in mortality was due to fewer deaths both from worsening heart failure and from sudden death.

This trial provides good evidence about the effect of CRT-P on mortality. However, just as in the COMPANION study, the use of a combined primary end point of *death or first unplanned hospitalisation for a major cardiovascular event* makes interpretation of this study difficult, since the results for this primary endpoint were mainly driven by the primary end point that stopped the observations rather than by the more relevant hard endpoint of death. Moreover, the fact that observations for the combined primary end point were stopped at the moment of the first event makes it impossible to know whether CRT did not only delay first hospitalisation, but also reduced the total number and duration of hospitalisations in those patients.

The secondary end point of death from any cause, and mode of death is easier to interpret and allows for comparison with other studies.

For the purpose of our economic evaluation this study offers little added value apart from mortality, since the observations stop at the moment of first hospitalisation (or death), and offer no information about the number nor the duration of those hospitalisations. Quality of life was measured using both a disease specific instrument and a generic QoL instrument, but in the absence of a baseline measurement of Quality of Live real comparisons become difficult.

4.3 Description of the most relevant meta-analyses and health technology assessments

Especially between 2003 and 2006 many meta-analyses were conducted on CRT compared to optimal medical treatment, mainly in NYHA class III/IV patients, while in recent years a few new meta-analyses were published.[28,29,30,31,32,6,5,4] We selected the three most recent and relevant meta-analyses and HTAs for a more complete description in this chapter: Lemos et al.,[4] Lam et al.,[5] and Fox et al.[6] Two of those were also included in the ESC update guideline while the third was not.[4] Details of included studies in the ESC guideline update and the meta-analyses are given in Table 4.1. Details on number of participants and proportion of patient in NYHA class II slightly differ, since not all meta-analyses used exactly the same publications.

The meta-analyses dealt mainly with mortality and morbidity while adverse events and Quality of Live were barely covered.

Table 4.1.: Overview of included trials in the different reviews

Trial	ESC	Lam	Lemos	Fox	Average follow-up (months)**	NYHA Class**	% NYHA III**	n*,**
MUSTIC-SR[33]	X	X	X	X	3	III	100	58
MIRACLE[22]	X	X	X	X	6	III, IV	91	453
MUSTIC AF[34]	X		X			III		43
PATH CHF[35]	X					III, IV		41
MIRACLE ICD[24]	X	X	X		6	III, IV	89	369
CONTAK CD[36]	X	X	X	X	4.7	II-IV	59	581
MIRACLE ICD II[24]	X	X			6	II	0	186
PATH CHF II[37]	X					III, IV		89
COMPANION[25]	X	X	X	X	14.8, 16.5,16.0	III, IV	86	1520
CARE HF[1,26]	X	X	X	X	37.4	III, IV	94	813
REVERSE[38,39]	X					I, II		610
MADIT CRT[40]	X					I, II		1800
RAFT[41]	X					II, III		1800
CAT[42]		X			66		35	104
AMIOVIRT[43]		X			24		20	103
DEFINITE[44]		X			29		21	458
MADIT II[45]		X			20		24	1232
SCD-HeFT[46]		X			45.5		30	2521

*Based on ESC guideline

**Based on Lam et al.

4.3.1 Lemos et al., 2009

Meta-analysis design In 2009, Lemos et al. published a meta-analysis of CRT in patients with heart failure with wide QRS and low ejection fraction.[4] The scope of this study was on the effectiveness of CRT on *mortality and morbidity* among patients with heart failure comparing optimal medical treatment with optimal medical treatment combined with either CRT-P or CRT-D. However, no subgroup analyses were presented separating the effects of CRT-P vs. CRT-D.

The search strategy is well described and logical. The authors used the normal bibliographic databases but also congress proceedings and covers the period from *1990 to 2006*. The inclusion criteria are randomised controlled trials comparing CRT-P or CRT-D in addition to optimal medical treatment in patients with heart failure with low ejection fraction (not > 35-40% depending upon trial), and wide QRS (QRS $\geq$ 120-200 ms depending upon trial) and classified as NYHA II, III or IV despite optimal medical therapy (or with a conventional univentricular pacemaker).

As shown in Table 4.1 this meta-analysis considers mainly NYHA functional class type III and IV patients making it relatively representative for the patients considered in this chapter. Only one trial in this meta-analysis also included patients in NYHA functional class II, but even in this CONTAK-CD trial,[36] the proportion of NYHA class III patients was almost 60%.

Seven trials met the inclusion criteria (n=3164):
- COMPANION,[25]
- MIRACLE,[22]
- MIRACLE ICD,[24]
- CARE-HF,[1]

– CONTAK-CD,[36]
– MUSTIC-SR,[33]
– MUSTIC AF.[34]

The follow-up duration was different but in general rather short, ranging from two months to 18 months. The specific outcomes documented also varied: *death (total death, death due to heart failure, sudden cardiac death) or hospitalisation:*

– all-cause mortality (5 studies),[22,25,1,36,24]
– death due to congestive heart failure (2 studies),[25,1]
– sudden cardiac death (3 studies),[25,1,24]
– hospitalisations due to congestive heart failure (6 studies).[22,33,1,36,34,24]

Main results

All-cause mortality In this meta-analysis, a significant absolute risk reduction of 4% for *all-cause mortality* was observed in the intervention group compared to the control group, corresponding to a relative risk (RR) of 0.70 (95% CI: 0.60 to 0.83) and NNT was 25. This analysis was done for a total of 3028 patients (see Figure 4.1)

Mortality due to heart failure For *death due to heart failure*, no significant risk reduction was found in the intervention group with a RR, 0.79 (0.60 to 1.03) for a total of 1716 patients (see Figure 4.1)

Sudden Cardiac Death For *sudden cardiac death* a significant absolute risk reduction of 1% was observed in the intervention group compared to the control group, corresponding to a RR of 0.67 (0.46 to 0.96) and a NNT of 100. This analysis included a total of 2085 patients (see Figure 4.1)

Hospitalisations due to heart failure A significant reduction in the intervention group of *first hospitalisations due to heart failure* with an absolute risk reduction of 9%, a RR of 0.69 (0.51 to 0.94), a NNT of 11 for a patient population of 2261 (see Figure 4.2)

Because of observed heterogeneity the authors made an additional analysis for *first hospitalisations due to heart failure but excluding one specific study* that compared ICD with and without CRT functionality (MIRACLE ICD,[24]). In that study, the hospitalisation rate was slightly (but not significantly) higher in the intervention group, but in this study the included patients had more severe heart failure and obviously an indication for ICD. The elimination of this study barely changed the results: the relative risk decreased slightly to a RR of 0.64 (0.50 to 0.80) for a total of 1892 patients (Forest plot not shown).

Forest plots The forest plots relating to all-cause mortality, mortality due to HF and sudden cardiac death are shown in Figure 4.1. Hospitalisations due to HF are shown in Figure 4.2

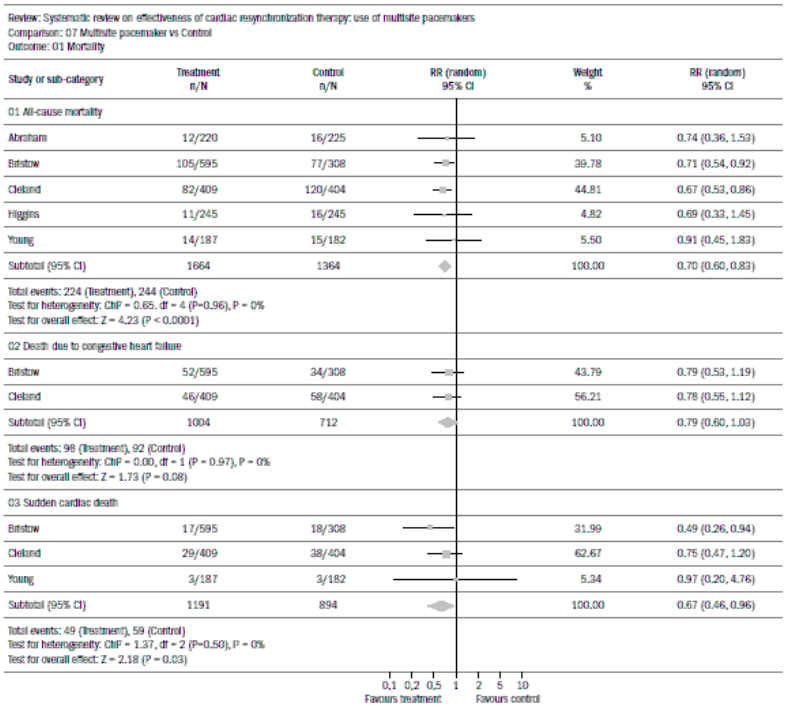


Figure 4.1.: Forest Plot of total mortality, death due to HF and sudden cardiac death.[4]

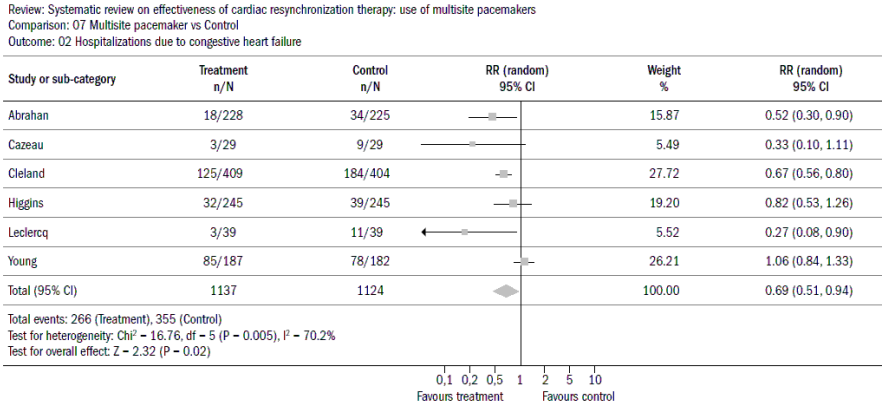


Figure 4.2.: Forest Plot of hospitalisations due to HF.[4]

Conclusions In this meta-analysis the authors conclude that the use of CRT was associated with functional improvements for patients with heart failure, thereby decreasing the rate of hospitalisation due to heart failure. From the results of this systematic review it appears that there is a statistically significant decrease in all-cause mortality, but no statistically significant evidence that CRT reduces death specifically due to congestive heart failure.

Since this is the most recent, well conducted, meta-analysis, covering mainly patients in NYHA class III and IV the results of this meta-analysis are important. However, although this study included studies with both CRT-P and CRT-D it did not differentiate between CRT-P and CRT-D in the analysis. It also included a study (MIRACLE ICD) that is essentially outside the scope of this report since it compares ICD with and without CRT functionality. Assumptions for the economic model will mainly be drawn from another meta-analysis, from individual studies, or from Belgian reimbursement data wherever possible, especially considering resource use and costs.

4.3.2 Lam et al., 2007

Meta-analysis design In 2007, Lam et al. published a Bayesian network meta-analysis of randomised controlled or crossover trials of CRT in patients with low ejection fraction.[5] The scope of this study was on the effectiveness of CRT on *mortality only* of either CRT (with or without defibrillator function) or ICD alone, all compared with optimal medical treatment. The analysis was on mortality outcomes from individual studies *expressed as odds ratios* using random effects models to estimate the mean and 95% credible intervals for the overall treatment effect.

The search strategy is well described and logical. The authors used the regular bibliographic databases but also congress proceedings and covers the period from *1966 to June 2006*. In addition, reports from the US Food and Drugs Administration and reference lists of identified studies and published meta-analyses were searched. No restrictions on types of CRT or ICD devices or on language were applied. The inclusion criteria are randomised controlled or crossover trials of CRT in patients with impaired left ventricular systolic function (ejection fraction <35%) comparing CRT-P or CRT-D with optimal medical therapy or with optimal medical therapy combined with ICD (without CRT function). Neither HF nor a prolonged QRS interval were formal inclusion criteria, since this meta-analysis also dealt with ICDs without CRT function. Secondary prevention trials of ICD were excluded.

As shown in Table 4.1 this meta-analysis considers several trials with patients not only in NYHA functional class type III and IV patients but also includes a few trials with patients in NYHA function class I and II making it slightly less comparable to the patients considered in this chapter. However, subgroup analyses for patients in NYHA class III and IV were performed.

Twelve trials met the inclusion criteria (n= 8307):
- COMPANION,[25]
- CARE-HF,[26]
- MUSTIC-SR,[33]
- CONTAK-CD,[36]
- MIRACLE,[22]
- MIRACLE ICD,[24]
- MIRACLE ICD II,[47]
- AMIOVIRT,[43]
- CAT,[42]
- DEFINITE,[44]
- MADIT-II,[45]
- SCD-HeFT.[46]

The follow-up duration was very different between studies, but in general rather short, ranging from 3 months to 66 months. The specific outcome documented in this meta-analysis is *mortality* in patients with optimal medical therapy compared to patients with CRT-D, CRT-P and ICD.

Main results In this meta-analysis, CRT-D reduced the number of deaths compared to optimal medical therapy: OR 0.57 (95% credible interval (CrI) 0.40-0.80), see Figure 4.4. CRT-P reduced the number of deaths compared to optimal medical therapy: OR 0.66 (0.50-0.89), see Figure 4.4. ICD reduced the number of deaths compared to optimal medical therapy: OR 0.69 (95% Cr I 0.55-0.87), see Figure 4.4. CRT-D did not statistically significantly reduce the number of deaths compared to optimal medical therapy combined with CRT-P, see Figure 4.4.

The overall mortality for CRT-D therapy was 9.1% compared with 14.0% for optimal medical therapy only, corresponding to a 35% relative risk reduction. However, due to the very varying follow-up times between studies this result is hard to interpret. This is especially illustrated in the subgroup analysis where the overall mortality in NYHA class III-IV with

medical therapy is lower than in the total group. This might be explained by the shorter follow-up time in those studies.

Bayesian network analysis results The direct evidence from different studies supporting the Bayesian network meta-analysis comparisons between therapeutical strategies is illustrated in Figure 4.3.

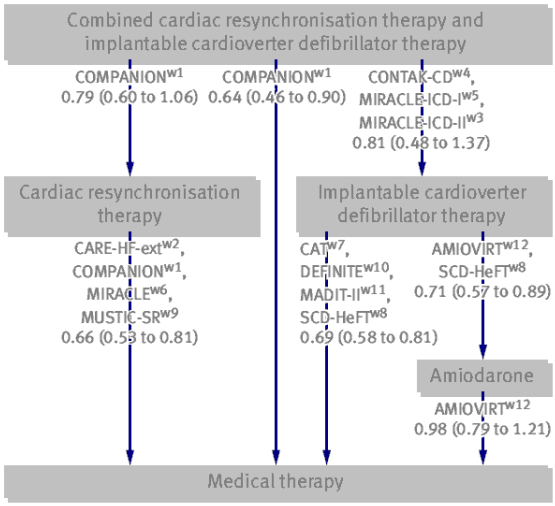


Figure 4.3.: Bayesian network analysis of 12 RCTs comparing treatment strategies for patients with left ventricular dysfunction. Summary odds ratios (95% confidence intervals) are shown for each comparison, with arrowhead indicating comparator treatment.[5]

The results of the Bayesian network meta-analysis of 12 RCTs of device therapies in 8307 patients with left ventricular dysfunction are illustrated in Figure 4.4

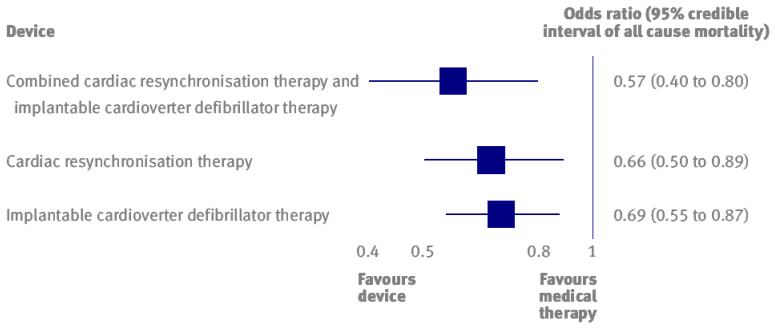


Figure 4.4.: Results of Bayesian network meta-analysis of 12 RCTs of device therapies in 8307 patients with left ventricular dysfunction.[5]

Forest plots The results of the pairwise meta-analysis and of the Bayesian network analysis of device therapies compared with medical therapy for patients with left ventricular dysfunction. (95% CI for pairwise comparisons, 95% credible interval for Bayesian network comparison) are illustrated in Figure 4.5.

The results for CRT-D compared with either therapy alone (CRT-P or ICD) in the Bayesian network comparison (95% CI for pairwise comparison, 95% credible interval for Bayesian network comparison) are shown in Figure 4.6 (including a subgroup analysis for NYHA III-IV).

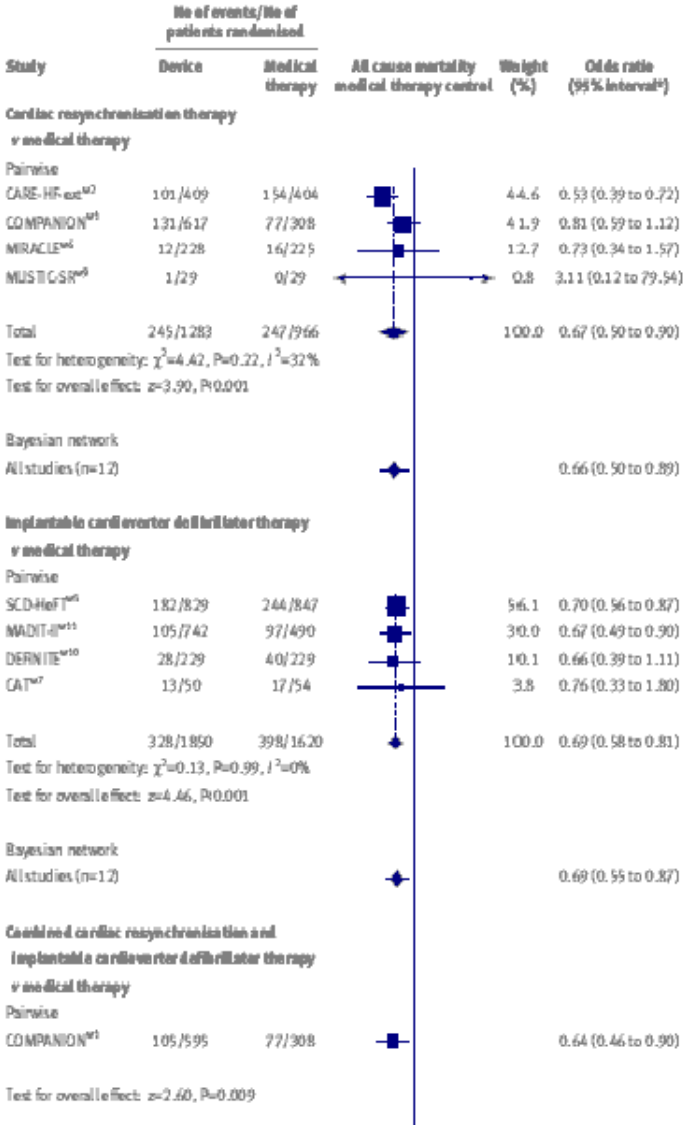


Figure 4.5.: Pairwise meta-analysis and Bayesian network analysis of device therapies compared with medical therapy.[5]

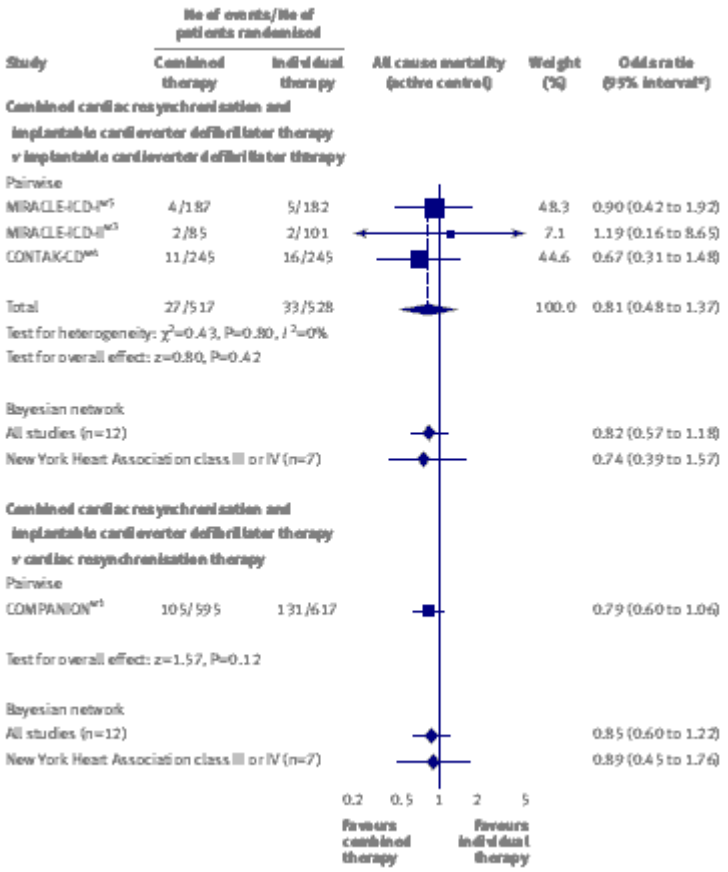


Figure 4.6.: Combined cardiac resynchronisation and implantable cardioverter defibrillator therapy compared with either therapy alone with 95% CI for pairwise comparison, 95% credible interval for Bayesian network comparison, including subgroup analysis for NYHA III-IV.[5]

Conclusions From this Bayesian network meta-analysis, the authors conclude evidence from RCTs is insufficient to show the superiority regarding mortality prevention of neither CRT-D nor single ICD therapy over CRT-P in patients with left ventricular impairment.

One of the major drawbacks of this Bayesian network meta-analysis is that it only considers mortality. However, an advantage is that it compares in its analysis several treatment modalities, i.e. CRT-D, CRT-P, ICD and optimal medical treatment. Although the meta-analysis included studies with patients in NYHA functional class II a subgroup analysis for patients in class III-IV was performed. Relative mortality can be assessed through this study, but absolute mortality is hard to interpret due to the extremely different follow-up times.

4.3.3 Fox et al., 2007

Meta-analysis design In 2007, the National Institute for Health Research (NIHR, UK) published this HTA with the objective to assess the clinical effectiveness and cost-effectiveness of CRT for patients with heart failure and evidence of dyssynchrony by comparing CRT devices, CRT-P and CRT-D, each with optimal pharmaceutical therapy, and with each other.[6]

Narrative reviews were undertaken and meta-analyses of the clinical trial data were conducted. For the economic model, a Markov model was developed. Incremental costs and quality-adjusted life-years (QALYs) were calculated. Extensive one-way sensitivity analyses,

threshold analyses, and probabilistic sensitivity analyses were carried out (see the relevant chapter of this report for more details on this model).

An update of this HTA was originally announced for 2010 but so far no update had been published. Direct enquiries to the authors and to the National Institute for Health and Clinical Excellence (NICE) learnt us that the update was indeed postponed and that the technology appraisal review for CRT will be combined with the review of the ICD appraisal (TA95 and TA120). It was announced that the Institute's Guidance Executive has decided that a review of the original guidance would be planned into the NICE work programme and that this work will start in May 2011.[48]

The search strategy is well described, comprehensive and logical. Relevant bibliographic databases were searched up to June 2006 and manufacturer submissions to NICE were searched for additional evidence. The inclusion criteria for clinical effectiveness were systematic reviews of RCTs or RCTs on an intervention with either CRT-P or CRT-D in a population with a diagnosis of HF due to LVSD, with NYHA class III and IV heart failure and evidence of dyssynchrony (QRS interval >120 ms) who were also receiving optimal medical treatment. However, although the search strategy formally included systematic reviews, the five systematic reviews retained were ultimately not used because they overlapped with the original RCTs identified. As shown in Table 4.1 this meta-analysis considers mainly NYHA class type III and IV patients making it representative for the patients considered in this chapter. It mainly considers the same trials as in the meta-analysis by Lemos et al. except for the MIRACLE ICD and MUSTIC AF studies which were not included in this HTA.

Five RCTs were finally included in this meta-analysis (n=3434):

- CARE-HF,[1,26]
- COMPANION,[25]
- CONTAK-CD,[36]
- MIRACLE,[22]
- MUSTIC-SR.[33]

The specific outcomes documented were all-cause mortality, HF mortality, sudden cardiac death, non-cardiac mortality, all-cause hospitalisation, hospitalisation for worsening HF and VT needing device therapy, NYHA class, six minutes walking distance, health-related QoL through Minnesota Living with Heart Failure Questionnaire (MLWHF),[23] adverse effects (CRT and non-CRT related events). Three specific comparisons are presented:

- CRT-P versus optimal medical therapy,
- CRT-D versus optimal medical therapy,
- CRT-P versus CRT-D.

Main results Quality of included studies was considered by the authors as good to moderate. Meta-analyses showed that both CRT-P and CRT-D devices *significantly reduced the mortality and level of heart failure hospitalisations and they improved health-related Quality of Live* in people with New York Heart Association (NYHA) class III and IV heart failure and evidence of dyssynchrony (QRS interval >120 ms) who were also receiving optimal medical therapy. The follow-up duration was again very different between studies, ranging from six months to 36 months. Although a number of issues were raised about the internal and external validity of the included trials, the authors believed that they are generally of good quality and that the issues identified are unlikely to have substantially biased the results or to have had a substantial impact on generalisability.

Unless otherwise specified results are presented as CRT vs. optimal medical treatment. When comparing the two CRT modalities, the comparison is CRT-D vs. CRT-P. All confidence intervals shown are two-sided 95% CI.

All-cause mortality All trials provided data on all-cause mortality (see Figure 4.7). When CRT-P data from the trials were combined (MUSTIC-SR, MIRACLE, COMPANION and CARE-HF), there was an *HR of 0.68* (95% CI 0.54 to 0.88, p = 0.001) for CRT-P compared with optimal medical treatment. For all-cause death with CRT-D compared with optimal medical treatment (CONTAK-CD and COMPANION) the pooled *HR was 0.65* (0.49 to 0.85, p < 0.0001). There was no evidence of significant heterogeneity between studies. Direct comparison of CRT-P vs. CRT-D in COMPANION showed no statistically significant difference in the risk of overall mortality: *RR 1.20* (0.96 to 1.51, p = 0.115). However, this estimate should be treated with caution, as this trial was not powered to compare the two devices directly. Meta-regression analysis (using an indirect comparison of outcomes between studies, i.e. comparison of CRT-P and CRT-D studies where the common comparator is optimal medical treatment), confirmed that there was *no evidence of significant difference between the two device types: HR 1.10* (0.78 to 1.53, p = 0.290). Excluding the small MUSTIC-SR trial, the annual risk of all-cause death ranged across trials from 14 to 20%. There was little evidence of heterogeneity in the effect of CRT across follow-up times.

Heart failure death Deaths due to HF were only reported by COMPANION and CARE-HF. A reduction in HF death with CRT-P was shown in the combined trial data with a *pooled HR 0.62* (0.46 to 0.83, p < 0.0001), but in the COMPANION trial for CRT-D this was not statistically significant likely due to a lack of power: *HR 0.73* (0.47 to 1.11, p = 0.143) (see Figure 4.8). There was no evidence of heterogeneity for CRT-P and there were insufficient data to undertake meta-regression analysis.

Cardiac death Only the COMPANION trial reported total cardiac deaths. The risks of cardiac death were *17.5, 17.1 and 12.8% at one-year follow-up* in patients in the optimal medical treatment group, CRT-P and CRT-D arms, respectively. Compared with optimal medical treatment there was a reduction in cardiac events with CRT-D (p = 0.006) but not with CRT-P (p = 0.334).

Sudden cardiac death (SCD) SCD was reported by MIRACLE (in an FDA report only), and in the MUSTIC-SR, COMPANION and CARE-HF trials. There was evidence of heterogeneity in the effect of CRT-P on the risk of SCD across trials. CARE-HF reported a reduction in SCD at both 29.4 and 36.4 months (in the trial extension phase) with CRT-P. However, COMPANION reported a higher risk of SCD with CRT-P (7.8%) than in the optimal medical treatment group (5.8%) (p = 0.485). *Based on a random effects model, the pooled HR across trials (MUSTIC-SR, COMPANION and CARE-HF) for CRT-P was a non significant 0.75* (95% CI 0.45 to 1.18, p = 0.198). *In contrast, the COMPANION trial shows there was a reduction in SCD with CRT-D compared with optimal medical treatment: HR 0.44* (0.23 to 0.86, p = 0.02) (see Figure 4.9). The risk of SCD in patients receiving a CRT-P device (7.8%) was higher than in patients who received a CRT-D device (2.9%) (p < 0.0001). Meta-regression analysis provides some evidence of a trend towards a larger treatment effect for CRT-D compared with CRT-P, although this difference was not statistically significant: HR 2.02 (0.49 to 8.78, p = 0.345). Excluding the small MUSTIC-SR trial, the annual risk of SCD in optimally treated patients across the trials ranged from 3.8 to 4.6%.

Other causes of death An analysis of causes of death in patients in the optimal medical treatment, CRT-P and CRT-D arms of the COMPANION trial showed *no evidence of important differences in vascular death* (0 vs. 0.8 vs. 0.5%), *non-cardiac death* (3.6 vs. 2.3 vs. 3.5%) *or unknown causes of death* (2.6 vs. 0.5 vs. 0.8%) at follow-up. Other trials did not provide information on non-cardiac deaths.

Hospitalisations related to heart failure Although all trials reported hospitalisation related to HF, it was defined in differing ways (unplanned, for worsening HF, for decompensated HF, ..), for different follow-up periods and either as risk ratios (risk for any hospitalisation for a patient) or as rate ratios (number of events). Therefore, these results are difficult to compare. Furthermore, the FDA report of COMPANION reported hospitalisation for HF or cardiovascular disease only as an event rate.

In general there is a substantial reduction in both risk ratios and rate ratios in favour of CRT-P or CRT-D vs. optimal medical therapy, ranging from 0.33 to 0.82 depending upon the definition used.

There was consistent and marked reduction in the number of people who had HF hospitalisations across trials with CRT-P: *pooled HR 0.48* (0.37 to 0.61, p < 0.0001) (see Figure 4.10). There was no evidence of heterogeneity in CRT-P effect across trials. Meta-regression analysis (indirect comparison) showed no evidence of significant difference between the two device types.

To allow some comparison, the authors of this report expressed the number of events as an event rate per 100 person years: no. of events x (100 / follow-up years x no. of patients). There was a significant reduction in the rate of HF hospitalisation with both CRT-P (pooled rate ratio *0.56,* 0.48 to 0.66, p < 0.0001) and CRT-D (rate ratio *0.59*, 0.49 to 0.70, p < 0.0001) (see Figure 4.10). Although the rate of hospitalisation in optimally treated patients varied across trials, there was no evidence of significant heterogeneity in CRT effect. The COMPANION trial did not report the number of hospitalisations in the CRT-P arm; therefore it was not possible to compare CRT-P and CRT-D directly (for more details see tables 12 and 13 in the original HTA report,[6] and also in the individual descriptions of the studies in the first part of this chapter).

Worsening heart failure Worsening HF was reported by MUSTIC-SR, MIRACLE and CARE-HF, although its definition varied across trials. The risk of worsening HF was consistently reduced with CRT-P: *pooled HR 0.67* (0.46 to 0.84, p = 0.026) (see Figure 4.11). There was no significant heterogeneity. No trial data for this outcome were available for CRT-D.

Arrhythmias MUSTIC-SR and CARE-HF reported differing measures of atrial arrhythmias in both CRT and optimal medical treatment groups, but given the difference in measures, pooling was deemed inappropriate. Compared with optimal medical treatment there was no evidence of a consistent effect of CRT-P on atrial arrhythmias.

NYHA class All trials reported the change in NYHA functional class during follow-up. There was a consistent increase in patients experiencing an improvement in one or more NYHA classes with both CRT-P (*pooled RR 1.69*, 1.51 to 1.88, p < 0.0001) and CRT-D (*pooled RR 1.52*, 1.28 to 1.82, p < 0.0001), compared with optimal medical treatment (CRT-P versus optimal medical treatment in CARE-HF, COMPANION, MIRACLE and MUSTIC-SR and CRT-D versus optimal medical treatment in COMPANION and CONTAK-CD). There was no evidence of significant heterogeneity.

The results of the COMPANION trial suggest that this improvement in NYHA class appears to occur within the first 3 months of CRT implantation. *Direct comparison in COMPANION of CRT-D versus CRT-P showed no significant difference in treatment effect: RR 1.07* (0.96 to 1.19, p = 0.202) and HR. Indirect comparison showed CRT-P to have somewhat larger treatment effect than CRT-D: RR 1.32 (1.03 to 1.70, p = 0.027).

Exercise capacity Most trials assessed exercise capacity at different moments of follow-up. Exercise capacity was reported either as absolute values at follow-up or as the change from baseline to follow-up. In this meta-analysis both sets of results were pooled assuming that the baseline values were equal. Significant differences were seen with CRT-P in six-minute walk distance: *pooled mean difference +35.3 m* (+20.0 to +50.7, p < 0.0001). Also the total exercise time (mean difference +62 s, +25 to +99, p < 0.0001) and the peak oxygen uptake (pooled mean difference +0.91 ml/kg/min, +0.9 to +1.82, p = 0.030) improved. Improvements were also seen for CRT-D in six-minute distance (pooled mean difference +30.1 m, +14.9 to +45.1, p < 0.0001) and total exercise time (mean difference +62.0 m, +24.9 to +99.1, p = 0.001). There was no evidence of significant heterogeneity for CRT-P or CRT-D versus optimal medical treatment. I*n direct comparison, there was no significant difference in six-minute walk distance between CRT-P and CRT-D* (mean difference –6 m, –19.9 to +7.0, p = 0.397). This was confirmed by meta-regression (mean difference –5.3, 95% CI –31.9 to 20.4, p = 0.685).

Quality of life Heath-related QoL was assessed at different moments of follow up using the Minnesota Living with Heart Failure Questionnaire (MLWHF).[23] scale in all trials and EQ-5D in CARE-HF. MLWHF scores were reported either as absolute values at follow-up or as the change from baseline to follow-up. Again, both were pooled. Improvements in MLWHF (for MLWHF a lower score is an improvement) were seen with both CRT-P (pooled mean difference –9.9, –12.2 to –7.6, p < 0.0001) and CRT-D (pooled mean difference –13.1, –16.8 to –9.3, p < 0.0001). No difference was seen in MLWHF in the direct comparison of CRT-P and CRT-D from COMPANION, or meta-regression: *mean difference –3.5*, (–7.6 to 1.2).

The CARE-HF trial also reported a significant difference at 90 days in EQ-5D, a generic measure of QoL: *mean difference +0.08* (+0.04 to +0.12, p < 0.001) (in EQ-5D a higher score corresponds to a better QoL). However, since no baseline measurement was available it is not possible to label this as an improvement.

Subgroup analyses Specific subgroup analyses were reported by CARE-HF, COMPANION, CONTAK-CD and MIRACLE, but only the authors of CARE-HF stated that they defined their subgroups in advance. No trial reported a significant subgroup effect for outcomes (either composite or single end-points). *However, none of these trials were powered to detect subgroup effects.*

Adverse events The published reports of trials included in this meta-analysis did not consistently report adverse event (also see detailed description of the trials in section 4.2. For this HTA, additional information was sought from FDA reports (for COMPANION, CONTAK-CD, MIRACLE and MUSTIC-SR). The focus of reporting was events and complications in patients receiving CRT.

The peri- and post-operative risks from individual studies and the pooled results were generally reported at 7 or 8 days from implant. These results should be treated with caution as the trials varied in how events were classified, particularly with regard to whether they were peri- or post-operative.

The procedure used to implant a CRT device is complicated and a significant minority of operations performed end in failure. From the studies included in this report, the combined population of *2823 attempted implants resulted in 265 failures (9.4%). There were 21 peri-operative deaths in 2757 patients: pooled risk 0.8%* (0.5 to 1.2%). *CRT device implants were successful on average in 90.8%* (89.6 to 92.0%) of patients and there was no clear evidence of a difference in implanting success between CRT-P and CRT-D devices.

In studies where details were given, implant failures were mainly due to problems with the left ventricle lead. The most frequent post-operative event was lead dislodgement: 7.9% (6.4 to 9.7%). Peri- and post-operative risk appeared to be consistent across trials and CRT devices. COMPANION reported a non-statistically significant risk of moderate to severe adverse

events of 10% (62/617) for CRT-P and 8% (48/595) for CRT-D (p = 0.42). COMPANION reported a slightly higher overall risk of moderate to severe adverse events for any cause with CRT (optimal medical treatment, 188/595, 61%; CRT-P, 407/617, 65%; CRT-D, 410/595, 69%).

Of heart failure patients, 11–46% apparently failed to benefit from CRT, clinical parameters suggesting a lower rate of failed response than echocardiographic measures.

There were no significant differences in risk of respiratory tract infection, hypotension, falls or syncope, acute coronary syndromes, ventricular arrhythmias and neurological events between CRT and control groups in CARE-HF.

Publication bias There was no direct evidence of significant funnel plot asymmetry across the principle outcomes reported. However, given the small number of trials included, the power of the statistical test was likely to be low.

Forest plots

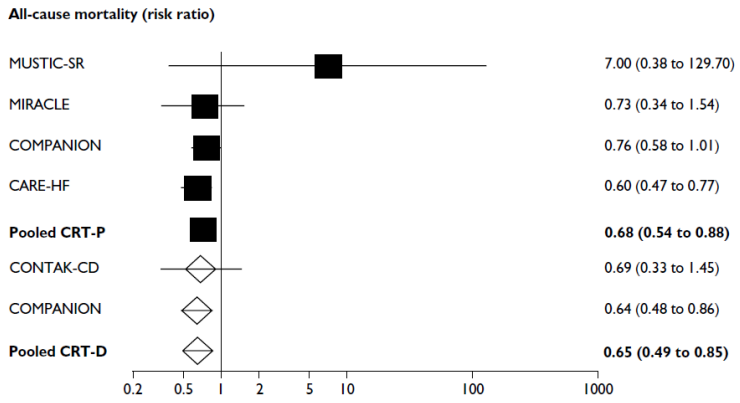


Figure 4.7.: Forest plot of all-cause mortality compared to optimal medical treatment.[6]

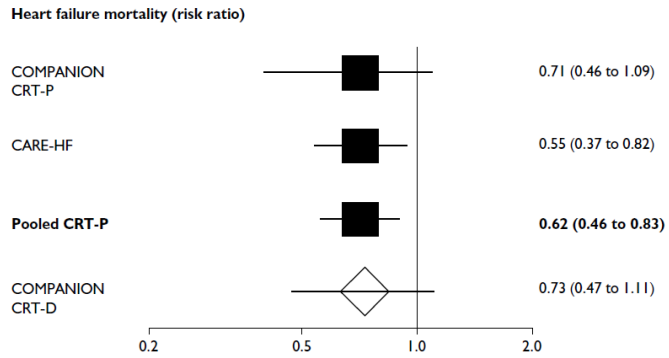


Figure 4.8.: Forest plot of heart failure death compared to optimal medical treatment.[6]

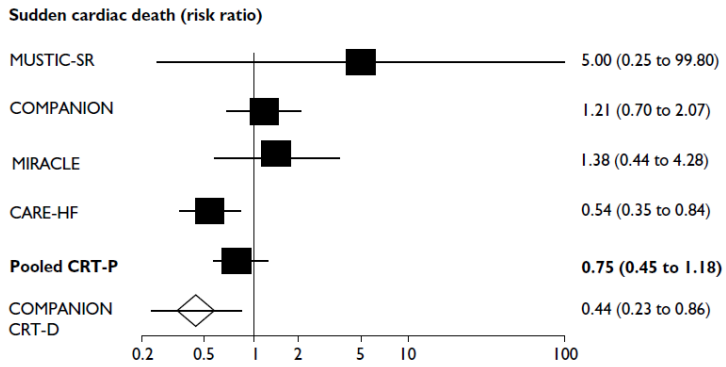


Figure 4.9.: Forest plot of sudden cardiac death compared to optimal medical treatment.[6]

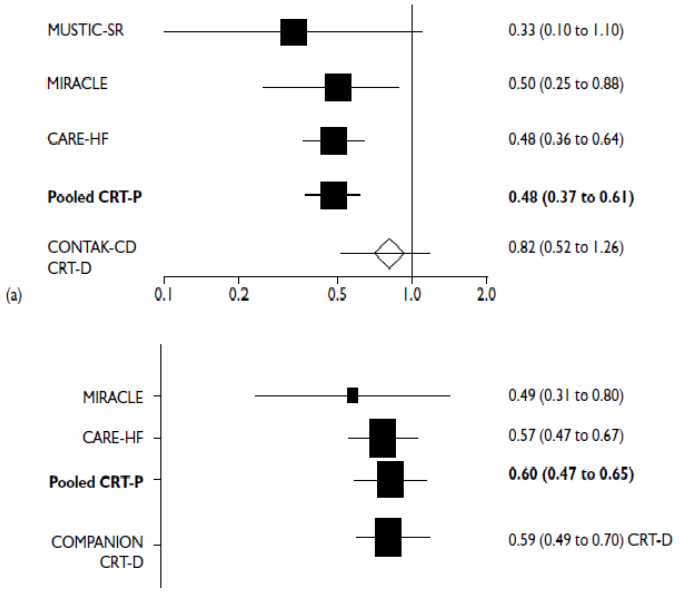


Figure 4.10.: Forest plots of hospitalisation due to heart failure: (a) risk ratio and (b) rate ratio.[6]

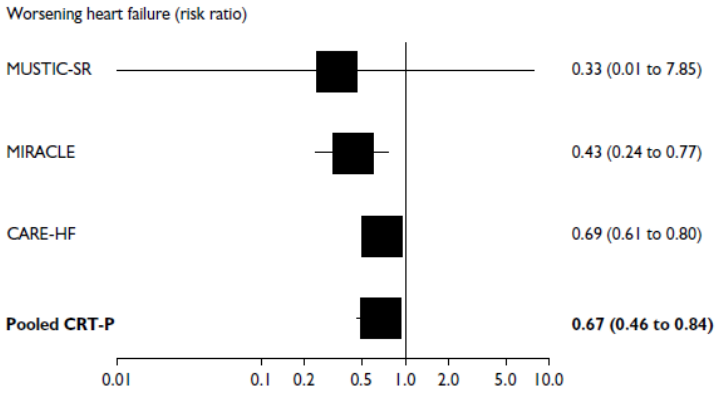


Figure 4.11.: Forest plot of worsening heart failure.[6]

Conclusions The authors of this HTA conclude that both CRT-P and CRT-D devices reduce mortality and hospitalisations due to heart failure, improve Quality of Live and reduce SCD in people with heart failure NYHA classes III and IV, and evidence of dyssynchrony. Further research is needed into the identification of those patients unlikely to benefit from this therapy, the appropriate use of CRT-D devices, the differences in mortality and heart failure hospitalisation for NYHA classes I and II, as well as the long-term implications of using this therapy.

This is a very elaborate and well conducted meta-analysis within an HTA and we will base many of our assumptions in the economic model on this HTA. The effects of CRT-P and CRT-D on mortality (all-cause, HF related, non-cardiac) were similar, with the exception of an additional reduction in SCD associated with CRT-D. This HTA concluded that, on average, implanting a CRT device in 13 people would result in the saving of one additional life over a 3-year period compared with optimal medical treatment while there were no statistically significant subgroup effects, although trials were not individually powered for their detection.

In its summary of clinical effectiveness the main conclusions of this HTA were that:
- Five RCTs (3434 participants) met the inclusion criteria for the review. All were randomised.
- Although there were some concerns about the internal and external validity of the trials, mainly due to inadequate reporting, overall they were of moderate to good quality.
- CRT devices reduce mortality and hospital admissions and improve health related QoL in NYHA class III or IV patients receiving optimal pharmaceutical therapy and with low EF ($\leq$35%) and dyssynchrony (QRS interval $>$120 ms).
- There is currently limited direct evidence comparing CRT-P and CRT-D devices. However, the effects of the two devices on patient-related outcomes appear to be equivalent, with the exception of an additional reduction in SCD with CRT-D.
- There was no clear evidence to support a differential effect of CRT in particular subgroups of patients, although none of the studies were powered to examine this. The trials excluded patients with AF or a specific indication for an ICD.
- Serious adverse events due to CRT devices appear to be infrequent at least up to 2 years after implantation (14% overall complications and 0.8% deaths). Complications that are reported include lead displacement, infection and mechanical dysfunction. A significant proportion (9%) of CRT implantations were unsuccessful.

4.4 CRT therapy in NYHA class III/IV patients: summary

The available evidence Several randomised trials have compared the use of CRT-P and/or CRT-D compared to optimal medical treatment. The most important of those are the COMPANION, CARE-HF and MIRACLE trials, described in this chapter, and together they have delivered a solid evidence base for the efficacy of CRT. The MIRACLE ICD trial, also described in this chapter, falls somewhat outside of the scope of this report as it compares ICD with or without CRT functionality.

One of the major difficulties is that those trials used different definitions, different composite primary end-points, different follow-up periods etc..., making the task of authors willing to perform a meta-analysis difficult.

We reviewed the three most important and most recent meta-analyses. The meta-analysis of Lam et al. (2007) is a Bayesian network meta-analysis comparing all treatment modalities (CRT-P, CRT-D, optimal medical treatment) against each other, but only considers mortality. The meta-analysis, conducted within an HTA from Fox et al. (2007) is the most comprehensive and went to great lengths to directly compare all relevant outcomes. The results

are also presented in much detail, making this study very valuable for our own economic model presented further in this report. The more recent study from Lemos et al. (2009) doesn't add much to the study performed by Fox, although it contained two more studies (MIRACLE ICD, which we considered less relevant within the scope of this report and the small MUSTIC-AF study).

Mortality The secondary end points of death are the only ones that can readily be compared between studies, and the conclusions is that CRT (with or without defibrillator function) lowers short term mortality (up to approximately 3 years). When looking for the reason of death the CARE-HF extension trial with only CRT-P showed a reduction of total death, but also of death due to heart failure and for sudden death. Consistent with this finding, the COMPANION study did not demonstrate a different mortality between CRT-P and CRT-D. Improved cardiac function can indeed also be expected to reduce the incidence of serious arrhythmia's thereby leading to a reduction in sudden cardiac death.

Morbidity The fact that in the large COMPANION study the primary endpoint was a combined death or hospitalisation *for any cause* makes interpretation of this study difficult, since the results for this primary endpoint were mainly driven by the *first hospitalisation for any cause* that stopped the observations rather than by the more relevant hard endpoint of death or hospitalisation for heart failure. The other large trial, CARE-HF also used a composite endpoint but they used death from any cause plus *first hospitalisation for a major cardiovascular event.* In both these largest studies, the follow-up was stopped after the first event under study. Therefore, the information of these studies for the purpose of economic evaluation is limited. The first hospitalisation appears to be delayed in patients randomised to CRT. But no information is given on number of hospitalisations or on the length of stay (LOS).

There are indications that the general condition of the patients in the intervention group is better as witnessed by later first hospitalisation (any cause or major cardiovascular event), physical and physiological parameters, increased walking distance, increased Quality of Live and a lower average NYHA classification. However, none of these studies has evaluated the morbidity and Quality of Live impact of the initial intervention to place the device. Adverse events related to the device implantation should be considered in any total evaluation of the impact of the technology and will be further addressed in the next chapter.

Quality of life For the evaluation of morbidity and Quality of Life, and potentially even for the effect on hospitalisations, the non blinded nature of the two largest studies (COMPANION and CARE-HF) is a potential problem. In this context it is remarkable that both trials were listed as double blinded trials in the recent ESC Guideline update (table 2 from the original publication,[12]).

KEY POINTS

- **In clinical trials and compared to optimal medical treatment, both CRT-P and CRT-D showed a lower all-cause mortality in patients in NYHA class III/IV without much evidence of the superiority of one therapy over the other. These studies, however, were not powered to detect such differences.**
- **Mortality directly related to heart failure or SCD showed similar trends, but often did not reach statistical significance in individual studies due to the limited power of these studies. Although evidence of a clear benefit of CRT-D compared to CRT-P is limited there are indications that in patients with a clear and conventional indication for an ICD, and in the case of secondary prevention, a CRT-D might provide an additional benefit on mortality specifically due to SCD.**
- **Morbidity was mainly measured through the need for unplanned hospitalisation (whether or not due to heart failure depending upon study). The probability of a first unplanned hospitalisation was in general lower for patients with CRT-P or CRT-D compared to optimal medical treatment. Adding CRT functionality to an ICD seems to have advantages for morbidity but not for mortality. In general there was a substantial reduction in both risk ratios and rate ratios in favour of CRT-P or CRT-D vs. optimal medical therapy.**
- **Health related Quality of Life is difficult to assess from these trials as both generic and disease specific instruments were used and often no baseline measurement was performed.**
- **The procedure to implant a CRT device is complicated and a significant minority of operations performed end in failure. From the meta-analyses it can be concluded that almost 10% of first attempted implants result in failure while peri-operative death rate is almost 1%.**

5 Clinical effectiveness of CRT in NYHA class I/II patients

The clinical effectiveness of CRT-P or CRT-D compared to optimal medical treatment in HF patients who are only mildly symptomatic (NYHA class I/II) has not been studied in clinical trials.

Patients enrolled in those NYHA I/II trials mostly had an established indication for a conventional ICD, and were randomised to a conventional ICD or to a CRT-D. Five clinical trials comparing CRT-D with ICD-only have been published: CONTAK CD (2003), MIRACLE ICD II (2004), REVERSE (2008), MADIT-CRT (2009) and RAFT (2010).

5.1 CONTAK CD, 2003

The CONTAK CD trial studied the safety and effectiveness of CRT-D in patients with malignant ventricular arrhythmias, requiring an ICD. 490 patients were randomised to CRT-D (n=245) or ICD (n=245).[36] The mean age of patients was 66±11 years. The design of this study was modified during its progression. Initially it had a cross-over design with two 3-month observation periods but later on, it was changed to a parallel design. Moreover, the primary endpoint of the study was changed from "peak VO2" in the initial design, to a composite endpoint, denoted as "progression of HF" including all-cause mortality, hospitalisation for HF and VT/VF requiring device intervention. An additional methodological complication was that investigators were permitted to optimise pharmacological therapy during 30 days after initiation of the ICD mode of therapy, but before randomisation the device to CRT or no-CRT. Many patients demonstrated significant symptomatic improvement with medical therapy during this period. At enrolment, no patients were in NYHA class I whereas, after the 1 month run-in period, 32% improved towards NYHA I. Accordingly, at randomisation, 227/490 (46%) patients were in NYHA class III/IV and 263 (54%) were in NYHA class I/II.

Relevant data from this study are depicted in Table 5.1. Of the 245 patients randomised to CRT, a total of 79 events (i.e. the primary endpoint "progression of HF") were observed, including 11 deaths, 32 patients with at least one HF hospitalisation, and 36 patients with at least one ventricular arrhythmia event. In the 245 patients randomised to no-CRT, 94 events were observed including 16 deaths, 39 patients with at least one HF hospitalisation, and 39 patients with at least one ventricular arrhythmia event. The overall relative reduction in "progression of HF" with CRT was not statistically significant. Even after stratification into NYHA class I/II (12% reduction) or NYHA class III/IV (22% reduction), no statistically significant reductions were found in any of these two subgroups. In the all-patients analysis, peak VO2 and 6 minutes walk test significantly improved in the CRT group, whereas NYHA class and QoL did not. In a subgroup analysis of these secondary outcome measures, the improvements were only noticed in NYHA class III/IV patients. In the NYHA I/II subgroup, none of these secondary endpoints were significantly altered by CRT.

5.2 MIRACLE ICD II, 2004

This was a randomised, double-blind, parallel-controlled clinical trial of CRT in NYHA class II patients on optimal medical therapy with a LVEF$\leq$35%, a QRS$\geq$130 ms, and a class I indication for an ICD.[47] One hundred eighty-six patients were randomised: 101 to the control group (ICD activated, CRT off) and 85 to the CRT group (ICD activated, CRT on). The mean age

Table 5.1.: Primary endpoint in CRT trials in patients in NYHA classes I or II

	TARGET POPULATION	N	AGE	FU	NYHA	PRIMARY ENDPOINT	EFFECT SIZE				
CONTAK CD 2003	ICD in secondary prevention and (initially) symptomatic HF	490	66± 11	≤ 6 mo	after run-in: 54% I/II 46% III/IV	**"PROGRESSION OF HF"**: all-cause mortality, hospitalisation for HF and VT/VF requiring device intervention.	CRT ON (+ICD)	CRT OFF (+ICD)	RRR	ARR	p
							79/245	94/245	16,0%	6,2%	0,35
MIRACLE ICD II 2004	NYHA II and established ICD indication	186	63± 12	6 mo	100% NYHA II	**CHANGE IN PEAK VO2**	CRT ON (+ICD)	CRT OFF (+ICD)			p
							0,5/16,4 mL/kg/min	0,2/16,8 mL/kg/min			0,87
REVERSE 2008	HF NYHA I or II	610	63 ± 11	12 mo	17% NYHA I 83% NYHA II	**"HF CLINICAL COMPOSITE RESPONSE"**: death, hospitalised for HF, cross-over, worser NYHA at 12 mo, worse patient global assessment at 12 mo.	CRT ON (±ICD)	CRT OFF (±ICD)			p
							41/191	67/419	25,9%	5,60%	0,10
MADIT CRT 2009	HF NYHA I or II and established ICD indication	1820	65 ± 11	2,4 yr	15% NYHA I 85% NYHA II	**"DEATH FROM ANY CAUSE or A NONFATAL HF EVENT"**: signs and symptoms consistent with HF that was responsive to intravenous decongestive therapy on an outpatient basis or an augmented decongestive regimen with oral or parenteral medications during an in-hospital stay	CRT-D	ICD	RRR	ARR	p
							187/1089	185/731	32,0%	8,10%	0,001
RAFT 2010	HF NYHA II or III and established ICD indication	1798	66 ± 9	3,3 yr	80% NYHA II 20% NYHA III	**"DEATH FROM ANY CAUSE OR HOSPITALISATION FOR HF"**	CRT-D	ICD	RRR	ARR	p
							297/894	364/904	17,6%	7,10%	<0,001

Source: KCE. See text for study acronyms. FU: average patient follow-up. CRT ON/OFF indicates that patients were implanted a full-feature CRT-D device, but with an inactivated CRT port in the control patient group.

of patients was 63±12 years. The primary efficacy endpoint was the change in peak VO2 from baseline to six months. Compared with the control group at 6 months, no significant improvement was noted in peak VO2. There were significant improvements in secondary endpoints such as LV diastolic and systolic volumes and LVEF. CRT patients also showed statistically significant improvement in NYHA class and a clinical composite response. The latter assigned patients to 1 of 3 response groups: worsened, improved or unchanged.[49] In the CRT group, 58% of patients improved, versus 36% in the control group. No significant differences were noted in 6-minute walk distance or QoL scores.

5.3 REVERSE, 2008

This trial enrolled 684 patients and in 642 of them CRT implantation was attempted. Implantation was successful in 621. 610 patients with NYHA class I (17% of patients) or II heart failure (83%) on optimal medical therapy were randomised. The mean age of patients was 63±11 years. They all had a QRS≥120 ms and a LVEF≤40% and were implanted a CRT (83% CRT-D and 17% CRT-P). They were randomised to active CRT (CRT-ON; n=419) or control (CRT-OFF; n=191) and were followed for 12 months.[38] The primary endpoint was the "HF clinical composite response" that was also used in the MIRACLE ICD II trial.[49] Because patients in NYHA class I could not lower their NYHA class, the percentage of patients that worsened was used to compare the efficacy of CRT between study groups. Patients were judged to be worsened if they died, were hospitalised during the 12 months because of or associated with worsening HF, crossed over or permanently discontinued double-blind treatment, demonstrated worsening in NYHA class at their 12-month visit, or reported a worse global assessment at the 12-month follow-up. In the CRT-ON group, 16% of patients worsened as compared with 21% in CRT-OFF (p=0.10). Patients assigned to CRT-ON experienced a statistically significantly greater improvement in some secondary endpoints related to left ventricular dimensions and in the time-to-first HF hospitalisation.

There were 26 peri-procedural complications among the 642 patients (4%) who underwent an implant attempt, including pneumothorax (n=4), coronary sinus dissection (n=3), cardiac tamponade (n=1), pericardial effusion (n=1). After implantation and during the 12-month follow-up, 101 of the 621 successfully implanted patients experienced a total of 138 procedure or system-related complications (16%). Of the 138 complications, the most common were lead dislodgements (left ventricular n=41, right ventricular n=15, and right atrial n=10) and diaphragmatic nerve stimulation (n=14). One complication resulted in death. There were 66 LV lead related complications in 59 patients (i.e., the LV lead related complication rate was 10%) which required re-operation in 48 patients (8% of successfully implanted patients). There was no statistically significant difference in complication rates between CRT-ON and CRT-OFF patients during the first 12 months of randomisation, which was to be expected because all patients enrolled in the trial had a LV lead implanted (randomisation was established by electronically switching the LV lead ON or OFF). These complications were not formally incorporated into the primary endpoint.

A 24 months follow-up subanalysis of the European cohort of this trial was published in 2009.[39] In the CRT-ON group, 19% of patients were worsened versus 34% in the CRT-OFF group (p=0.01). As in the original trial, secondary endpoints were also significantly better in the CRT-ON group.

5.4 MADIT-CRT, 2009

This study enrolled 1820 patients with a LVEF≤30%, a QRS≥130 ms, and NYHA class I (15%) or II on optimal medical therapy.[40] Patients were randomly assigned in a 3:2 ratio to receive CRT-D (1089 patients) or a stand-alone ICD (731 patients). The mean age of patients was 65±11 years. The primary objective was to determine whether CRT-D in eligible patients

significantly reduced the combined endpoint of death from any cause or a nonfatal "heart-failure event", whichever came first, when compared to ICD-only therapy.[50] The latter was defined as a patient having symptoms and/or signs consistent with HF and receiving (1) either intravenous decongestive therapy, that did not involve formal in-patient hospital admission, regardless of the setting (i.e. in an emergency room setting, in the physician's office, etc.) or (2) an augmented HF regimen with oral or intravenous medications during an in-hospital stay. Hospitalisations related to the initial device implant or reattempted implants were not counted as primary effectiveness endpoint unless there was evidence of treatment for HF during that hospitalisation.

Of 1089 patients randomised to CRT-D, 11 did not receive any device at all and 82 received an ICD instead because of failed LV lead positioning. The main study results are depicted in Table 5.2. During an average follow-up of 2.4 years, the primary endpoint occurred in 187 of 1089 patients in the CRT–D group (17.2%) and 185 of 731 patients in the ICD-only group (25.3%) (hazard ratio in the CRT–D group: 0.66 ; 95%CI 0.52-0.84; P = 0.001). There was no significant difference between the two groups in the overall risk of death, with a 3% annual mortality rate in each treatment group. The superiority of CRT was driven by a 41% reduction in the risk of heart-failure events, a finding that was evident primarily in a prespecified subgroup of patients with a QRS duration of 150 ms or more.

The left ventricular volume was reduced and the ejection fraction was increased to a significantly greater degree in patients in the CRT-D group than in the ICD-only group.

Complications induced by the treatment were not included in the primary endpoint. CRT-D therapy was shown to substantially increase the risk of system-related complications. CRT-D therapy versus ICD-only induced a 7.7% absolute and a 97.4% relative increase in system-related complications within the first 91 days.

Table 5.2.: MADIT-CRT trial, main results.

			CRT-D		ICD		ARR
N (%)			1089	%	731	%	%
Prim. endpoint (=death + nonfatal HF event)			187	17,2	185	25,3	8,1
Death	2,4 yr	as first event	36	3,3	18	2,5	-0,8
		any time	74	6,8	53	7,3	0,5
Nonfatal HF event (as primary endpoint)			151	13,9	167	22,8	9,0
System related complications (91 days)				15,2		7,7	-7,5

Nonfatal HF events	full study period	0,10 per patient-year	0,19 per patient-year	
Serious device related adverse events	after day 30	0,54 per device-year	0,62 per device-year	

Source: Moss et al.[40] and FDA report (Panel question #1). ARR: absolute risk reduction.

One death due to pulmonary embolism occurred in the CRT-D group during the index hospitalisation. In the 30 days after device implantation, the following percentages of patients had serious adverse events: pneumothorax (1.7% in the CRT-D group and 0.8% in the ICD-only group), infection (1.1% in the CRT-D group and 0.7% in the ICD-only group), and pocket haematoma requiring evacuation (3.3% in the CRT-D group and 2.5% in the ICD-only group). The LV lead was repositioned during the first 30 days for a variety of reasons in 44 patients (4.0%).

During long-term follow-up after the first 30 days, serious device-related adverse events occurred with a frequency of 4.5 per 100 device-months (0.54 per device-year) in the CRT-D group and of 5.2 per 100 device-months (0.62 per device-year) in the ICD-only group. Adverse events were considered as serious if they were life-threatening, required an invasive

intervention, or resulted in hospitalisation, permanent loss of device therapy, permanent disability, or death. Adverse events observed in MADIT-CRT were provided in more detail in the proceedings of a March 18, 2010 FDA meeting and are displayed in Table 5.3.[a] When both clinical and device related serious adverse events are added, the overall proportion of patients with serious adverse events is similar for both study groups: 60.4% of the patients in the CRT-D group and 59.7% in the ICD group.

Table 5.3.: MADIT-CRT trial, serious adverse events (any time during the trial).

Serious adverse events		% of patients	
		CRT-D	ICD
Leads	Right atrial lead related	4,3	1,7
	Right ventricular lead related	1,9	2,1
	Defibrillator lead related	0,5	0,7
	LV lead related events	8	0,8
Pulse generator		5,9	4,4
System related complications total		20,6	9,7
Procedure related adverse events		7,9	5,5
Clinical events	Cardiovascular, HF related	15,7	25,9
	Cardiovascular, non-HF related	27,5	28,9
	Non cardiovascular	34	35
Total serious adverse events		60,4	59,7

Source: FDA Circulatory System Devices Panel Meeting, March 18, 2010 (www.fda.gov).

5.5 RAFT, 2010

In the RAFT (Resynchronisation/ Defibrillation for Ambulatory Heart Failure Trial), 1798 patients were enrolled and randomly assigned to receive either an ICD alone or a CRT-D.[51] Patients were in NYHA class II or III, had a LVEF of 30% or less, and a QRS duration of 120 ms or more. The primary outcome was death from any cause or hospitalisation for HF. During the study that ran between January 2003 and February 2009, data from other clinical trials suggested a mortality benefit for CRT in NYHA class III patients, leading the investigators to revise the original study protocol in February 2006 to include patients in NYHA class II only. Accordingly, 80% of patients enrolled in the study were in NYHA class II. In contrast to previous large CRT trials, sinus rhythm was no prerequisite for enrolment in this trial. Almost 13% of patients were in permanent atrial fibrillation or flutter.

The primary outcome occurred in 297 of 894 patients (33.2%) in the CRT-D group and in 364 of 904 patients (40.3%) in the ICD group (hazard ratio, 0.75; 95%CI: 0.64 to 0.87; P<0.001). In the CRT-D group, 186 patients died, as compared with 236 in the ICD group (hazard ratio, 0.75; 95%CI, 0.62 to 0.91; P = 0.003), and 174 patients were hospitalised for HF, compared to 236 in the ICD group (hazard ratio, 0.68; 95%CI, 0.56 to 0.83; P<0.001).

One death from worsening HF occurred in the ICD group within 24 hours after device implantation. During the first 30 days after device implantation, adverse events had occurred in 124 patients in the ICD-CRT group, compared to 58 in the ICD group (P<0.001). A total of 1018 patients (56.6%) were hospitalised at least once during follow-up (509 patients in each group).

Prespecified analyses of the relationship between outcome and NYHA class were conducted. Overall, 20% of patients had NYHA class III at study entry. Among patients with NYHA class II and among those with class III, the two study interventions were associated with similar reductions in the risk of death or hospitalisation for HF, death from any cause, and hospitalisation for HF.

a. www.fda.fgov; PMA number P010012/S230

The main trial outcomes are summarised in Table 5.4

Table 5.4.: RAFT trial, main results

	CRT-D		ICD		ARR
N (%)	894	%	904	%	
Prim. endpoint (death + HF hospitalisation	297	33,2	364	40,3	7,1
Death from any cause (3,3 yr)	186	20,8	236	26,1	5,3
Hospitalised for HF (primary endpoint)	174	19,5	236	26,1	6,6
System related complications (30 days)	118	13,3	61	6,8	-6,5
Hospitalised, any	509	56,9	509	56,3	-0,6
Hospitalised for cardiac cause	423	47,3	404	44,7	-2,6
Hospitalised, device related	179	20	110	12,2	-7,8

The effect of treatment on 11 prespecified subgroups were examined. There was a significant interaction between treatment and QRS duration with CRT-D therapy being more effective in patients with a QRS duration of 150 ms or more.

5.6 CRT therapy in NYHA class I/II patients: summary

The clinical effectiveness of CRT-P or CRT-D compared to optimal medical treatment in HF patients who are only mildly symptomatic (NYHA class I/II) has not been studied in clinical trials. Patients in NYHA I/II trials mostly had an established indication for a conventional ICD, and were randomised to ICD-only or to CRT-D.

Among the trials in NYHA class I/II patients, the CONTAK CD trial was atypical because it focused on patients with an indication for ICD therapy in secondary prevention. The MIRACLE ICD II trial focused on the effect of CRT on surrogate endpoints in NYHA class II patients. After six months of follow-up, no improvement in peak VO2, the primary endpoint was noticed. The paper reported that 58% of patients improved in the "clinical response composite" in the CRT group, versus 36% in the control group. This is at odds with the observation that no significant difference could be identified between the two patient groups in the quality of life score, exercise duration or the 6-min walking distance. In the REVERSE trial the "clinical composite response" was the primary endpoint and no statistically significant difference was found between study groups.

In MADIT-CRT, CRT conferred a statistically significant 34% reduction in the combined risk of death or the so-called "heart failure event". In essence the latter indicated that a given patient needed an increase in diuretic dosage at a given moment during the study. The observed benefit of CRT-D over ICD was driven by a 41% reduction in the risk of heart failure events, a finding that was evident primarily in a prespecified subgroup of patients with a QRS duration of $\geq$150 ms. There was a considerable number of adverse events related to the treatment. When both clinical and device related serious adverse events over the entire study period were added, the overall proportion of patients with such events was similar in both study groups. Total mortality by the end of the study was not significantly different between the two study groups.

The recently published trial results of RAFT did show that the addition of CRT to an ICD reduced rates of death in optimally treated patients with mild-to-moderate HF (predominantly NYHA class II), a reduced left ventricular ejection fraction, and a wide QRS complex. As in MADIT-CRT, there were a substantial number of adverse events in the CRT-D treated patients. The proportion of patients with at least one hospital admission during the trial was similar in the two study groups. System related complications were almost twice as numerous in the CRT-D as compared to the ICD group.

We performed a meta-analysis of mortality data from REVERSE,[38] MADIT-CRT[40] and RAFT,[51] in order to estimate the overall survival benefit of CRT-D over ICD-only in NYHA class II patients (Figure 5.1).

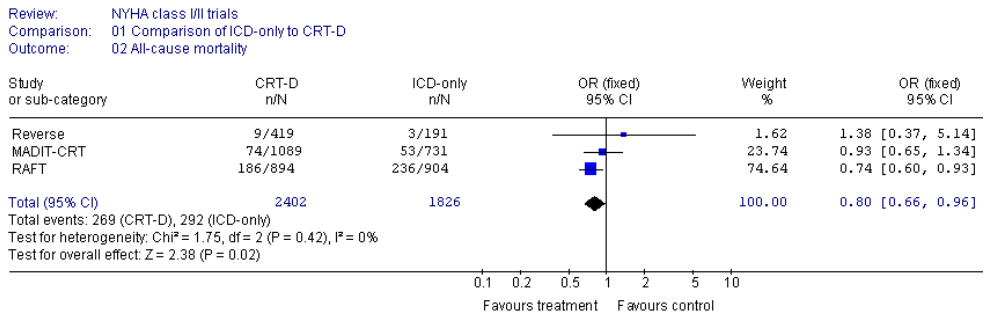


Figure 5.1.: Forest plot for all-cause mortality in CRT-D versus ICD-only trials.
Source: KCE.

We found a significant reduction in pooled all-cause mortality in patients treated with a CRT-D versus an ICD-only (pooled odds ratio 0.80; 95%CI 0.66-0.96). It should be noticed however that there is a substantial clinical heterogeneity between the included trials: although they all enrolled HF patients with comparable ages and the majority being in NYHA class II, the overall 1-year mortality in the CRT-D group varied from 2.1% in REVERSE and 3.1 in MADIT-CRT, to 6.5% in RAFT.

KEY POINTS

- **The clinical effectiveness of CRT-P or CRT-D compared to optimal medical treatment in HF patients who are only mildly symptomatic (NYHA class I/II) has not been studied in clinical trials.**
- **The majority of patients with only mild HF symptoms enrolled in clinical trials were in NYHA class II. These trials studied the incremental effect of cardiac resynchronisation therapy in optimally treated patients who had an established indication for conventional ICD treatment. In those studies, CRT-D decreased the subsequent need for hospitalisation because of HF in comparison with a conventional ICD+optimal medical treatment.**
- **Trial results indicated that the need for hospitalisation for HF was reduced by a CRT-D as compared to those treated with a conventional ICD only. It has not been shown whether the overall hospitalisation rate is affected by treatment.**
- **The most recently published study (RAFT) also showed a mortality benefit for CRT-D over conventional ICD therapy.**
- **Although the stated inclusion criteria for these trials were similar, they apparently enrolled clinically dissimilar patients as suggested by the mortality risk in the CRT-D treated group that in one study (RAFT) was twice that than in the other. This suggests that the generalisation of the treatment effect from one study to the other may not be valid.**
- **A substantially higher number of early and late device related complications of CRT-D versus ICD-only therapy has been observed.**

6 Adverse effects of CRT

The complications of CRT treatment can be related to any of three separate components of the technology: (1) the procedure involving the implantation of a pacemaker-like device below the skin and the introduction of a right atrial and a right ventricular lead, (2) the insertion of the left ventricular (LV) lead, representing the typical CRT part of the hardware, and (3) the ICD component in case the patient is treated with a CRT-D device.

6.1 Adverse effects related to the insertion of a pacemaker

The implantation of a conventional pacemaker can lead to surgical complications such as wound infection and wound haematoma. Rarely, complications can arise by perforating perforating the vascular structures through which the leads are advanced, leading to pneumothorax, haemothorax or perforation of the heart and pericardial effusion. These complications all occur in less than 1% of primo-implantations. Very rarely (0.07 to 0.06%) they lead to death.[10]

6.2 Adverse effects related to the insertion of a conventional ICD

The implantation of an ICD is a relatively safe procedure, with a perioperative mortality rate of 0.0 to 1.2%. Adverse events are poorly reported in clinical trials but significant morbidity may occur in 1 to 3% of patients, the most common complications being related to the surgical procedure, device failure and inappropriate shocks. The most frequently encountered early surgical complications are haematoma (3%) and haemothorax or pneumothorax (1 to 2%). Later on, infection at the site of the pocket sometimes occurs with an overall rate of 2% within 30 days after implantation and 1% later on. Lead dislodgement, if it occurs, usually happens within the first few months after implantation with rates varying between 0.5 and 7.0%. Along with an increase of the number of patients implanted for primary prevention, the mean survival of patients following implant will increase which may lead to a future increase of lead problems that are typically long-term complications. In a single-centre German study, 990 consecutive patients who underwent a first ICD implant between 1992 and 2005 were analysed in order to assess the annual rate of transvenous lead defects.[52] Overall, 15% of defibrillation leads failed during follow-up. The estimated lead survival rates at 5 and 8 years after implantation were 85% and 60%, respectively. The annual failure rate increased progressively with time after implantation and reached 20% in 10-year-old leads. Lead defects affected newer as well as older models. Other problems associated with ICD therapy include inappropriate shock discharge mostly for atrial fibrillation with rapid ventricular response, defibrillator storm with appropriate recurrent ICD discharge for recurrent ventricular tachyarrhythmia or inappropriate discharge for a multiplicity of reasons. The occurrence of inappropriate shocks varies across studies in between 0.5 and 19% of patients within 30 days of implantation, and in 14% of them later on. Heart failure can exacerbate due to the ICD implant, when a high percentage of the heartbeats are paced from the right ventricular apex, especially when left ventricular function is already compromised.[21]

6.3 Adverse effects related to the insertion of a left ventricular lead

The surgical procedure for a CRT device may be more likely to induce adverse effects as compared to the implantation of a conventional pacemaker because it is mostly performed under general anaesthesia and generally lasts longer because of the involvement of the left ventricular and the defibrillation leads. The insertion of the LV lead can be established via the venous system of the heart (coronary sinus), but if no appropriate stimulation site can be achieved, the surgeon can decide to proceed with a transthoracic approach. In this case, the LV lead is stitched on the outer side of the heart, involving an additional surgical incision through the chest wall and inducing additional risks. These adverse events have to be balanced against the beneficial effects of the treatment, i.e. the prolongation of life and prevention of HF related events.

The CARE-HF study was a trial in which HF patients were randomised to CRT-P or optimal treatment. In other words, device related adverse events could only happen in one of both patients groups in the study.[1] CRT-P implantation was attempted in 404 patients. It was successful at the first attempt in 349 (86.4%). It required more than one attempt in 41 (10.1%) and did not succeed in 14 (3.5%). 73 patients (15.6%) had at least one major adverse event within 30 days following the procedure. Most events (63.4%) occurred during the procedure or within 24 hours thereafter.[53]

In the COMPANION trial, adverse events were common in all study groups.[25] Adverse events were defined as any undesirable clinical outcome and included device-related events as well as events related to the patients' general condition. A total of 61% of patients in the medical therapy group had a moderate or severe adverse event from any cause, as compared with 66% of patients in the CRT-P group and 69% of patients in the CRT-D group. Moderate or severe adverse events related to the implantation procedure occurred in 10% of patients in the CRT-P group and 8% of those in the CRT-D group.

In some CRT trials, all study patients had a device implanted, either an ICD (with or without an activated left ventricular port) or a CRT-D. In REVERSE, there were 26 peri-procedural complications among the 642 patients (4%) who underwent an implant attempt. After implantation and during the 12-month follow-up, 101 of the 621 successfully implanted patients experienced a total of 138 procedure or system-related complications (16%). One complication resulted in death. The LV lead related complication rate was 10%. Of 1079 CRT-D patients that were included in the safety endpoint of MADIT-CRT, 164 unique patients (15.2%) experienced 214 system-related complications within 91 days post-implant. One death due to pulmonary embolism occurred in the CRT-D group. During the first 30 days after device implantation in RAFT, there were 13.3% device or implantation related complications among patients in the CRT-D group and 6.8% patients in the ICD group.[51]

Complications related to the implantation of a CRT device are concentrated in the first days and weeks after the procedure, although late problems with the leads are by no means uncommon.[54] In RAFT the number of device-related hospitalisations over the entire study period was higher in the CRT-D group (20.0%), as compared with in the ICD group (12.2%).[51] In MADIT-CRT, during long-term follow-up after the first 30 days, serious device-related adverse events occurred with a rate of 4.5 per 100 device-months in the CRT-D group and of 5.2 per 100 device-months in the ICD-only group. Because these events are not necessarily constant over time nor across patients, they can only be considered to represent an average rate of device-related adverse events in 1 out of 2 patients.[40]

6.4 Adverse effects related to device replacement

The occurrence of complications related to the replacement or upgrade of a device has been documented in recently published results from the US REPLACE registry.[55] Two procedure groups were studied over 6 months of follow-up: plain replacements (cohort-1) and replacements with a planned transvenous lead addition (cohort-2). Major complications occurred in 4.0% of cohort-1 patients and 15.3% of cohort-2 patients. In both cohorts, major complications were higher with ICD compared with pacemaker replacements. Complications were highest in patients who had an upgrade to, or a revised CRT device (18.7%). No periprocedural deaths occurred in either cohort, although eight late procedure-related deaths occurred in cohort-2. The 6-month infection rates were 1.4% and 1.1% for cohort-1 and cohort-2, respectively.

KEY POINTS

- **Adverse effects related to CRT include complications due to the implantation of a conventional pacemaker, those related to the implantation of a left ventricular lead and those that are confined to the ICD component of the treatment in case one has opted for a CRT-D implantation.**
- **The implantation of a conventional pacemaker can lead to surgical complications such as wound infection and wound haematoma. Rarely, complications can arise by perforating the vascular structures through which the leads are advanced. These complications all occur in less than 1% of primo-implantations. Pacemaker implantation is complicated by death in less than 1 per 1000 primo-implantations.**
- **Surgical complications accompanying ICD insertion occur in 1 to 3% of patients. Later on, the delivery of inappropriate shocks and problems with the right ventricular lead occur quite often. The estimated lead survival rates at 5 and 8 years are 85% and 60%, respectively. The occurrence of inappropriate shocks varies between 0.5 and 19% within 30 days of implantation, and occurs in 14% of patients later on.**
- **In addition to the abovementioned potential complications, CRT can be complicated by adverse events related to the left ventricular lead. Even in the most recently published studies a very high number of serious device related adverse events was reported. In RAFT, device-related hospitalisations occurred in 20.0% of CRT-D treated patients. In MADIT-CRT, average crude late device-related serious adverse events were reported in half of the devices over 1 year.**

Part III.

Economic aspects of cardiac resynchronisation therapy

7 Description of Belgian practice

7.1 Data source and methodology

The purpose of the Intermutualistic Agency (IMA) is to organise and manage a common interface to the health care data and patient characteristics that are collected by all seven Belgian Sickness Funds. The IMA database contains four types of data: data about all reimbursed health care use per attestation per patient; demographic data (e.g. date of birth, gender, decease date); data on the insurance status; data on professional status. A full description of the layout of the database and available variables can be found in KCE report 30 that inventories Belgian health databases.[56] For the present study, IMA was asked to provide all the health care records of patients who received a CRT device between 2005 and the first semester 2009 (included) as well as basic demographics such as year of birth, gender and, when applicable, deceased date.

The CRT devices were identified through their identification number billed to the national health insurance. The list of identification numbers of the selection can be found in Appendix B. The CRT-P identification numbers were in force since July 21, 2005 while CRT-D numbers were in force since July the first, 2007 only. Finally it was decided to work on the most recent data of 2008 and the first semester of 2009. Numbers beginning with 120003 or 120004 refer to plugged CRT-Ds, numbers beginning with 120005 and 120006 refer to full-feature CRT-Ds devices. Plugged CRT-D refer to ICD devices were the left ventricular electrode port is plugged, which allows to add the electrode later in order to convert the device into a full-feature CRT-D device. In 2008, a full-feature device was reimbursed at €18 900 and a plugged feature at €16 650. At the time of the report writing (September 2010), the reimbursement amounted respectively to €17 388 and €15 318. The hospital receives a supplementary device reimbursement amounting to €2250 (€2070 in September 2010) if the upgrading is done in the 2 months after the plugged device implantation. There is no such a differentiation for CRT-Ps.

The classification also allows to distinguish tariff class A CRT-Ds from cheaper tariff class B CRT-Ds devices but this was not considered relevant for the present analysis (only 1 class B CRT-D was billed in 2008).

Data were cleaned in order to discard aberrant values and to obtain a database with one record per patient and per CRT device. As the patient can be followed longitudinally in the IMA data, patients with several implantations were identified. The first implantation in a patient that has never had a CRT before is called a primo-implantation, as opposed as a replacement of an existing device. Primo-implantations and replacements can be distinguished based on the pseudo-code [a] recorded for each device. The list of codes retrieved in the data are given in Appendix B.

Concerning the localisation of the device implantation, the province of the hospital was available but not the province of residence of the patient.

The daily lump-sums billed for the hospitalisation during which the device was implanted were added in order to compute the length of stay. The selected daily lump-sums are presented in Appendix B. The hospitalisation of the implantation was identified using the date of implantation, the hospital admission dates and discharge dates available in the IMA data. Length of stay was plotted in a boxplot. The box shows the interquartile range (IQR) between the

a. Nomenclature codes are published in the Royal Decrete of 14 September 1984. Pseudo-codes are created by the RIZIV/INAMI in the accounting and statistical documents. For more information, see KCE report 30 that inventories Belgian health databases.[56]

lower quartile and the upper quartile; whiskers are drawn down until the minimum observation above 1.5 IQR and up until the maximum observation below 1.5 IQR. Observations beyond these fences are represented with a star. The horizontal line inside the box is the median and the dot represents the mean.

The outpatient medication was studied to identify the patients who were treated outside hospital for cardiovascular conditions. Drugs were considered as a treatment for cardiovascular conditions if belonging to ATC class "C" (cardiovascular system) or ATC class "B01A" (antithrombotic agents). In particular, patients who purchased at least one package of the following groups of products in the year before their primo-implantation were identified:

- Antithrombotic agents: ATC=B01A
- ACE-inhibitors: ATC=C09A or C09B
- Angiotensin II antagonists: ATC=C09C or C09D
- Beta-blocking agents: ATC=C07
- Spironolactone: ATC=C03DA01
- Loop diuretics: ATC=C03CA (furosemide, bumetanide and torasemide)
- Digoxin: ATC=C01AA05
- Amiodarone: ATC=C01BD01

The age of the patient was the difference between year of birth and year of implantation. Age was analysed on the adult population (age$\geq$20 years) who received a primo-implantation. Differences in age were tested with a t test for the means. Differences in length of stay were tested with a non-parametric Wilcoxon Mann-Whitney test. Differences in proportion of female patients or proportion of medicated patients were tested with a Chi-square test. All tests were performed at a 0.05 significance level. The survival time was the difference between implantation date and time of death expressed in months (since the day of the death is not available). Data were censored for the patients alive at the end of the observation period (before July the first, 2009). The Kaplan Meier method was applied to estimate the mortality rate after each type of device, at 1 year and 1.5 year. A Cox Proportional Hazards (PH) model was used to study the influence of the type of device on the risk of mortality.

A 6 months follow-up period was studied for patients alive at least 6 months after their primo-implantation of 2008. System integrity checks and contacts with general practitioners (GPs), geriatricians, cardiologists and internists were studied. Contacts were defined as consultations or home visits. A table in appendix Appendix B shows which codes were considered to define contacts.

7.2 Results

7.2.1 Clinical use of CRT in Belgium

In total, 1067 devices of both types (CRT-D and CRT-P) have been implanted in Belgium from January 1, 2008 until June 30, 2009. In 2008, 400 CRT-Ps and 321 CRT-Ds were implanted. (Table 7.1).

Table 7.1.: Number of CRT devices identified in IMA data 2008, mid-2009

Year		2008	2009 (1/2 year)	TOTAL
CRT-Ds		321 (100%)	154 (100%)	475
	Plugged	93 (29%)	36 (23.4%)	129
	Full-feature	228 (71%)	118 (76.6%)	346
CRT-Ps		400	192	592
	TOTAL	721	346	1067

The RIZIV/INAMI register indicates 280 CRT-D devices implanted in 2008, which is lower than our 321 CRT-D devices. Plugged CRT-D refers to a ICD device where the left ventricular electrode port is plugged, which allows to add the third electrode later in order to convert the device into a full-feature CRT-D device. A hypothesis would have been that the register includes only (full-feature) reimbursed CRT-D devices, thus no plugged CRT-Ds. This hypothesis cannot be confirmed as there were only 228 full-feature CRT-Ds implanted in 2008, thus less than in the RIZIV/INAMI register. The RIZIV/INAMI colleagues were contacted to clarify those apparent discrepancies, but together we did not find any particular explanation for the lower number of CRT-Ds in the register, other than administrative delays. However, it should be emphasized that different administrative databases serve different purposes and do not always cover the same population.

On the contrary, Eucomed figures are superior to the IMA data (Eucomed is an international association of manufacturers and suppliers technology). On its website the numbers of CRT devices sold in Belgium in 2008 reached 39 CRT-Ds per million inhabitants and 46 CRT-Ps per million inhabitants, corresponding to 416 CRT-Ds and 491 CRT-Ps.[57] As these are sales volumes, they might be higher than the reimbursement IMA data. Nonetheless this is in contradiction with the findings of the KCE's "Conventional Pacemaker" report in which a close correspondence between the Belgian Eucomed and the implantation numbers according to IMA were found.

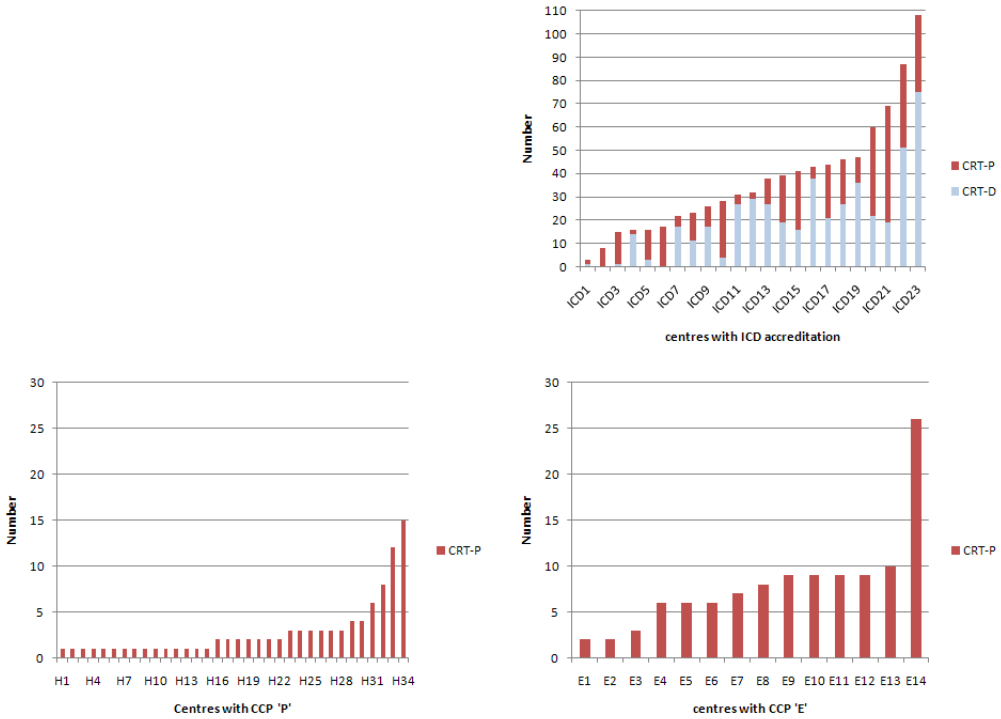
The 1067 devices have been implanted in 1062 patients, as 5 patients had 2 implantations. All five replacements seemed to have been premature as the period of time between both implantations varies from 14 days to 102 days. Besides those five replacements, the other implantations may have been replacements of devices implanted before 2008. Fortunately, the IMA data allow to differentiate between primo-implantations and replacements based on a pseudo-code recorded for each device. The pseudo-codes recorded for the five second implantations mentioned above were indeed replacement codes. Table 7.2 shows that 72% of the CRT-Ds and 74.5% of the CRT-Ps were a first implantation in the patients. The first percentage is close to 68.21% and 78.14% of CRT-D primo-implantations found in 2008 and in 2009 in the conventional ICD register managed by the RIZIV/INAMI.

Table 7.2.: Primo-implantations and replacements amongst CRT devices (2008, mid-2009)

Frequency (Row Percent)	Primo-implantations	Replacements	Regularisations	Total
CRT-D	342 (72%)	133 (28%)	-	475 (100%)
CRT-P	441 (74.5%)	148 (25%)	3 (0.5%) [a]	592 (100%)
Total	783 (73.4%)	281(26.3%)	3(0.3%)	1067 (100%)

There are 23 Belgian hospitals with an ICD accreditation where ICD implantations may be reimbursed.[58] All CRT-D implantations and 64.9% of the CRT-Ps (n=384) took place in these hospitals. ICD hospitals have also a cardiac care program "E" (see chapter 3 for the definition of cardiac care programs). Other hospitals that are not ICD centres may also have a CCP "E". Figure 7.1 and Table 7.5 shows the repartition between the hospitals according to their cardiac care programs. Amongst ICD hospitals, 8 of them implanted less than 10 CRT-Ds and 6 of them less than 10 CRT-Ps.Two of the 23 ICD centres did not implant CRT-Ds, those two hospitals appear with an entirely dark bar on the chart (they had 8 and 17 CRT-Ps). Amongst centres with a CCP "E" that are not ICD centres, only one of them implanted more than 10 CRT-Ps. Two out of 34 hospitals without ICD or CCP E implanted more than 10 CRT-Ps.

Figure 7.1.: Number of CRT-Ps and CRT-Ds implanted per hospital (2008, mid-2009)



Source: KCE. Numbers depicted on y-axes are related to 18 months.

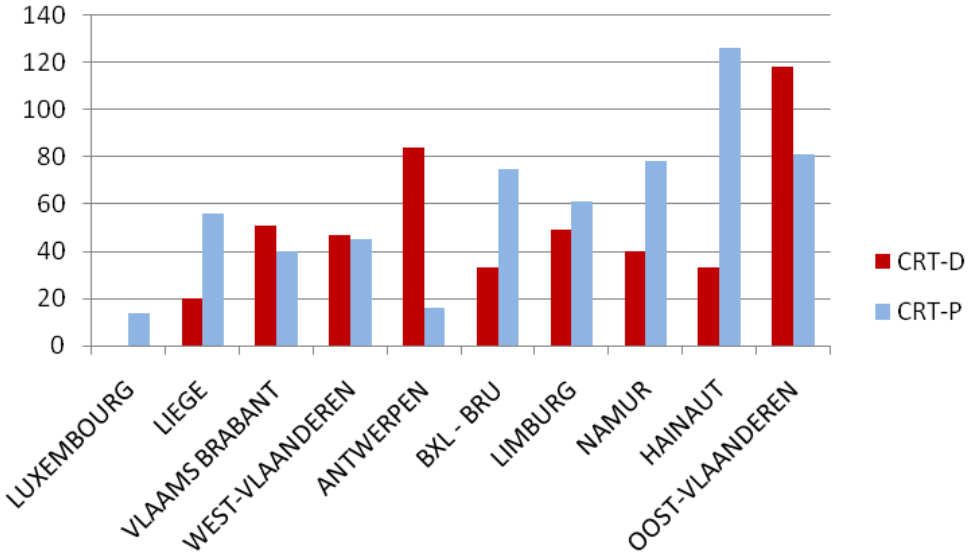
Table 7.3.: Number of CRT-Ps and CRT-Ds implanted per CCP (2008, mid-2009)

Type of device	CCP 'E'	ICD accreditations	CCP 'P'	TOTAL
CRT-D	0	475	0	475
CRT-P	127	384	81	592
TOTAL	127	859	81	1067

7.2.2 Geographic distribution

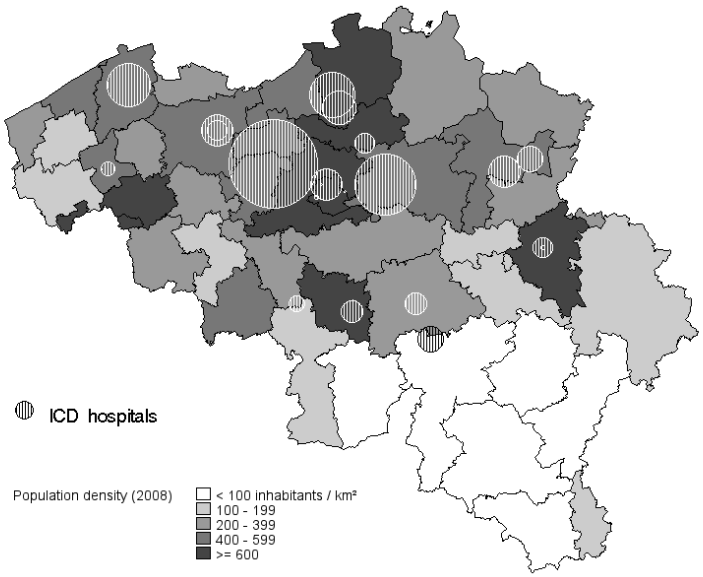
The number of CRT devices per type and per hospital province is shown on Figure 7.2. There are no CRT device implanted in Brabant Wallon and only CRT-Ps are implanted in the province of Luxembourg. The highest number of CRT-Ps are implanted in the province of Hainaut. The highest number of CRT-Ds (and the highest total number of CRT devices) are implanted in the province of Oost-Vlaanderen .

Figure 7.2.: Number of CRT-Ps and CRT-Ds implanted per province (2008, mid-2009)



In Figure 7.3, hospitals are located on a map with the size of the dot defined by the number of CRT-Ds implanted in the hospital, between 0 and 75 CRT-Ds. Brussels has five ICD centres (from which one where no CRT-D was implanted) but only one where an important number of CRT-Ds were implanted (n=27).

Figure 7.3.: ICD Hospitals and their relative number of CRT-Ds implantations (average rate 2008 - mid2009)



7.2.3 Length of stay

Length of stay was studied separately for primo-implantations and replacements. Implantations performed in patient aged less than 20 years (n=8 CRT-P) were set aside for the calculation of the length of stay. The length of stay was not calculated for the cases for which

it was not possible to retrieve enough information in the IMA healthcare file (n=9 CRT-D, n=10 CRT-P). [a]

Figure 7.4 and Table 7.4 present the distributions of the length of stay per CRT device type, which are quite close for primo-implantations (in average around 12 to 13 days, median=5 for both types) but dissimilar between replacements of different CRT types. The difference between both type of device was not statistically significant for primo-implantations (Wilcoxon Mann-Whitney test, p=0.0597) and the lower quartiles and the medians were respectively equal for both types of devices. For replacements, the difference was statistically significant between CRT-D and CRT-P (p=0.0112).

Figure 7.4.: Length of stay of primo-implantation hospitalisation per type of CRT device (2008, mid-2009)

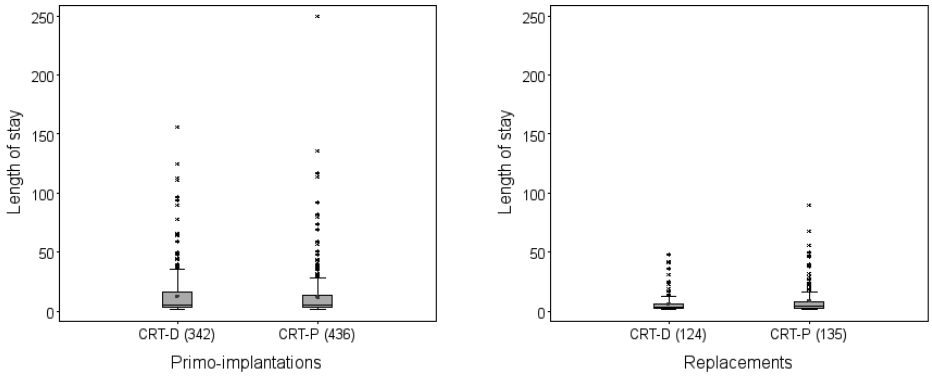


Table 7.4.: Length of stay of primo-implantation (2008, mid-2009)

Type	Nb hospitalisations	Mean	Std	Min	Q1	Median	Q3	Max
CRT-D	342	12.86	19.01	1	3	5	16	156
CRT-P	436	12.03	20.35	1	3	5	13	250
TOTAL primo-implantations	778	12.39	19.76	1	3	5	14	250
CRT-D	124	6.39	8.82	1	2	3	6	48
CRT-P	135	9.17	13.73	1	2	4	8	90
TOTAL replacements	259	7.84	11.70	1	2	3	7	90

7.2.4 Patients characteristics

Age was calculated on the adult population who received a primo-implantation. The small paediatric subgroup of patients who received a CRT-P as primo-implantation (n<20 years=4) was not included in the analysis. Figure 7.5 present the distribution of the age of the patient at the time of first implantation.CRT-Ds are generally implanted in statistically significantly younger patients than CRT-Ps (M=65.5, SD=10.9 [Median=67, IQR=14] versus M=71.6, SD=10.5 [Median=74, IQR=13], p<0.0001). The CRT-Ds population included a lower proportion of female patients than the CRT-Ps population (17.8% versus 34.5%, p<0.0001). Those results are similar to the population studied by Floré, et al. in a large Belgian hospital between 2001 and 2005.[59] Table 7.5 shows the patient profile per cardiac care program (of the hospital where primo-implantation was performed). The proportion of CRT-P male

a. (3 CRT-D patients and 1 CRT-P patient in 2008, 1 CRT-D patient in 2009).

patients did not differ between the different cardiac care programs. Globally, there was a statistical difference in age between the hospital and, more specifically, there was a difference of 3.5 years (95%CI: 1.2, 6) between the centres with CCP 'E' and the centres with ICD accreditation.

Figure 7.5.: Patient age distribution per type of CRT device - primo-implantations (2008, mid-2009)

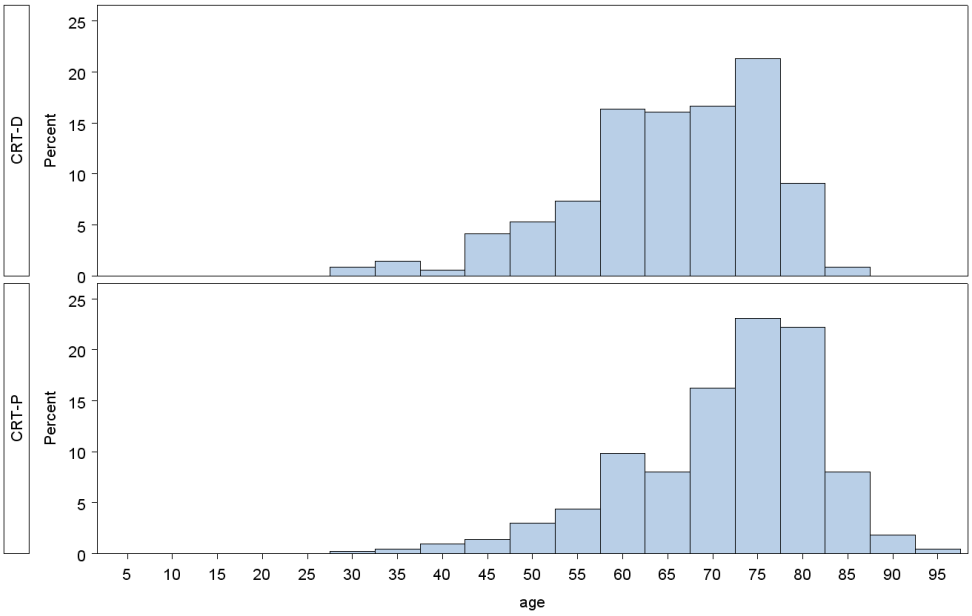


Table 7.5.: Patient characteristics per type of device and cardiac care program - primo-implantations (2008, mid-2009)

Type of device		CCP 'E' (no ICD accreditation)	ICD accreditations	CCP 'P'	p-value
CRT-D	N =342	.	342	.	
	% Male patients	.	82.2%	.	
	Age (mean ± Std)	.	65.5 ± 10.9	.	
CRT-P	N =437	95	281	61	
	% Male patients	62.1%	65.84%	68.85%	0.6701
	Age (mean ± Std)	74.1 ± 9.8	70.5 ± 10.9	72.6 ± 9	0.0101

7.2.5 CRT-D upgrades

Only 9 patients having a CRT-D between January 1, 2008 and mid-2009 also received an upgrade in the same period. Eight of them had a plugged CRT-D implanted before the upgrade. In two cases the so-called upgrade was done on the same day as the CRT-D implantation, in two other cases in the same week, in the following other two cases in the forthnight, in two other cases in the same month and the last one after two months. No other patient who received a plugged CRT-D from January 1, 2008 until June 30, 2009 was billed an upgrade in the same period. The data do not include information on patients who received an upgrade more than 2 months after the implantation.

7.2.6 Heart Failure medication

The year before the primo-implantation was studied to identify the patients who purchased, in ambulatory sector, at least one pack of drugs before their primo-implantation. There were more CRT-D patients with ACE-inhibitors or with beta-blocking agents. For the other drug groups, the percentage was similar between CRT-D and CRT-P (Table 7.6).

Table 7.6.: Percentages of patients having purchased at least 1 package the year before the first implantation (2008, mid-2009)

	CRT-D n=342	CRT-P n=437	p value
Antithrombotic agents	52.9%	47.6%	0.14
ACE-inhibitors	69.6%	61.6%	0.0196
Angiotensin II antagonists (ARB)	19.6%	21.5%	0.5114
ACE-inhibitors OR ARB	84.8%	79.9%	0.0752
Beta-blocking agents	74.0%	64.3%	0.0039
Spironolactone	35.7%	32.7%	0.3885
Loop diuretics	61.7%	60.4%	0.7154
Dioxin	12.6%	8.7%	0.0785
Amiodarone	24.3%	22.4%	0.5455

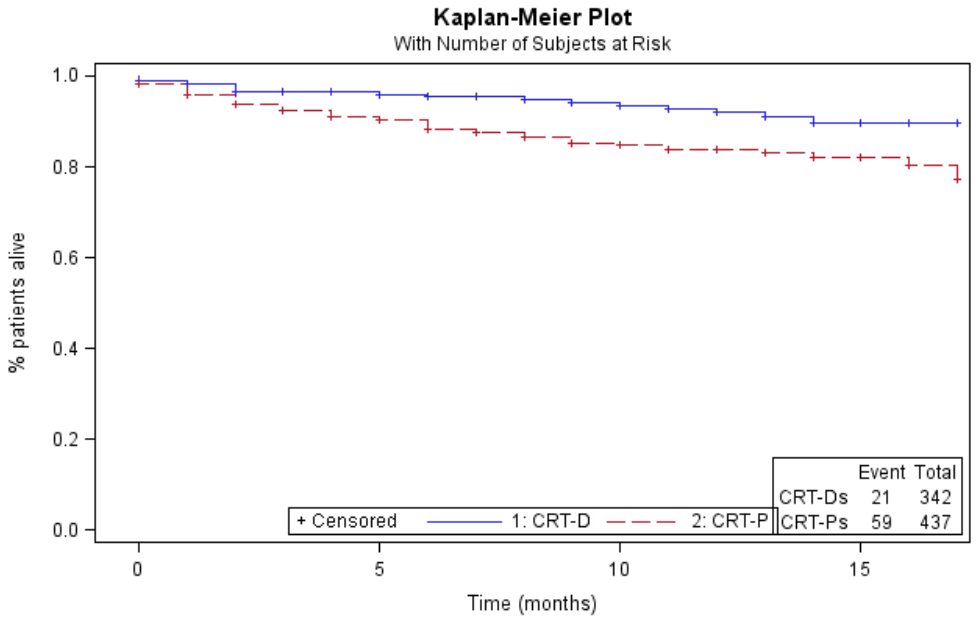
7.2.7 Mortality

As many of the patients were still alive at the end of the period (right-censored), we calculated the estimated mortality rate using the Karlan-Meier method. Table 7.7 presents the estimated number of deceased patients amongst the 779 adult patients who had a primo-implantation in the period 2008, mid-2009. Figure 7.6 presents the survival time curves by types of CRT devices. Note that the survival time was calculated from the first implantation date in case of patients who had 2 implantations (they all survived until the end of the period). After one year 92.8% (95% CI: 88.6%, 95.6%) of the patients survived their CRT-D implantation while 83.7% (95% CI: 79.1%, 87.3%) of the patients were still alive after their CRT-P implantation. The mortality at 12 month reached thus respectively for CRT-D 7.2% (95% CI: 4.4%, 11.4%) and for CRT-P 16.3% (95% CI: 12.7%, 20.9%). It is important to remember that the mortality can be influenced by different factors. For example, the age distributions are different for both types of devices. Therefore, it is to be expected for the mortality rate after a CRT-P implantation to be higher than after a CRT-D implantation.

Table 7.7.: Mortality rate (2008, mid-2009)

Type of device	Nb patients	Events	Censored	Survival rate 12 months	CI 95% Lower bound	CI 95% Upper bound	Survival rate 18 months	CI 95% Lower bound	CI 95% Upper bound
CRT-D	342	21	321	0.928	0.886	0.956	0.897	0.836	0.936
CRT-P	437	59	378	0.837	0.791	0.873	0.772	0.678	0.842
Total	779	80	699						

Figure 7.6.: Survival time after CRT primo-implantation (2008, mid-2009)



A Cox proportional hazards (PH) regression was used in order to verify if there were differences in risks of mortality between the patients receiving one of the two types of device. Type of device and gender were introduced in the model as binary variables (type=1 for CRT-D, gender = 1 for male) while age was introduced in classes (1: 20-62 years, 2: 63-71 years, 3: 72-77, 4:78-99 following the quartiles). The proportion of CRT-Ds differs between each age class, as presented in Table 7.8.

Table 7.8.: Number of CRT-Ds and CRT-Ps per age class (2008, mid-2009)

	CRT-Ds (%)	CRT-Ps (%)	Total (100%)
20-62 years	123 (58.3)	88 (41.7)	211
63-71 years	102 (53.4)	89 (46.6)	191
72-77 years	83 (41.3)	118 (58.7)	201
78-99 years	34 (19.3)	142 (80.7)	176

The survival curves did not overlap by type of device, which is a supportive argument for the proportionality assumption of the hazards. The test of proportionality was not significant so no time-dependent variable had to be included in the model. Interactions were considered but did not enter the final model. The model results are presented in Table 7.9.

Table 7.9.: Results of the PH Cox regression modelling the survival time after CRT implantation (2008, mid-2009)

			Interval confidence	
Variable	p-value	Hazard Ratio	Lower bound	Upper bound
Type of device CRT-D vs CRT-P	0.0041	0.469	0.279	0.786
Gender Male vs Female	0.9271	0.978	0.604	1.582
Age class 1 vs 4	0.3235	0.699	0.344	1.422
Age class 2 vs 4	0.5325	1.220	0.653	2.278
Age class 3 vs 4	0.4725	1.236	0.693	2.205

The age and gender adjusted hazard ratio for type of device shows that patients receiving a CRT-D have a 53.1 % lower risk of mortality (95%CI: 21.4%, 72.1%) compared to patients receiving a CRT-P. As the patients were not randomised, we obviously cannot compare the effect of both treatments. Comorbidities were most probably superior in the CRT-P patients. In the study by Floré, et al. CRT-P patients had a worse functional capacity, and their NYHA class was higher than CRT-D patients.[59]

7.2.8 Follow up: CRT system integrity checks

The proper functioning of a pacemaker or a defibrillator needs to be regularly controlled. The nomenclature codes for CRT-P and CRT-D system integrity checks are in Appendix B. The number of integrity checks done in the 6 months following the implantation was calculated from the primo-implantation of patients discharged in 2008 and alive at 6 months, so that each patient had a complete follow-up of 6 months. From the 779 primo-implantations on adults studied before, 528 were performed in 2008 and 492 patients survived this implantation at least 6 months (corresponding to 220 CRT-Ds and 272 CRT-Ps).

Table 7.10.: CRT system integrity checks performed within 6 months following primo-implantation

Type of device	Nb patients	variable	mean	std	min	Q1	median	Q3	max
CRT-D	220	ICD system check	2.39	1.28	0	2	2	3	9
		PM system check	0.39	0.89	0	0	0	0	6
CRT-P	272	ICD system check	0.04	0.21	0	0	0	0	2
		PM system check	2.19	1.19	0	1	2	3	8

As seen on Table 7.10, the primo-implantation was followed in average by 2 to 3 system integrity checks in the next 6 months of survival.

7.2.9 Follow-up: ambulatory medical contacts

For the 492 patients who survived at least 6 months after their primo-implantation of 2008, the number of contacts with the general practitioner (GP) and some specialists were studied. Contacts were defined as consultations or home visits. Table 7.11 shows the distribution of the number of contacts with physicians.

Table 7.11.: Number of contacts with GPs and specialists within 6 months following primo-implantation

Type of device	Nb patients	contact with	mean	std	min	Q1	median	Q3	max
CRT-D	220	GP	8.42	7.28	0	3	7	12	52
		geriatrician	0.01	0.10	0	0	0	0	1
		cardiologist	2.39	1.51	0	1	2	3	9
		internist	0.38	0.96	0	0	0	0	7
CRT-P	272	GP	7.94	5.59	0	4	7	11	32
		geriatrician	0.01	0.09	0	0	0	0	1
		cardiologist	2.13	1.32	0	1	2	3	8
		internist	0.35	0.86	0	0	0	0	7

Six months after a CRT-D primo-implantation patients had on average 8 to 9 GP contacts, and more than 2 contacts with a cardiologist. Similar figures were observed after CRT-P treatment. Overall 10.4 (CRT-P) and 11.2 (CRT-D) medical ambulatory contacts were registered during six months follow-up.

7.3 Conclusion and discussion

During the year 2008 and the first six months of 2009, 1067 CRT devices (CRT-D and CRT-P) have been implanted in Belgium. In 2008, the 721 CRT implantations were divided into 229 CRT-D and 302 CRT-P primo implantations (totalling 531 primo CRT implantations), 92

CRT-D replacements and 95 CRT-P replacements (totalling 187 CRT replacements) plus 3 undetermined CRT-P implantations.

Eighty percent of all CRT implantations took place in an ICD-accredited hospitals. Among 23 ICD centres, 8 had less than 20 CRT implantations per year. Of 48 non-ICD hospitals that performed at least 1 CRT implantation during the study period (2008/mid-2009), only two implanted more than 10 devices per year.

Belgian patients treated with a CRT-D are younger (median age 67, IQR 14) than those treated with a CRT-P (median age 74, IQR 13). The CRT-D population included a lower proportion of female patients than the CRT-Ps population (17.8% versus 34.5%). These HF patients seem to be in a very poor health. They have on average more than 20 ambulatory medical contacts a year. Their 1 year mortality risk is almost six times as high as people of the same age from the general population (Table 7.13).

In clinical trials, CRT treatment is only tested in chronic HF patients that remain symptomatic despite optimal medical treatment. We assessed the use of HF drugs in Belgian 2008/2009 CRT recipients, based on administrative data. Since it may require several weeks before the optimal treatment effect of these drugs is obtained, we assumed that the decision to proceed to CRT treatment could not be taken during a first hospitalisation for HF. In other words, the assumption is that HF patients have to be treated with these drugs at least on an ambulatory basis before it can be decided that this medical treatment failed. This assumption is in agreement with the design of clinical trials that set a minimum duration of HF before enrolment of 6 weeks[60] or at least 3 months, with stable doses of these drugs.[38] We counted the number of CRT patients that purchased in the ambulatory sector at least one packet of these drugs during the year preceding the primo implantation of the CRT device. The results are shown in Table 7.12, along with drug use as reported in clinical trials.

Table 7.12.: Use of selected medications in CRT patients (percentage, age in years).

	BELGIUM 2008/2009		CARE-HF 2001/2003		COMPANION 2000/2002			MADIT-CRT 2004/2008		RAFT 2003/2009	
	CRT-P	CRT-D	OPT	CRT-P	OPT	CRT-P	CRT-D	ICD	CRT-D	ICD	CRT-D
median age	74	67	66,0	67,0	68	67	66	64	65	66	66
ACE and/or ARB	79,9	84,8	95,0	95,0	89	89	90	NA	NA	97,1	96,1
Beta-blocker	64,3	74	74,0	70,0	66	68	68	93,2	93,3	89	90,4
Diuretic	60,4	61,7	44,0	43,0	94	94	97	72,9	75,7	83,6	84,7
Spironolacton	32,7	35,7	59,0	54,0	55	53	55	30,9	32,3	41,8	41,6

Source: Belgian IMA data. See text for study acronyms.

Kaplan-Meier estimates for one year survival were 92.8% (95%CI: 88.6%, 95.6%) for CRT-D primo implantations. For CRT-P treated patients, it was 83.7% (95% CI: 79.1%, 87.3%). Thus, 12 month mortality was 7.2% (95% CI: 4.4%, 11.4%) for CRT-D treated patients and 16.3% (95% CI: 12.7%, 20.9%) for CRT-P treated patients (Table 7.13).

Table 7.13.: 1 year all-cause mortality of CRT patients

	NYHA class	Optimal medical		CRT-P		CRT-D	
		Age	1 yr mort	Age	1 yr mort	Age	1 yr mort
CARE-HF	93% NYHA III	66	12,6	67	9,7	-	-
COMPANION	86% NYHA III	68	19,0	67	15,0	66	12,0
MADIT-CRT	85% NYHA II	-	-	-	-	65	3,1
RAFT	80% NYHA II	-	-	-	-	66	6,5
BELGIAN CRT patients		-	-	74	16,3	67	7,2

Age is presented as median value. See text for study acronyms. One year overall mortality of the general Belgian population equals 2.6% at age 74, and 1.3% at age 67 (source: statbel.gov.be).

From Table 7.13 it can be inferred that Belgian CRT-P patients are 7 years older than those enrolled in the COMPANION trial and have a slightly higher 1 year mortality risk. CRT-D patients have an age that is comparable to that of patients enrolled in clinical trials. Based on the 1 year mortality, they seem to be healthier than those enrolled in COMPANION, but comparable to those enrolled in RAFT. This suggests that Belgian patients treated with a CRT-D in 2008/2009 on average belong rather to the "RAFT-trial type" of NYHA class II HF patients.

KEY POINTS

- **The results in this chapter are purely descriptive and should not be causally interpreted.**
- **In 2008, 721 CRT devices were implanted in Belgium: 321 CRT-Ds and 400 CRT-Ps. Three quarters of these devices were implanted for the first time, the remaining quarter being device replacements.**
- **Eighty percent of the CRT implantations occurred in the 23 hospitals with an ICD accreditation. Eight of those hospitals implanted less than 20 CRT in the year 2008. That same year, none of the non-ICD hospitals reached this number.**
- **Patients receiving a CRT-D were younger than those who received a CRT-P. CRT-D were also implanted more in men (82.2%) than CRT-P (65.5%). They received the same drug treatment except that the proportion of patients under ACE-inhibitors and beta-blocking agents was higher in CRT-D patients than in CRT-P patients (respectively 74% versus 64% and 70% versus 62%).**
- **The length of the hospital stay of both groups was approximately 12 days for a first implantation. For replacements, the length of stay was shorter in the case of CRT-D (mean 6 versus 9, median 3 versus 4).**
- **The one year mortality of CRT patients is six times higher than people of the same age from the general population.**
- **CRT patients had on average more than 10 medical ambulatory contacts with a physician (general practitioner, geriatrician, cardiologist or internist) in the first six months after the CRT implantation.**

8 Review of the literature on cost-effectiveness

8.1 Aim

The aim of this chapter is to summarise and review existing literature that assessed the cost-effectiveness of cardiac resynchronisation therapy by pacemaker (CRT-P) combined with optimal pharmacological therapy (OPT) relative to only OPT, as well as literature that did similarly for the augmented therapy of cardiac resynchronisation therapy by defibrillator (CRT-D) in combination with OPT relative to CRT-P with OPT. In this context, it is important to note that CRT-D truly is an augmented therapy of CRT-P since a CRT-D device delivers exactly the same cardiac resynchronisation therapy as a CRT-P device does, added with the ability of a defibrillator to stop life-threatening ventricular arrhythmia and hence prevent sudden cardiac death (SCD). CRT-D defibrillators accordingly cost more than CRT-P pacemakers. If the cost-effectiveness ratio of CRT-P+OPT turns out to be lower than that of CRT-D+OPT, CRT-P+OPT becomes the *relevant alternative* to which to compare CRT-D+OPT for its *incremental* cost-effectiveness ratio (ICER). Finally, this chapter also aims at providing valuable input data for the Belgian cost-effectiveness model presented in the succeeding chapter.

$$OPT \quad \overset{+\text{CRT}}{\longleftrightarrow} \quad \text{CRT-P+OPT} \quad \overset{+\text{D}}{\longleftrightarrow} \quad \text{CRT-D+OPT}$$

Figure 8.1.: A schematic representation of augmented heart failure therapies with the bidirectional arrows indicating valid health-economic assessment comparisons

8.2 Methods

8.2.1 Search strategy

Given the fact that this economic review is performed in the context of a rapid health technology assessment (HTA) and due to time constraints, a very limited search was performed. As a first step, a quick search was done in the HTA database of the Centre for Reviews and Dissemination (CRD) of the UK's National Health Service (NHS). [a] The 2007 HTA of Fox et al.[6] appeared out of this search as the most recent health-economic evaluation. This report featured a well-documented, systematic search performed in January 2006 on the following databases:

- Ovid MEDLINE®,
- EMBASE,
- PreMEDLINE Ovid MEDLINE® In-Process and Other Non-Indexed Citations,
- Science Citation Index,
- Web of Science Proceedings,
- NHS Economic Evaluation Database (NHS-EED), and
- EconLit.

No language restriction was applied to the above-mentioned systematic search. In a second step, the search as mentioned in the Fox report[6] was updated with a literature search from January 2006 to August 2010.

a. http://www.crd.york.ac.uk/crdweb/

Table 8.1.: An overview of the twelve retained economic evaluations

First author, published	Principal source of input data	Intervention(s) and comparator(s)	Country perspective (ISO 3166-1)	Resource use model(s)	Initial NYHA class	Mean cohort / base case age	Time horizon	Cycle-length or evaluation points	Conflicts of interest
Aidelsburger, 2008	COMPANION	CRT-D+OPT vs. OPT	DE	Decision analytic model for first 30 days followed by Markov model	III & IV	COMPANION: median 66	2 years	6-month cycle	Guidant grant
Banz, 2005	MIRACLE	CRT-P+OPT vs. OPT	DE	Two linked decision analytic models: for first 30 days and long-term	III & IV	DE patient population	1 year	at 30 days, 6, 12 & 18 months and years 2, 3, 4 & 5	Multiple industry grants
Blomström, 2008	CARE-HF	CRT-P+OPT vs. OPT	DK FI SE	as registered in CARE-HF	III & IV	CARE-HF: 67, IQR: 60-73	lifetime	not applicable	None
Bond, 2009	PenTAG review[1]	CRT-P+OPT vs. OPT CRT-D+OPT vs. CRT-P+OPT	UK	Markov model with Monte Carlo simulation	III & IV	PenTAG[1] base case: 74, range: 35-83	lifetime	4-week cycle	None
Calvert, 2005	CARE-HF	CRT-P+OPT vs. OPT	resource use: EU costs: UK	as registered in CARE-HF	III & IV	CARE-HF: 67, IQR: 60-73	end-of-study 29.4 months	not applicable	Medtronic grant
Caro, 2006	CARE-HF	CRT-P+OPT vs. OPT	UK	Discrete event simulation with Monte Carlo simulation	III & IV	CARE-HF: 67, IQR: 60-73	5 years	at 0, 1, 6, 9, 12, 18, 24, 30, 36 & 42 months	Medtronic co-author
Fattore, 2005	MIRACLE	CRT-P+OPT vs. OPT	IT	Decision analytic model for first 30 days followed by Markov model with Monte Carlo simulation	III & IV	64	3 years	1-month cycle	Assobiomedica grant & industry co-authorship
Feldman, 2005	COMPANION	CRT-P+OPT vs. OPT CRT-D+OPT vs. OPT	US	Markov model based on COMPANION data	III & IV	COMPANION: median 66	7 years	1-month cycle	Guidant co-author
Fox, 2007	PenTAG review[1]	CRT-P+OPT vs. OPT	UK	Markov model with Monte Carlo simulation	III & IV	PenTAG[1] base case: 74, range:35-83	lifetime	4-week cycle	None
McAlister, 2004	Systematic review	CRT-P+OPT vs. OPT	US	Markov model with Monte Carlo simulation	III	base case 60, range: 50-70	lifetime	1-month cycle	None
Nichol, 2004	9-trial review[2]	CRT-P+OPT vs. OPT	US	Markov model with Monte Carlo simulation	III	Nine-trial model[2]: 60	lifetime	1-month cycle	Multiple industry grants
Yao, 2007	CARE-HF & COMPANION	CRT-P+OPT vs. OPT CRT-D+OPT vs. CRT-P+OPT CRT-D+OPT vs. OPT	UK	Decision analytic model for first month followed by Markov model with Monte Carlo simulation	III & IV	65	lifetime	1-month cycle	Medtronic grant

Note:

[1] The PenTAG systematic review was commissioned by NICE and included data from the MUSTIC-SR, MIRACLE, CONTAK-CD, COMPANION and CARE-HF trials.

[2] Nine-trial review including MUSTIC-SR, MUSTIC-AF, Garrigue et al. 2002, PATH-CHF, CONTAK-CD, MIRACLE, MIRACLE-ICD, COMPANION and Leclercq et al.

8.3 Results of the search strategy

The search up to January 2006 of the Fox report[6] resulted in seven published economic evaluations of CRT:

- McAlister et al.[61] published in 2004,
- Nichol et al.[62] published in 2004,
- Banz[63] published in 2005,
- Feldman et al. abstract[64] published in 2005,
- Fattore et al.[65] published in 2005,
- Feldman et al. article[66] published in 2005, and
- Calvert et al.[67] published in 2005.

The abstract of Feldman et al. was withheld from our review because of being an abstract. Our own search to update this report, from January 2006 to mid-August 2010 yielded five published health-economic evaluations:

- Caro et al.[2] published in 2006,
- Yao et al.[3] published in 2007
- Aidelsburger et al.[68] published in 2008
- Blomström et al.[69] published in 2008, and
- Bond et al.[70] published in 2009 (presenting the same model as in Fox[6]).

The extraction of data for below overview was performed independently by two researchers, except for the economic evaluation of Fattore et al. which was analysed by only one researcher due to the Italian language hurdle.

8.4 Overview of the economic literature

Table 8.1 provides an overview of the twelve retained economic evaluations, mentioning the principal source of input data, the comparators, the country perspective, intervention(s) and comparator(s), the applied model(s) for resource use calculation, a description of the pertinent patient population in terms of New York Heart Association (NYHA) functional classification and age, the time horizon of the evaluation, the cycle length of the model where applicable as well as possible conflicts of interest. A number of observations can readily be made:

- All studies were performed from the perspective of the payer.
- The economic evaluations differ largely with regard to the applied time horizon. Time horizons vary from one year to lifetime.
- All but one study compared CRT-P+OPT with OPT. Two studies additionally compared CRT-D+OPT with CRT-P+OPT. Another two studies compared CRT-D+OPT with OPT, of which one in combination with CRT-P+OPT versus OPT. Hence, only thee studies compared all three levels of heart failure therapy, being Bond,[70] Feldman[66]and Yao.[3]
- Of the twelve retained evaluations only four evaluations were completely free of any possible conflict of interest. Most of the published studies were conducted either with financial support from device manufacturers and / or with co-authorship involvement of employees of such companies. Notable exceptions were the evaluations by Blomström,[69] Bond[70] (commissioned by the UK's National Institute for Health and Clinical Excellence (NICE)), Fox[6] (idem) and McAlister[61] (commissioned by the US Agency for Healthcare Research and Quality (AHRQ)).
- Only three economic evaluations had access to and employed the per patient trial data of CARE-HF[1] in the cases of Blomström[69] and Calvert,[67] and of COMPANION[25] in the case of Feldman.[66]
- Most evaluations employed a Markov model for total cost and resource-use calculation, some preceded by a short-term decision tree. A single evaluation, Caro,[2] is based on a discrete event simulation (DES) model. The stated advantage of a DES model over a Markov model, lies with the fact that in a DES model, patients are individually tracked,

Table 8.2.: Clinical baseline characteristics and their distribution for each of the economic evaluations

First author of evaluation	Pertinent population	Initial NYHA class considered	Baseline NYHA class distribution	Mean cohort / base case age	Subgroup analyses
Aidelsburger	Hypothetical COMPANION cohort	III & IV	Same as Banz	COMPANION: median 66	none
Banz	Hypothetical COMPANION cohort	III & IV	Abraham: hypothetical 90% NYHA III, 10% NYHA IV	DE patient population	none
Blomström	CARE-HF trial population	III & IV	CARE-HF trial distribution: 93.8% NYHA III, 6.2% NYHA IV	CARE-HF: 67, IQR: 60-73	none
Bond	PenTAG review[1] UK-based hypothetical cohort	III & IV	Same as Calvert	PenTAG[1] base case: 74, range: 35-83	1) Starting age: 30-90 with increments of 10 and 2) SCD probability
Calvert	CARE-HF trial population	III & IV	CARE-HF trial distribution: 93.8% NYHA III, 6.2% NYHA IV	CARE-HF: 67, IQR: 60-73	none
Caro	CARE-HF trial population	III & IV	CARE-HF trial distribution: 93.8% NYHA III, 6.2% NYHA IV	CARE-HF: 67, IQR: 60-73	none
Fattore	Hypothetical MIRACLE cohort	III & IV	Same as Banz	64	none
Feldman	COMPANION trial population	III & IV	COMPANION distribution	COMPANION: median 66	none
Fox	PenTAG review[1] UK-based hypothetical cohort	III & IV	CARE-HF trial distribution: 93.8% NYHA III, 6.2% NYHA IV	PenTAG[1] base case: 74, range:35-83	1) Starting age: 30-90 with increments of 10 and 2) SCD probability
McAlister	Hypothetical systematic review cohort with NYHA III and prolonged QRS-duration	III	not applicable	base case 60, range: 50-70	NYHA II &IV
Nichol	Hypothetical 9-trial review[2] cohort with NYHA III and prolonged QRS-duration	III	not applicable	Nine-trial model[2]: 60	NYHA IV
Yao	CARE-HF trial population	III & IV	CARE-HF trial distribution: 93.8% NYHA III, 6.2% NYHA IV	65	Starting age: 55-75 with increments of 5

Note:

[1] The PenTAG systematic review was commissioned by NICE and included data from the MUSTIC-SR, MIRACLE, CONTAK-CD, COMPANION and CARE-HF trials.

[2] Nine-trial review including MUSTIC-SR, MUSTIC-AF, Garrigue et al. 2002, PATH-CHF, CONTAK-CD, MIRACLE, MIRACLE-ICD, COMPANION and Leclercq et al.

allowing for a "memory" of previous health states whilst doing away with the limitations of fixed cycle lengths and mutual exclusivity among states.

8.4.1 Population and subgroup analyses

8.4.1.1 Clinical baseline characteristics and their distribution

The clinical baseline characteristics and their distribution for each of the economic evaluations are listed in Table 8.2. The pertinent patient populations are either actual trial populations or hypothetical cohorts. Most evaluations consider a distribution with both NYHA class III and IV patients at baseline, except for McAlister[61] and Nichol[62] who only considered a population of NYHA class III patients at baseline. All other evaluations have NYHA class distributions based on actual trial distributions except for the hypothetical distributions of Aidelsburger,[68] Banz[63] and Fattore.[65] The mean starting age of the economic evaluations corresponds either to that of an actual trial population or is sometimes chosen slightly higher to mimic the epidemiological age distribution of heart failure patients in the United Kingdom. The CARE-HF trial[1] appears in many evaluations as the basis for the pertinent patient population. Coincidentally, CARE-HF was conducted entirely in Europe. Its age, sex and NYHA class distribution are given in Table 8.3.[2]

Table 8.3.: Baseline demographic and clinical characteristics of the CARE-HF[1] population according to Caro[2]

Characteristic	Base case proportion	
Male	73.0%	
Initial NYHA class		
III	93.8%	
IV	6.2%	
Age distribution	Male	Female
30 – 49 years	7.9%	6.5%
50 – 59 years	19.1%	15.8%
60 – 69 years	38.7%	34.9%
70 – 79 years	28.3%	34.4%
80+ years	6.0%	8.4%

8.4.1.2 Subgroup analyses

Different subgroup analyses were performed in some of the considered evaluations to identify patients who would most benefit from CRT-P or CRT-D. Subgroup analyses were performed for either (see Table 8.2):

- Patient age,[70,6,3]
- Annual probability of sudden cardiac death (SCD),[70,6] or
- NYHA class.[61,62]

Both the Fox[6] and Bond[70]health-economic evaluations included subgroup analyses for patient starting age as well as an annual probability of SCD. None of these two evaluations featured a subgroup analysis for NYHA class. Both evaluations coincidentally originated from the same workgroup that considered the NYHA taxonomy to be too subjective to serve as a measure for functional ability.

Two evaluations, Nichol[62] and McAlister[61] –again originating from a same workgroup–, considered exclusively NYHA class III patients at baseline. Finally, the evaluation of Yao[3] performed subgroup analyses for different patient starting ages only.

Table 8.4.: Costs (continues on the next page)

	Aidelsburger	Banz	Blomström			Bond	Calvert	Caro	Fattore	Feldman	Fox	McAlister	Nichol	Yao
Prices valid for	2005	2002	2006			2005 (2006 for drugs)	2001-2005	2004	2004	2004	2005 (2006 for drugs)	2003	2003	2001-2005
Principal source of cost data	DE	DE	DK	FI	SE	NHS	CARE-HF & NHS	CARE-HF	IT	COMPANION	NHS	Owens & Kaul	US	Calvert
Country perspective (ISO 3166-1 code)	DE	DE	DK	FI	SE	UK	UK	UK	IT	US	UK	US	US	UK
Drug treatment (OPT) (yearly cost)		€ 780						£ 99						€ 1 449
NYHA I						£ 65					£ 65			
NYHA II						£ 65					£ 65			
NYHA III						£ 143					£ 143			
NYHA IV						£ 195					£ 195			
Drug treatment (CRT+OPT) (yearly cost)		€ 815						£ 99						€ 1 449
NYHA I						£ 65					£ 65			
NYHA II						£ 65					£ 65			
NYHA III						£ 143					£ 143			
NYHA IV						£ 195					£ 195			
Implantation (device, leads, capital, surgery & stay)														
CRT-P		€ 7 500	€ 9 420	€ 7 630	€ 12 316	£ 5 074	€ 9 409	£ 8 106	€ 10 580.14	$ 20 500	£ 5 074	$ 33 495	$ 33 495	
CRT-D	€ 26 540		€ 31 239	€ 23 500	€ 29 286	£ 17 266	€ 23 578			$ 29 500	£ 17 266			
ICD						£ 11 596					£ 11 596			
Device & leads cost (without surgery nor stay)														
CRT-P														€ 5 279
CRT-D														€ 22 194
LV-lead cost (without surgery nor stay)							€ 844							
Unsuccessful LV-lead implantation		€ 2 300	€ 2 080	€ 1 830	€ 3 985			£ 4 266	€ 2 300.00					
LV-lead reoperation			€ 2 080	€ 1 830	€ 5 044									
Periprocedural death		€ 36 500												
CS dissection or perforation requiring intervention		€ 340												
Pneumo- or haemothorax		€ 2 400												
Cardiac tamponade		€ 2 400												
Phrenic nerve stimulation		€ 190												
Lead dislodgement or failure (revision)	€ 3 128							£ 2 885	€ 4 872.25			$ 30 997	$ 30 997	
LV-lead		€ 1 800				£ 1 624					£ 1 624			
ICD-lead						£ 857					£ 857			
Infection														
CRT-P		€ 6 800				£ 9 384		£ 8 106	€ 11 327.96		£ 8 853		$ 30 997	
CRT-D	€ 2 273					£ 20 625					£ 21 045			
ICD						£ 19 785					£ 15 375			

Table 8.5.: Costs (continued)

	Aidelsburger	Banz	Blomström			Bond	Calvert	Caro	Fattore	Feldman	Fox	McAlister	Nichol	Yao
Prices valid for	2005	2002	2006			2005 (2006 for drugs)	2001-2005	2004	2004	2004	2005 (2006 for drugs)	2003	2003	2001-2005
Principal source of cost data	DE	DE	DK	FI	SE	NHS	CARE-HF & NHS	CARE-HF	IT	COMPANION	NHS	Owens & Kaul	US	Calvert
Country perspective (ISO 3166-1 code)	DE	DE	DK	FI	SE	UK	UK	UK	IT	US	UK	US	US	UK
Outpatient follow-up (yearly cost)						£ 194					£ 194			
OPT		€ 360												
CRT+OPT		€ 455												
Outpatient follow-up and drug treatment (yearly cost)														
OPT	€ 892													
CRT+OPT	€ 971													
All-cause hospitalisation (including device-related)														
OPT										$ 10 683				
CRT-P+OPT										$ 8 330				
CRT-D+OPT										$ 8 854				
Non-elective hospitalisation for heart failure						£ 1 298				$ 9 142	£ 1 298	$ 15 427	$ 15 427	
OPT		€ 5 921†						£ 11 040†	€ 3 091.51	$ 8 375				
CRT-P+OPT		€ 2 590†						£ 5 264†	€ 3 091.51	$ 8 632				
CRT-D+OPT										$ 8 799				
Non-elective hospitalisation for arrhythmia						£ 606				$ 6 922	£ 606			
Battery replacement (including procedure)														
CRT-P						£ 4 687				$ 7 849	£ 3 320	$ 28 835	$ 28 835	
CRT-D						£ 14 391				$ 20 461	£ 15 024			
ICD						£ 11 526					£ 11 526			
Percutaneous coronary intervention	€ 4 439		€ 6 947	€ 6 121	€ 5 416		€ 3 356							€ 3 356
without stent										$ 11 183				
with stent or acute myocardial infarction										$ 13 114				
Coronary artery bypass graft	€ 10 851		€ 15 958	€ 14 342	€ 14 966		€ 8 710							€ 8 710
Heart transplantation	€ 26 978		€ 67 955	€ 51 216	€ 109 151	£ 34 024	€ 33 160			$ 96 143	£ 34 024			€ 33 160
Conversion rate							€ 1.47 = £ 1							€ 1.47 = £ 1

Note:

† Not published in cited paper, but here approximately calculated from the published mean resource use data.

8.4.2 Costs

Table 8.4 and Table 8.5 provide an overview of all cost items included in each of the considered evaluations. A number of economic evaluations had direct access to the actual per patient cost data of a major trial and for this reason do not mention specifically all cost items. This is the case for Calvert[67] and Caro[2] who obtained actual costs from the CARE-HF trial,[1] as well as Feldman[66] who obtained actual cost data from COMPANION.[25]

8.4.2.1 Cost of optimal pharmacological therapy

The cost of the optimal pharmacological treatment (OPT) in the form of prescription medication is, depending on each evaluation, treated in different ways (see also Table 8.4):

- Aidelsburger,[68] Blomström,[69] Fattore,[65] Feldman,[66] McAlister,[61] and Nichol[62] did not consider the optimal pharmacological treatment cost specifically in their economic evaluation. In these evaluations it was decided to do so because all treatment groups (i.e. OPT, CRT-P+OPT and CRT-D+OPT) received OPT.
- Caro[2] and Yao[3] did include a specific cost for OPT, but did not differentiate across treatment groups. Please, note that the *total* OPT cost of each treatment group can still be different due to the different mortality rates in both groups. Furthermore, note that the cost of OPT differs significantly among these authors; respectively £99 and € 1 449 (£ 972) on a yearly basis or respectively £ 0.27 and € 3.97 (£ 2.66) on a daily basis. This is remarkable since both authors state to have estimated drug cost from CARE-HF[1] and both work from the same UK country perspective with comparable reference years.

Table 8.6.: Proportion of drugs at baseline in CARE-HF[1] according to Caro[2]

Characteristic	Base case proportion
Pharmacological treatment	
Digitalis	43%
Diuretic	99%
ACE-inhibitor	95%
Beta-blocker	72%

- Banz[63] and Calvert[67] included specific OPT costs differentiated over the treatment groups,
- Whereas Bond[70] and Fox[6] included specific OPT costs differentiated in function of the NYHA classification.

Of the authors excluding OPT costs, some give an explanation why. Blomström[69] excluded drug costs from the evaluation for reason of no observed significant differences between the treatment groups in terms of pharmacological consumption during the CARE-HF trial.[1] Whereas Feldman[66] excluded drug costs from the evaluation because of no significant observed difference across the three treatment groups at the date of last follow-up in the COMPANION trial[25] (based on unpublished data from M.R. Bristow on about 90% of patients in each treatment group.)

8.4.2.2 Implantation cost

The cost of implantation for the different economic evaluations is tabulated in Table 8.4. This cost item generally includes the cost of the pulse generator (CRT-P or CRT-D), the leads, the surgery cost of the implantation as well as the cost of the related hospital stay. The only exception is Yao[3] who specifically mentioned the price of the implantable devices (i.e. pulse generator and leads) free of any costs for surgery or hospital stay. In the latter evaluation, the hospitalisation cost related to the implantation was actually calculated via a resource use model.

8.4.2.3 Cost of periprocedural complications

The remainder of Table 8.4 shows the cost of periprocedural complications as taken into account by many but not all economic evaluations. Over all evaluations combined, the following periprocedural complications have been identified, most of which can be considered as serious adverse events:

- Unsuccessful left-ventricular (LV-) lead implantation, often implying an LV-lead reimplantation,
- Periprocedural death,
- Coronary sinus (CS) dissection or perforation requiring an intervention,
- Pneumo- or haemothorax,
- Cardiac tamponade,
- Phrenic nerve stimulation,
- Lead dislodgement or failure often implying a revision,
- Device infection.

8.4.2.4 Cost of out-patient follow-up

Only three evaluations, namely Banz,[63] Bond[70] and Fox,[6] specifically mentioned the cost of out-patient follow-up (Table 8.5), of which only Banz counted different follow-up costs per treatment group. Other evaluations either did not take into account follow-up costs, hence considering these equal over the treatment groups, or had direct access to the actual per patient follow-up costs of a trial.

8.4.2.5 Hospitalisation costs

The treatment effect in trials is measured most objectively when all causes of hospitalisation are taken into account in an equal way. All-cause hospitalisation comprises both elective and non-elective or acute hospitalisations, including device-related hospitalisations. Only Blomström,[69] Calvert[67] and Feldman[66] had access to the all-cause per patient hospitalisation cost data of a trial (Table 8.1). Other economic evaluations had to resort to taking into account only non-elective hospitalisations for heart failure (HF) and, in a few cases (Bond[70] and Fox[6]), also non-elective hospitalisations for arrhythmia, apart from a number of additional interventions. (Additional interventions are described in subsubsection 8.4.2.7.)

Of the evaluations not based on trial data registries, Banz,[63] Caro[2] and Yao[3] deduced their cost for non-elective HF hospitalisations on fairly intricate resource-use models that were diversified per treatment group (Table 8.7). In the case of the former two, these were sufficiently detailed allowing us to approximately calculate the non-elective HF hospitalisation cost per treatment group and contrast these values with those of other evaluations (Table 8.5). In that respect, it is interesting to see that both Banz and Caro calculated with substantially more expensive HF hospitalisations for the OPT group as compared to the CRT+OPT group, which effectively influences outcomes in favour of CRT. This stands in contrast to the other evaluations where HF hospitalisation costs are considered equal for both treatment

groups, or where trial-based cost differences slightly favour the OPT group, as is the case with Feldman.[66]

8.4.2.6 Battery replacement cost

The economic evaluations with a longer time horizon inevitably included the cost of battery replacement (Table 8.5) which comprises the cost of the pulse generator (CRT-P or CRT-D) without leads as well as the related costs of surgery and hospital stay.

8.4.2.7 Cost of additional interventions

A surprising number of evaluations took into account the cost of additional cardiovascular interventions (Table 8.5) which, apart from percutaneous coronary interventions (PCI) and heart transplantation, are rather rare with advanced heart failure patients, according to the COMPANION data as presented by Feldman.[66]

8.4.3 Resource use

8.4.3.1 Use of healthcare resources

Healthcare resource use (Table 8.7) generally includes hospital stay in different wards, outpatient follow-ups and primary care in the form of general practitioner (GP) visits, most of which details were discussed in the preceding section. However, interestingly, the evaluation of Calvert[67] is unique in also, very appropriately, counting the use of residential and nursing homes as well as revalidation centres.

8.4.3.2 Device longevity

As mentioned before, economic evaluations differ with regard to whether the cost of device replacement is accounted for or not, and this in function of the time horizon of the evaluation. For example; Banz,[63] Caro[2] and Fattore[65] did not take into account device replacements (Table 8.7) because their respective time horizons are one, five and three years (Table 8.1). Economic evaluations with longer time horizons of seven years or lifetime, mostly did take into account battery replacement, however in varying ways:

- In some evaluations it was assumed that all devices fail after a specified number of years.
- Other evaluations assumed an annual or monthly probability of battery replacement, either from start or after a number of years. Feldman[66] for instance, modelled a monthly probability of battery depletion for the Guidant Contak TR model 1241 CRT-P and the Contak CD model 1823 CRT-D, based on manufacturer estimates. These estimates comprised 46 different device settings. Modelling a monthly replacement probability from the start appears actually an elegant way to also account somewhat for device failures and/or recalls.

Pulse generator life is generally estimated between 6 to 6.5 years for CRT-P devices and 1 to 1.5 years less for CRT-D. Notable exceptions are Calvert[67] who puts the lifespan for both device types in his model equal to 6 years and Yao[3] who assumes that modern CRT-Ds outlast CRT-Ps by one year, to total a relatively optimistic 7 years CRT-D device life.

Table 8.7.: Resource use

	Aidelsburger	Banz	Blomström			Bond	Calvert	Caro	Fattore	Feldman	Fox	McAlister	Nichol	Yao
Principal source of resource use data	not applicable	MIRACLE	CARE-HF			Fox	CARE-HF	CARE-HF	Banz, MIRACLE & Nichol	COMPANION	not applicable	Systematic review	PRAISE 2	CARE-HF
Country perspective (ISO 3166-1 code)	DE	DE	DK	FI	SE	UK	EU	UK	IT	US	UK	US	US	UK
Hospitalisation costs (cost per day)														
Intensive care unit		€ 940	€ 1 482	€ 1 809	€ 3 172		€ 1 715							
Coronary care unit			€ 630	€ 695	€ 1 285		€ 456							
Cardiac ward			€ 536	€ 500	€ 572		€ 240	£ 215						
Other wards		€ 340	€ 580	€ 249	€ 488									
Cardiac day case							€ 165		€ 310					€ 82
Revalidation centre							€ 263							
Residential home							€ 78							
Nursing home							€ 111							
Cardiac outpatient visit (cost per visit)			€ 188	€ 74	€ 318	£ 97	€ 91				£ 97			
Primary care (GP) visit							€ 41							
Resource use	2 linked models	2 linked models	trial data			model	trial data	model	model	model based on trial data	model		model	CARE-HF probabilities
OPT														
Mean number of hospitalisations per patient								2.263 events						
Mean number of hospitalisations per hospitalised patient		1.5 events												
Mean duration of a hospitalisation		15.50 days						22.69 days						
								99×β(0.407,4.142)						
In intensive care unit		1.09 days												7.6 days
In coronary care unit														7.8 days
In normal ward		14.42 days												
Mean duration of a non-elective hospitalisation														11.80 days
Mean duration of an elective hospitalisation														7.16 days
CRT+OPT														
Mean number of hospitalisations per patient								1.764 events						
Mean number of hospitalisations per hospitalised patient		1.4 events												
Mean duration of hospitalisation		7.00 days						13.88 days						
								94×β(0.3164,4.052)						
In intensive care unit		.35 days												5.7 days
In coronary care unit														6.8 days
In normal ward		6.65 days												
Mean duration of a non-elective hospitalisation														11.80 days
Mean duration of an elective hospitalisation														5.68 days
Mean duration of a device-related hospitalisation												5 days	5 days	
Idem for an implantation							5 days							3.3 days
Device life in years														
CRT-P	1 – 7, base case: 2 years	not applicable	6			6.5	6	not modelled	not modelled	6.0	6.5	10.8% annual replacement	10.8% annual replacement	6
CRT-D						5.5	6			4.5	5.5			7
ICD						5.0					5.0			

8.4.4 Transition probabilities

CRT-related decision analytic models and Markov models require a fair amount of transition probabilities that have been listed in the subsequent tables (Table 8.8 to Table 8.12). With this respect, it is important to note that the transition probabilities of one specific economic evaluation are generally listed relative to the probability period applied in the model of that economic evaluation.

8.4.4.1 Risk of periprocedural complications

The transition probabilities for implantation success and periprocedural complications including periprocedural death are summarised in Table 8.8 except for those of the Yao[3] evaluation which have been listed separately in the upper part of Table 8.9. Incidentally, this evaluation is the only one to detail success probabilities in function of the implantation attempt number.

Table 8.9.: Periprocedural and NYHA class transition probabilities according to Yao[3]

	Expected rate	Success	Failed	Total	Distributions
Implantation history (inclusive of CRT and control group in CARE-HF)[a]					
First attempt	0.87	409	60	469	Beta
Second attempt	0.86	62	10	72	Beta
Third attempt	0.80	8	2	10	Beta
	NYHA class I	NYHA class II	NYHA class III	NYHA class IV	
Transition probability in first month after implant between NYHA class[b]					
CRT(±ICD)					
NYHA class III	0.298	0.459	0.227	0.016	Dirichlet
NYHA class IV	0.091	0.455	0.409	0.045	Dirichlet
MT					
NYHA class III	0.103	0.303	0.528	0.067	Dirichlet
NYHA class IV	0.000	0.200	0.600	0.200	Dirichlet
Long-term monthly transition probability between NYHA class[c]					
CRT(±ICD)					
NYHA class in current cycle					
NYHA class I	0.906	0.075	0.016	0.003	Dirichlet
NYHA class II	0.067	0.896	0.033	0.004	Dirichlet
NYHA class III	0.007	0.121	0.864	0.009	Dirichlet
NYHA class IV	0.048	0.048	0.181	0.723	Dirichlet
MT					
NYHA class I	0.7956	0.1245	0.0738	0.0061	Dirichlet
NYHA class II	0.0710	0.8448	0.0765	0.0077	Dirichlet
NYHA class III	0.0047	0.0893	0.8845	0.0216	Dirichlet
NYHA class IV	0.0000	0.1064	0.1064	0.7872	Dirichlet

[a]Indicates the rate of implant success based on data from the CARE-HF trial.
[b]The probability that NYHA class III/IV patients will transition to NYHA class I–IV in the month following CRT (±ICD) implantation is shown.
[c]The probability that patients in NYHA class I–IV will remain in their current class or move to a different class each month is shown. Probabilities are given for patients on MT receiving a CRT (±ICD) device and for those receiving MT alone.

Source: Yao et al.[3]

8.4.4.2 Risk of hospitalisation

All evaluations included lower all-cause hospitalisation risks for the CRT (-P and -D) group compared to OPT (Table 8.10), except for Feldman[66] where the hospitalisation rate equalises over the treatment groups after 24 months. A number of studies expressed the hospitalisation propability in the CRT groups as a risk ratio (RR) or hazard ratio (HR) relative to hospitalisation risk in the OPT group.

The sources for hospitalisation rates were the following:
- Cleland et al.[1] reporting the CARE-HF trial for Blomström,[69] Calvert,[67] Caro[2] and Yao,[3]
- Bristow et al.[25] reporting the COMPANION trial for Aidelsburger[68] and Feldman,[66]
- Abraham et al.[22] reporting the MIRACLE trial for Banz[63] and Fattore,[65]
- Pooled results from respectively five or nine randomised and controlled trials (RCTs) (see notes of Table 8.10) for Bond,[70] Fox,[6] McAlister[61] and Nichol.[62]

Table 8.8.: Periprocedural transition probabilities

	Aidelsburger	Banz		Blomström	Bond	Calvert	Caro	Fattore				Feldman		Fox	McAlister	Nichol	Yao
Principal source of transition data	COMPANION & Banz	MIRACLE		CARE-HF	Fox	CARE-HF	CARE-HF	Banz, MIRACLE & Nichol				COMPANION		PenTAG review[1]	Systematic review	9 trials[2]	CARE-HF & COMPANION
Country perspective (ISO 3166-1 code)	DE	DE		DK FI SE	UK	EU	UK	IT				US		UK	US	US	UK
Probability period	first 0.5 year	first month	first 0.5 year first year		4-week cycle	29.4 months	5 years	first 0.5 year	first year	first 2 years	first 3 years	per month [0,24]	per month]24,...	4-week cycle	yearly	yearly	monthly
Successful implantations																	
CRT-P												87.4%					See separate table.
CRT-D	91.0%	92.5%										90.9%					See separate table.
ICD																	
Procedural failure																	
CRT-P		7.2%			9.38%		9.40%							9.38%			See separate table.
CRT-D	8.5%				9.38%									9.38%			See separate table.
ICD																	
Average number of implantation attempts																	
CRT-P												1.07					
CRT-D												1.09					
ICD																	
Periprocedural complication																	
CRT-P					10.63%									10.63%			
CRT-D					10.63%									10.63%			
ICD														10.63%			
CS dissection or perforation requiring intervention		0.5% of non-failures															
Pneumo- or haemothorax		1% of non-failures															
Cardiac tamponade		0.9% of non-failures															
Periprocedural death																	
CRT-P		0.3%			0.76%			0.3%	0.3%	0.3%	0.3%			0.76%	0.4%	0.67%	
CRT-D	1.8%				0.76%									0.76%			
ICD														0.76%			
Lead dislodgement or failure (revision)																	
CRT-P		0.7% of non-failures	5.2%		1.5%		16.0%	5.2%	5.2%	5.2%	5.2%			1.5%	13.7%	13.7%	
CRT-D	5.2%				1.5%									1.5%			
ICD					0.0%									0.0%			
Phrenic nerve stimulation		1.3% of non-failures															
Infection																	
CRT-P			1.3%		0.22%		0.8%	1.3%	1.3%	1.3%	1.3%			0.22%	2.0%	2.0%	
CRT-D	1.3%				0.22%									0.22%			
ICD														0.22%			

Note:

[1] The PenTAG systematic review was commissioned by NICE and included data from the MUSTIC-SR, MIRACLE, CONTAK-CD, COMPANION and CARE-HF trials.

[2] Nine-trial review including MUSTIC-SR, MUSTIC-AF, Garrigue et al. 2002, PATH-CHF, CONTAK-CD, MIRACLE, MIRACLE-ICD, COMPANION and Leclercq et al.

Elective hospitalisations The evaluation of Yao[3] is sole in employing a transition probability for elective hospitalisations which, unsurprisingly, is higher in the CRT treatment groups.

Hospitalisation probabilities in function of treatment group or NYHA class Both Caro[2] and Yao[3] assigned probabilities to the different NYHA classes rather than to the treatment groups. All other evaluations assigned probabilities to the treatment groups directly.

Extrapolation of hospitalisation rates Most evaluations assumed hospitalisation rates to remain constant over the full time horizon. This is the case for Bond,[70] Caro,[2] Fox,[6] McAlister,[61] Nichol[62] and Yao,[3] whereas Aidelsburger, Banz and Calvert did not extrapolate hospitalisation rates.

Fattore[65] extrapolated the risk for hospitalisation in the first six months to risks of hospitalisation in the first, second and third year.

In Feldman,[66] monthly hospitalisation rates for the first 24 months are based on the observed data in the COMPANION trial,[25] whereas beyond 24 months, the monthly admission rate is based on the one observed during the months 19 to 24 averaged across the three treatment groups of the COMPANION trial.

8.4.4.3 Risk of additional interventions

As mentioned before, a number of evaluations took into account the risk of additional cardiovascular interventions such as percutaneous coronary interventions (PCI) and heart transplantation (Table 8.11).

Probability of battery replacement Only two evaluations, McAlister[61] and Nichol[62] included battery replacement as a risk instead of specifying a device lifespan.

Upgrade probability Both Bond[70] and Fox[6] employed the probability of an upgrade to ICD or CRT-D in their model, whereby the Bond evaluation is based on the data of the Fox evaluation. However, in the Fox evaluation, 0.15% is listed for OPT in the original citation of the CARE-HF[1] data, which was rounded to 0.2% both in the model summary tables of both Fox and Bond. (The evaluations of Fox and Bond actually originated from the same working group.) The rounding error is substantial when compared to the corresponding upgrade probability for the CRT-P+OPT group (0.05%). In the first mentioning, the upgrade probability for the OPT group is three times higher as for CRT-P+OPT, whereas in the latter, mentioning this rounded upgrade probability appears to be four times higher.

8.4.4.4 Mortality

As can be inferred from Table 8.12, all economic evaluation models considered a mortality reduction for the CRT-P+OPT, and when applicable, the CRT-D+OPT treatment group versus OPT. Baseline mortality and hazard risks in the retained evaluations were either derived from Cowie et al.,[71] MIRACLE,[22] CARE-HF[1] and/or COMPANION[25] trial data or data pooled from five or nine RCTs (see notes of Table 8.12).

Table 8.10.: Transition probabilities of hospitalisations

	Aidelsburger	Banz		Blomström	Bond	Calvert	Caro	Fattore				Feldman		Fox	McAlister	Nichol	Yao
Principal source of transition data	COMPANION & Banz	MIRACLE		CARE-HF	Fox	CARE-HF	CARE-HF	Banz, MIRACLE & Nichol				COMPANION		PenTAG review[1]	Systematic review	9 trials[2]	CARE-HF & COMPANION
Country perspective (ISO 3166-1 code)	DE	DE		DK FI SE	UK	EU	UK	IT				US		UK	US	US	UK
Probability period	first 0.5 year	first month	first 0.5 year	first year	4-week cycle	29.4 months	5 years	first 0.5 year	first year	first 2 years	first 3 years	per month [0,24]	per month]24,...	4-week cycle	yearly	yearly	monthly
All-cause hospitalisation (incl. device-related)																	
OPT	21.7%						226.3%	18.7%	37.3%	65.4%	86.6%	11.7%	8.9%				
CRT-P+OPT							176.4%	13.6%	27.2%	47.7%	63.1%	9.8%	8.9%				HR 0.79 [0.613,1.019]
CRT-D+OPT	19.7%											9.7%	8.9%				HR 0.79 [0.613,1.019]
NYHA I							26%/year										
NYHA II							42%/year										HR 1.184 [0.818,1.715]
NYHA III							79%/year										HR 1.834 [1.265,2.659]
NYHA IV							181%/year										HR 4.991 [2.974,8.376]
Non-elective hospitalisation for heart failure																	
OPT			15.1%	25.0%	3.81%									3.81%	56.0%	56.0%	
CRT-P+OPT			7.9%	13.0%	RR 0.65 [0.45,0.94]									HR 0.65 [0.45,0.94]	RR 0.68	RR 0.68	
CRT-D+OPT					RR 0.65 [0.45,0.94]									HR 0.65 [0.45,0.94]			
ICD+OPT					RR 1.00									HR 1.00			
Non-elective hospitalisation for arrhythmia																	
OPT					0.77%									0.77%			
CRT-P+OPT					0.77%									0.77%			
CRT-D+OPT					0%									0%			
ICD+OPT					0%									0%			
ICU stay given non-elective hospitalisation																	
OPT																	7.15%
CRT-P+OPT																	9.08%
CRT-D+OPT																	9.08%
CCU stay given non-elective hospitalisation																	
OPT																	25.62%
CRT-P+OPT																	31.55%
CRT-D+OPT																	31.55%
Elective hospitalisation																	
OPT																	17%
CRT-P+OPT																	20%
CRT-D+OPT																	20%

Note:

Square brackets [,] indicate 95% confidence intervals

[1] The PenTAG systematic review was commissioned by NICE and included data from the MUSTIC-SR, MIRACLE, CONTAK-CD, COMPANION and CARE-HF trials.

[2] Nine-trial review including MUSTIC-SR, MUSTIC-AF, Garrigue et al. 2002, PATH-CHF, CONTAK-CD, MIRACLE, MIRACLE-ICD, COMPANION and Leclercq et al.

Table 8.11.: Transition probabilities of additional interventions

	Aidelsburger	Banz		Blomström	Bond	Calvert	Caro	Fattore				Feldman		Fox	McAlister	Nichol	Yao
Principal source of transition data	COMPANION & Banz	MIRACLE		CARE-HF	Fox	CARE-HF	CARE-HF	Banz, MIRACLE & Nichol				COMPANION		PenTAG review[1]	Systematic review	9 trials[2]	CARE-HF & COMPANION
Country perspective (ISO 3166-1 code)	DE	DE		DK FI SE	UK	EU	UK	IT				US		UK	US	US	UK
Probability period	first 0.5 year	first month	first 0.5 year	first year	4-week cycle	29.4 months	5 years	first 0.5 year	first year	first 2 years	first 3 years	per month [0,24]	per month]24,...	4-week cycle	yearly	yearly	monthly
Battery replacement																	
CRT-P															10.8%	10.8%	
Upgrade to ICD or CRT-D post HF hospitalisation																	
OPT					0.2%									0.15%			
CRT-P+OPT					0.05%									0.05%			
Percutaneous coronary intervention																	
OPT	0%					1.73%						3.1%					
CRT-P+OPT						1.47%						2.0%					
CRT-D+OPT	0%											0.5%					
Coronary artery bypass graft																	
OPT	0%					0.25%											
CRT-P+OPT						0.00%											
CRT-D+OPT	0%																
Heart transplantation post HF hospitalisation					0.14%									0.14%			
OPT	0.9%		0.9%	4.0%		2.23%						0.9%					
CRT-P+OPT			0.0%	3.0%		2.44%						0.2%					
CRT-D+OPT	0.0%											1.0%					

Note:

[1] The PenTAG systematic review was commissioned by NICE and included data from the MUSTIC-SR, MIRACLE, CONTAK-CD, COMPANION and CARE-HF trials.

[2] Nine-trial review including MUSTIC-SR, MUSTIC-AF, Garrigue et al. 2002, PATH-CHF, CONTAK-CD, MIRACLE, MIRACLE-ICD, COMPANION and Leclercq et al.

All-cause mortality versus cause-specific mortality The most objective way to measure mortality effects of a therapy is by only considering effects in all-cause mortality. The following evaluations included reductions of all-cause mortality: Aidelsburger,[68] Banz,[63] Blomström,[69] Calvert,[67] Caro,[2] Fattore,[65] Feldman,[66] McAlister[61] and Nichol.[62] Other evaluations classified mortality by cause. In Bond[70] and Fox[6] only heart failure death, sudden cardiac (arrhythmic) death and death by other causes were considered. The model of Yao[3] is yet different in that it took as inputs: the absolute risk of all-cause death given a hospitalisation, sudden cardiac death and death by other causes.

Extrapolation of mortality rates beyond trial end-date Mortality rates beyond trial end-date are treated differently among the models. Some evaluations extrapolated mortality by fitting survival curves to trial data, others assumed constant mortality rates over the remainder of their time horizon.

The following evaluations fitted survival curves to trial data:
- Blomström[69] extrapolated up to six years using exponential survival curves based on the CARE-HF trial.[1] Beyond six years, mortality rate equalised in both groups, following an exponential survival curve estimated from the treatment groups combined.
- Both Bond[70] and Fox[6] extrapolated using Weibull distributions based on CARE-HF trial data.
- Calvert[67] extrapolated survival curves beyond the CARE-HF trial using exponential, Weibull, log-normal, and log-logistic models. The exponential model was selected as having the best fit based on the Akaike information criterion.
- Feldman[66] extrapolated survival curves by fitting an exponential survival model to the COMPANION trial data.[25]
- Yao[3] extrapolated using a Weibull distribution with hazard ratios deduced from the CARE-HF and COMPANION trial.

The following evaluations assumed constant mortalities:
- Aidelsburger,[68]
- Caro,[2]
- Fattore,[65]
- McAlister[61] and
- Nichol.[62]

Banz[63] did not present the need to extrapolate given the short time horizon. Most evaluations assumed that the treatment effect present in trials continues over the remainder of the time horizon of the model. Only Blomström's[69] evaluation assumed that the treatment effect disappears after 6 years.

Age and other mortality risk-modifiers Age-dependent risk-modifiers for mortality rates were solely employed in the evaluations of Bond,[70] Fox[6] and in the sensitivity analysis of Yao.[3] In Caro,[2] and Yao death hazards were modified in function of NYHA class. Moreover, Yao is the only evaluation to express the ICD-effect of a CRT-D over a CRT-P as a hazard ratio of 0.367 [CI: 0.215, 0.626] (Table 8.12).

Table 8.12.: Mortality

	Aidelsburger	Banz			Blomström	Bond	Calvert	Caro	Fattore				Feldman		Fox	McAlister	Nichol	Yao
Principal source of transition data	COMPANION & Banz	MIRACLE			CARE-HF	Fox	CARE-HF	CARE-HF	Banz, MIRACLE & Nichol				COMPANION		PenTAG review[1]	Systematic review	9 trials[2]	CARE-HF & COMPANION
Country perspective (ISO 3166-1 code)	DE	DE			DK FI SE	UK	EU	UK	IT				US		UK	US	US	UK
Probability period	first 0.5 year	first month	first 0.5 year	first year		4-week cycle	29.4 months	5 years	first 0.5 year	first year	first 2 years	first 3 years	per month [0,24]	per month]24,...	4-week cycle	yearly	yearly	monthly
Survival of non-elective hospitalisation																		Weibull: λ=0.051 γ=0.77
Heart failure death																		
OPT						Weibull: λ=0.0027 γ=1.21									Weibull: λ=0.0027 γ=1.21			
CRT-P+OPT						RR 0.68 [0.46,0.98]									HR 0.68 [0.46,0.98]			
CRT-D+OPT						RR 0.68 [0.46,0.98]									HR 0.68 [0.46,0.98]			
ICD+OPT						RR 0.95 [0.74,1.21]									HR 0.95 [0.74,1.21]			
Sudden cardiac death																		
OPT						Weibull: λ=0.0015 γ=1.29									Weibull: λ=0.0015 γ=1.29			
CRT-P+OPT						RR 0.75 [0.45,1.18]									HR 0.75 [0.45,1.18]			HR 0.522 [0.318,0.858]
CRT-D+OPT						RR 0.44 [0.23,0.86]									HR 0.44 [0.23,0.86]			
ICD+OPT						RR 0.37 [0.27,0.50]									HR 0.37 [0.27,0.50]			
NYHA I								2%/year										Weibull: λ=0.0058 γ=0.9206
NYHA II								7%/year										HR 1.014 [0.532,1.931]
NYHA III								10%/year										HR 1.014 [0.519,1.978]
NYHA IV								44%/year										HR 0.891[0.249,3.187]
ICD-effect																		HR 0.367 [0.215,0.626]
Cardiac death																		
OPT																20.3%	20.3%	
CRT-P+OPT																RR 0.6	RR 0.6	
CRT-D+OPT																		
ICD+OPT																		
All-cause death given hospitalisation																		
OPT																		11.3%
CRT-P+OPT																		7.4%
CRT-D+OPT																		
All-cause death																		
OPT	9.1%		6.3%	19.0%			exp. extrapolation of Kaplan-Meier curve: 14.3% at 1year	47.1%	12.4%	24.7%	43.3%	57.3%	1.7%	1.7%		24.3%	24.7%	
CRT-P+OPT			4.9%	15.0%			exp. extrapolation of Kaplan-Meier curve: 9.4% at 1year	34.8%	9.8%	19.5%	28.2%	45.9%	1.3%	1.3%		RR 0.75	RR 0.79	
CRT-D+OPT	5.8%												1.1%	1.1%				

Note:

Square brackets [,] indicate 95% confidence intervals

[1] The PenTAG systematic review was commissioned by NICE and included data from the MUSTIC-SR, MIRACLE, CONTAK-CD, COMPANION and CARE-HF trials.

[2] Nine-trial review including MUSTIC-SR, MUSTIC-AF, Garrigue et al. 2002, PATH-CHF, CONTAK-CD, MIRACLE, MIRACLE-ICD, COMPANION and Leclercq et al.

8.4.5 Utilities

Besides increased survival, an improvement in health-related quality of life (QoL) may also contribute to the effectiveness of the studied therapies. Health-related quality of life can be expressed as a utility value.

8.4.5.1 Sources for utility values

Table 8.13.: Sources of utilities and their distribution

	Principal source of utilities	Source of utility distribution
Aidelsburger	Lewis	Distribution assumptions primarily based on registry data.
Banz	Lewis	Distribution assumptions primarily based on registry data.
Blomström	Calvert	Based on exponential mixed EQ-5D & MLWHF interpolation with the last observation carried forward
Bond	Calvert, Kirsch & McAlister	CARE-HF NYHA-class distribution at baseline, 90 days & 18 months
Calvert	CARE-HF	Based on exponential mixed EQ-5D & MLWHF interpolation of CARE-HF data with the last observation carried forward
Caro	CARE-HF	CARE-HF MLWHF data
Fattore	Lewis	Distribution from Banz, Abraham & Ricci, improvements from MIRACLE
Feldman	COMPANION	COMPANION MLHFQ data with carry-forward
Fox	Calvert, Kirsch & McAlister	CARE-HF distribution with straight-line interpolation
McAlister	Own survey	(Not applicable)
Nichol	Own survey	(Not applicable)
Yao	CARE-HF	CARE-HF EQ-5D data

The evaluations at hand cited several sources for the utility weights:

Lewis Lewis[72] measured the utilities for different severities of heart failure. The utility estimates were derived from a sample of people with advanced heart failure, rather than from a sample of general public opinion. Lewis utility values were used by Aidelsburger,[68] Banz[63] and Fattore.[65]

Kirsch Kirsch[73] used the time trade-off technique with a representative but relative small sample of 64 members of the British public to derive NYHA class-specific utility estimates. The utility data of Kirsch was used by Bond[70] and Fox[6] for NYHA classes I and II.

CARE-HF trial In this trial, the EuroQol[a] five-dimensional (EQ-5D) self-reported generic preference-based health utilities were assessed at baseline and at 90-days. In addition, Minnesota Living With Heart Failure Questionnaire (MLWHFQ) scores were assessed at baseline, 90 days, 18 months and at the end of the study. The data from the CARE-HF trial was used by Bond[70] (for NYHA classes III and IV), Calvert,[74,67] Caro,[2] Fox[6] (for NYHA classes III and IV) and Yao.[3]

Calvert[74] converted the EQ-5D health states at baseline and 90 days into utilities using UK general population preference data. The MLWHFQ scores were translated into utilities at 18 months and end-of-study using a mixed model of the relationship between change in EQ-5D score to change in MLWHFQ score and accounting for baseline EQ-5D, MLWHFQ scores and clinical variables, with clinical centres as random effects. The utility scores for the different NYHA classes (at baseline) were not reported but could be derived from other data

a. http://www.euroqol.org/

published in that report.[a] It is also interesting to note is that of the 813 patients enrolled, fifty (6.2%) patients were NYHA class IV. Nevertheless, of the 748 patients that responded about mobility, only nine (1.2%) reported extreme problems with mobility. This seems to indicate that most of the NYHA class IV patients were still somewhat ambulant.

Blomström[69] used utility data as reported in the health-economic evaluation by Calvert.[67] Bond[70] and Fox[6] only employed the utility values of NYHA class III and IV as reported in the utility publication by Calvert.[74] Caro[2] independently converted the MLWHF score of the CARE-HF trial to an EQ-5D score using a published regression equation derived from the CARE-HF trial,[b] whereas Yao[3] employed the EQ-5D utility scores as registered in the CARE-HF trial[1] at baseline and 90 days.

COMPANION trial Feldman[66] derived utilities from the MLWHFQ scores as registered in the COMPANION trial,[25] following the Havranek algorithm. However, the correlation between the measured utilities and the MLWHF score resulted weak ($r_2 = 0.1$ only for the curvilinear equation derived by Havranek and colleagues.)[6] The utility scores as obtained for the different NYHA classes were not reported.

McAlister The utilities employed in the health-economic evaluation by McAlister[61] were obtained by applying standard gambling technique on a sample of elderly adults in the USA, using health state descriptions developed by cardiologists from Health Utilities Index descriptors. Nichol[62] who collaborated with McAlister, employed this very same technique, however with a smaller sample size of 66 instead of the 90 of McAlister. The utility data from McAlister was used by Bond[70] and Fox[6] for the heart failure hospitalisation state. In that sense, the work of McAlister is unique in having derived a utility weight for a description of "congestive heart failure severe enough to require hospitalisation."

a. The baseline estimate for all CARE-HF trial participants was 0.6 (95% CI 0.58 to 0.62), and the mean EQ-5D utility score for NYHA class III participants was 0.17 greater than for NYHA class IV participants; therefore, the NYHA class III- and IV-specific utility values can be calculated and are 0.61 and 0.44, respectively.[6]

b. $EQ-5D\,utility = 0.9554 - Norm(0.00795, 0.00046) \times MLWHF$

8.4.5.2 Overview of utility estimates

Figure 8.2 shows for HF hospitalisation and the different NYHA classes the utility estimates as published in the above-mentioned works. As can be inferred from this graph, HF utility estimates vary substantially between publications for the same NYHA class. The same can be said for the differences in utility between adjacent NYHA classes compared over the various publications. These utility differences or spread is notably higher with Kirsh[73] and Lewis,[72] hence allowing for more utility to be gained in health-economic simulations. Finally, it needs to be noted that the utility values as published by McAlister[61] and Nichol[62] appear to be relatively high, e.g. 0.84 for NYHA class III, whereas Caro[2] reported a value of 0.86 for the asymptomatic NYHA I class patients of the same age. The values given by McAlister and Nichol need to interpreted preferably as relative utility preferences rather than absolute utility values.

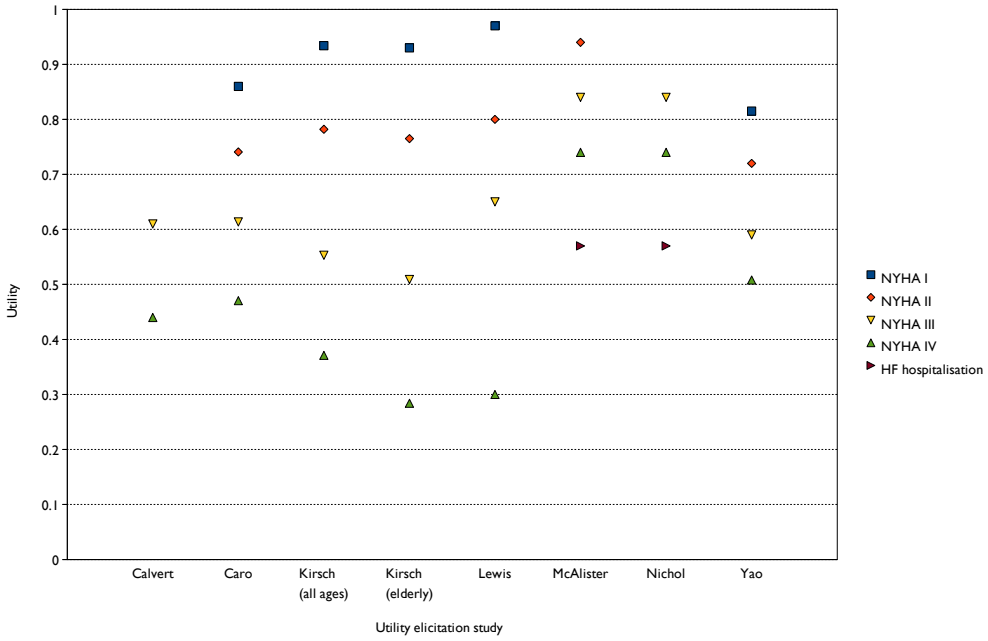


Figure 8.2.: Published utility estimates for living with different severities of heart failure

8.4.5.3 Improvement in health-related QoL

Improvement in health-related quality of life can enter a health-economic model in one of the following manners:

- Either directly based on the per patient utility weights as registered over time in one or more trials, or
- By grouping the simulated patients by NYHA class and then assigning a NYHA class-specific utility weight to patients in each class. Over time, and triggered by interventions and different transition probabilities, patients change NYHA class and therefore associated quality of life.

The first method receives our preference as it is less prone to errors. For each of the retained health-economic evaluations Table 8.14 shows how improvement in quality of life was incorporated.

Table 8.14.: Utility values with their distribution over treatment groups and NYHA classes

	Aidelsburger	Banz		Blomström	Bond	Calvert	Caro	Fattore	Feldman			Fox			McAlister	Nichol	Yao
Principal source of utility values	Lewis	Lewis		Calvert	Calvert, Kirsch & McAlister	CARE-HF	CARE-HF	Lewis	COMPANION			Calvert, Kirsch & McAlister			Survey	Survey	CARE-HF
Principal source of utility distribution	Banz	MIRACLE		Calvert	Calvert	CARE-HF	CARE-HF	Banz	COMPANION			CARE-HF			not applicable	not applicable	CARE-HF
Time	post-implantation	base-line	month [0,6]	month [0,12]					base-line	month 3	month 6	baseline	90 days	18 months			
Utilities																	
NYHA I	0.97		0.97			0.93		0.86	0.97				0.93				0.815
OPT	0%	0%	0%	0%								0.0%	10.1%	12.7%			
CRT-P+OPT	20%	0%	20%	20%								0.0%	29.5%	31.5%			
NYHA II	0.80		0.80			0.78		0.74	0.80				0.78		0.94		0.720
OPT	0%	0%	0%	0%								0.0%	29.9%	37.3%			
CRT-P+OPT	55%	0%	55%	55%								0.0%	41.5%	44.4%			
NYHA III	0.65		0.65		0.61	0.61	0.61	0.61	0.65				0.61		0.84	0.84	0.590
OPT	90%	90%	90%	90%								93.8%	54.8%	45.7%			
CRT-P+OPT	20%	90%	20%	20%								93.8%	27.2%	22.5%			
NYHA IV	0.30		0.30		0.44	0.44	0.44	0.47	0.30				0.44		0.74	0.74	0.508
OPT	10%	10%	10%	10%								6.2%	5.2%	4.3%			
CRT-P+OPT	5%	10%	5%	5%								6.2%	1.8%	1.5%			
Non-elective hospitalisation for heart failure						0.57							0.57		0.57	0.57	
Utilities																	
OPT									0.61	0.68	0.70						
CRT-P+OPT									0.61	0.78	0.79						
CRT-D+OPT									0.61	0.77	0.77						
Conversion of MLWHF to utility							0.9554 -Norm. (0.00795, 0.00046) × MLWHF		MLHFQ to utility conversion formula is cited.								

Improvement in OPT patients Some evaluations like Aidelsburger[68] and Banz[63] assumed no improvement of NYHA class for the OPT group. Other evaluations like Caro[2] did include a possibility of NYHA class improvement with OPT, based on the findings of the clinical trials.[22,1,25]

Improvement in CRT-P patients Improvement of NYHA class/preference weights was either based on:
- MIRACLE,[22] as is the case with Fattore,[65] or
- CARE-HF,[1] as is the case with Blomström,[69] Bond,[70] Calvert,[67] Caro,[2] Fox[6] and Yao,[3] or
- COMPANION,[25]as is the case with Feldman,[66] or
- other registry data, as is the case with Banz,[63] or
- simply not taken into account as in the case of McAlister[61] and Nichol.[62]

Improvement in CRT-D patients In those studies that evaluated CRT-D, improvement in NYHA class/preference weights was assumed equal to that of CRT-P patients. This was also the case with the CRT-D+OPT versus OPT evaluation of Aidelsburger[68] (no CRT-P+OPT), who used the same improvement sources as Banz.[63]

8.4.5.4 Extrapolation of QoL improvements

Most models assumed constant NYHA class or constant utilities, either after:
- 6 months: Feldman,[66]
- 12 months: Aidelsburger,[68]
- 18 months: Bond[70] and Fox,[6]
- 42 months: Caro,[2] or
- the end of the CARE-HF trial[1] (i.e. 29.4 months): Blomström.[69]

These models effectively assumed that initial utility gains are never lost to disease progression except at death, which is in contradiction with the prognosis of heart failure. The approach of Yao[3] was completely distinct from the previous, in that constant monthly transition probabilities between NYHA classes and dependent on the current NYHA-class were assumed to continue on the long term.

8.4.6 Results of the economic evaluations

8.4.6.1 Base case analyses

The base case outcomes of the retained health-economic evaluations are summarised in Table 8.15. As can readily be appreciated from this table, ICERs for a same comparison between treatment groups vary substantially among evaluations; for example for CRT-P+OPT versus OPT the highest reported ICER is US$ 107 800/QALY, compared to a lowest value of € 3 571/QALY (Quality-Adjusted Life Year). We purposely refrain from commenting any further on these outcomes because they are inherently nontransferable to country perspectives other than the intended. This is mainly due to the fact that costs are only valid in the country of analysis. Furthermore, resource use is largely determined by clinical practice (e.g. length of hospital stay) and is therefore also mainly country-dependent. However, one remark needs to be made: The evaluation of Feldman[66] compared CRT-D+OPT with OPT whereas CRT-P+OPT data was also available. As outlined in section 8.1, since CRT-P+OPT has a better cost-effectiveness than CRT-D+OPT, it is only reasonable from a health-economic point of view to compare CRT-D+OPT with CRT-P+OPT. For the latter comparison, approximate outcomes were calculated from the published data. Outcomes obtained in this manner are indicated in Table 8.15 with a dagger symbol.

Table 8.15.: Outcomes of health-economic evaluations

	Aidelsburger	Banz	Blomström			Bond	Calvert	Caro	Fattore	Feldman	Fox	McAlister	Nichol	Yao
Prices valid for	2005	2002	2006			2005 (2006 for drugs)	2001-2005	2004	2004	2004	2005 (2006 for drugs)	2003	2003	2001-2005
Base case evaluation limited to	2 years	1 year	lifetime			lifetime	end-of-study 29.4 months	5 years	3 years	7 years	lifetime	lifetime	lifetime	lifetime
Mean cohort / base case age	COMPANION: median 66	DE patient population	CARE-HF: 67, IQR: 60-73			PenTAG[1] base case: 74, range: 35-83	CARE-HF: 67, IQR: 60-73	CARE-HF: 67, IQR: 60-73	64	COMPANION: median 66	PenTAG[1] base case: 74, range:35-83	base case 60, range: 50-70	9-trial review[2]: 60	65
Initial cohort / base case NYHA class	III & IV	III & IV	III & IV			III & IV	III & IV	III & IV	III & IV	III & IV	III & IV	III	III	III & IV
Device life in years														
CRT-P		not applicable	6			6.5	6	not modelled	not modelled	6.0	6.5	10.8% annual replacement	10.8% annual replacement	6
CRT-D	1 – 7, base case: 2 years								not modelled	4.5	5.5			7
ICD											5.0			
Country perspective (ISO 3166-1 code)	DE	DE	DK	FI	SE	UK	EU	UK	IT	US	UK	US	US	UK
Discounted cost										(undiscounted)				
OPT	€ 4 618	€ 4 210	€ 15 834	€ 12 385	€ 16 645	£ 9 367	€ 15 795	£ 4 900	€ 3 110	$ 46 021	£ 9 367	$ 34 700	$ 34 400	€ 39 060
CRT-P+OPT		€ 10 090	€ 20 165	€ 15 635	€ 22 553	£ 20 997	€ 20 110	£ 11 423	€ 13 666	$ 59 870	£ 20 997	$ 67 600	$ 64 400	€ 53 996
CRT-D+OPT	€ 31 292					£ 32 687				$ 82 236				€ 87 350
Life-years gained										(undiscounted)				
OPT				6.72		4.90	1.92	3.66	1.813	3.64				6.10
CRT-P+OPT				7.51		5.80	2.02	3.99	2.055	4.19				8.23
CRT-D+OPT						6.20				4.51				9.16
Discounted QALYs gained										(undiscounted)				
OPT	0.958	0.54		5.11		3.10	1.19	2.39	1.115	2.48	3.10	2.68	2.64	4.08
CRT-P+OPT		0.70		6.02		3.80	1.42	2.82	1.601	3.26	3.80	3.03	2.92	6.06
CRT-D+OPT	1.261					4.09				3.42				6.75
Incremental cost														
CRT-P+OPT vs OPT		€ 5 880	€ 4 331	€ 3 250	€ 5 908	£ 11 630		£ 6 522	€ 10 556	$ 13 800	£ 11 630	$ 32 900	$ 30 000	€ 14 935
CRT-D+OPT vs CRT-P+OPT						£ 11 689				$ 22 400†				€ 33 354
CRT-D+OPT vs OPT	€ 26 674									$ 36 200				€ 48 288
Incremental life-years							0.10							
CRT-P+OPT vs OPT				0.79		0.90		0.33	0.242	0.49				2.13
CRT-D+OPT vs CRT-P+OPT						1.30				0.29†				0.93
CRT-D+OPT vs OPT										0.78				3.06
Incremental QALYs														
CRT-P+OPT vs OPT		0.16		0.91		0.70	0.22	0.43	0.486	0.71	0.70	0.35	0.28	1.98
CRT-D+OPT vs CRT-P+OPT						0.29				0.13†				0.70
CRT-D+OPT vs OPT	0.303									0.84				3.06
ICER (per LY gained)														
CRT-P+OPT vs OPT			€ 6 563	€ 4 048	€ 7 525	£ 12 922	€ 43 596	£ 19 764	€ 43 628	$ 28 100				€ 7 011
CRT-D+OPT vs CRT-P+OPT						£ 8 992				$ 77 241†				€ 35 864
CRT-D+OPT vs OPT	€ 193 996									$ 46 700				€ 15 780
ICER (per QALY gained)														
CRT-P+OPT vs OPT		€ 36 600	€ 4 759	€ 3 571	€ 6 493	£ 16 738	€ 19 319	£ 15 247	€ 21 720	$ 19 600	£ 16 735	$ 90 700	$ 107 800	€ 7 538
CRT-D+OPT vs CRT-P+OPT						£ 40 160				$ 172 308†				€ 47 909
CRT-D+OPT vs OPT	€ 88 143									$ 43 095				€ 18 017
Discount rate for both costs and benefits	3%	not applicable		3%		3.5%	3.5%	3.5%	3%	not mentioned	3.5%	3%	3%	3.5%
Conversion rate							€ 1.47 = £ 1							

Note:

† Not published in cited paper, but here approximately calculated from the published data.

[1] The PenTAG systematic review was commissioned by NICE and included data from the MUSTIC-SR, MIRACLE, CONTAK-CD, COMPANION and CARE-HF trials.

[2] Nine-trial review including MUSTIC-SR, MUSTIC-AF, Garrigue et al. 2002, PATH-CHF, CONTAK-CD, MIRACLE, MIRACLE-ICD, COMPANION and Leclercq et al.

8.4.6.2 Sensitivity analyses

Calvert In Calvert,[67] the cost-effectiveness result for CRT-P+OPT versus OPT was found to be robust to:
- Reasonable changes in the estimated lifetime of the device (in the range from 5 to 7 years),
- Various discount rates, and
- Hospitalisation cost.

However, the results were sensitive to changing the cost of the CRT device and to the cost associated with the implantation procedure.

Feldman In Feldman,[66] health-economic outcomes for CRT-P+OPT and CRT-D+OPT versus OPT appeared to be sensitive to:
- The survival benefit of CRT (assuming equalised survival across treatment groups after 24 months instead of continued survival benefit in the base case),
- Increasing Medicare payment rates, and
- The time horizon (the base case was seven years.)

The study furthermore demonstrated that increasing the time horizon from 2 to 7 years reduced the ICER considerably (from $ 109 700/QALY to $ 38 500/QALY).

Banz Banz[63] conducted a best- and worst-case scenario by varying the values of the most sensitive model parameters comprising of:
- The length of hospital stay,
- The unit cost per hospital day,
- A reduction in the probability of hospitalisation for the CRT group,
- CRT implantation costs, and
- The distribution of patients into the different NYHA classes.

The analysis showed that the results for CRT-P+OPT versus OPT were rather robust with regard to these parameters.

McAlister and Nichol Results for CRT-P+OPT versus OPT appeared sensitive in both McAlister[61] and Nichol[62] to reasonable changes in the value of:
- The relative risk for death,
- The relative risk for hospitalisation,
- The mortality due to lead failure or battery replacement,
- A greater health-related quality of life for CRT-P+OPT, and
- A lower risk for device-related adverse effects.

Bond and Fox Extensive one-way sensitivity analyses in the Bond[70] and Fox[6] evaluations showed that the cost-effectiveness of CRT-P+OPT and CRT-D+OPT were sensitive to a number of model input parameters:
- In the case of CRT-P+OPT versus OPT: time horizon, age, discount rate, device lifetime, arrhythmic event with CRT-P, perioperative mortality, sudden cardiac death with CRT-P, heart failure death with CRT-P, heart failure death with ICD,
- In the case of CRT-D+OPT versus CRT-P+OPT: time horizon, age, discount rate, device lifetime (of both device types), arrhythmic event with CRT-P, infection with CRT, sudden cardiac death and hearth failure death with CRT-P and CRT-D.

Caro Sensitivity analyses by Caro[2] indicated that the results are most sensitive to the time horizon and the implantation costs and, to a smaller extent, sensitive to the length of stay, the mortality at implantation, the risk of lead-revision, the cost of hospitalisation and the discount rate. Age, gender, the initial NYHA class, the risk of unsuccessful implantation, the hazard of re-implantation and the costs of unsuccessful implantation or revision were found to have little influence on the model outcome.

Yao Whilst the base case of the Yao[3] evaluation assumed a starting age of 65, the extent to which this patient starting age (and thus life expectancy) affected the results was examined through sensitivity analyses.

8.5 Discussion

Please, refer to chapter 11 for a discussion about data of some of the above-mentioned health-economic evaluations that was used as input to our Belgian health-economic model.

KEY POINTS

- **The outcomes of the health-economic models presented in this chapter are not immediately transferable to the Belgian context. This is mainly due to country-specific differences in what cost items need to be considered (i.e. differences in the organisation of health care), differences in the amounts of these costs, as well as differences in clinical practice and in health care resource use (e.g. the length of hospital stay).**
- **The cost-effectiveness literature review presented in this chapter aims at providing input data for the Belgian cost-effectiveness model presented in the succeeding chapter.**
- **If the cost-effectiveness ratio of CRT-P+OPT turns out to be lower than that of CRT-D+OPT, CRT-P+OPT becomes the relevant comparator for CRT-D+OPT for its incremental cost-effectiveness ratio (ICER).**
- **Utility estimates vary substantially between various publications, both in their absolute value for the same NYHA class as in their increment between adjacent NYHA classes. Indirect measurement of utility values for the different treatment groups through NYHA classification may be unreliable.**
- **The obtained ICERs vary considerably across the health-economic evaluations, both for CRT-P+OPT as for CRT-D+OPT.**

9 Belgian cost-effectiveness model

In this chapter, the cost effectiveness of CRT-P and CRT-D versus relevant comparators is calculated. In the methods section several aspects of the model are described: analytic technique, perspective, time window and discounting, population, intervention and comparator, model structure, and input parameters. Belgian pharmaco-economic evaluation guidelines[75] are followed and more details are provided in the relevant sections. Details on both sensitivity and scenario analyses are also provided. In a subsequent section, results are presented.

9.1 Methods

9.1.1 Analytic technique

A Markov simulation model is developed in Excel in order to assess the efficiency of CRT-P and CRT-D implantation. Both cost-effectiveness (with outcomes expressed in life-years gained) and cost-utility analyses (with life-years gained adjusted for quality of life) are performed. The @Risk adds-on tool is used for probabilistic modelling and probabilistic sensitivity analyses. Half-cycle corrections were performed.

9.1.2 Perspective

In accordance with the Belgian pharmaco-economic guidelines, the analysis includes direct health care costs from the perspective of the health care payer. Payments out of the government's health care budget as well as patients' co-payments are included. Since baseline employment rates are expected to be low in this population, indirect productivity costs are ignored.

9.1.3 Time horizon and discount rate

A lifetime horizon is applied since we build a model for a chronic disease (heart failure). For the base-case, conform to the Belgian guidelines, future costs and benefits are discounted at a rate of 3% and 1.5%, respectively. These rates are changed in scenario analyses (subsubsection 9.1.9.2).

9.1.4 Population

The model simulates a hypothetical cohort of 1,000 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. In the base case scenario, our population is 67 years old and 67.4% of them is male, which reflects the COMPANION trial population.[25] A health economic evaluation of CRT in NYHA I/II patients has not been done because of insufficient data being available. In these patients, no studies have been performed that directly compare CRT with optimal medical treatment.

9.1.5 Intervention and comparators

The interventions of interest are CRT-P and CRT-D. CRT-P or CRT-D can be implanted on top of providing optimal medical treatment (OPT), which is also the initial comparator for CRT-P. The comparator for CRT-D is the previous intervention on the cost-efficiency frontier, i.e. probably CRT-P.

9.1.6 Model

The primary endpoints considered in the review of effectiveness are mortality and hospitalisation (due to heart failure). This is reflected in our Markov model which tracks a cohort of 1000 patients who receive either OPT or CRT-P or CRT-D (Figure 9.1). Patients receiving a CRT-P or CRT-D are faced with a procedure-related mortality. Each month (the length of a Markov cycle), patients are at risk of death (death due to heart failure, sudden cardiac death and death due to other causes altogether). Survivors receive OPT each month, are at risk of hospitalisation due to heart failure and may receive an upgrade (from OPT to ICD and from CRT-P to CRT-D). In this part we provide information on (transition) probabilities. Details on costs are provided in the next part (subsection 9.1.7).

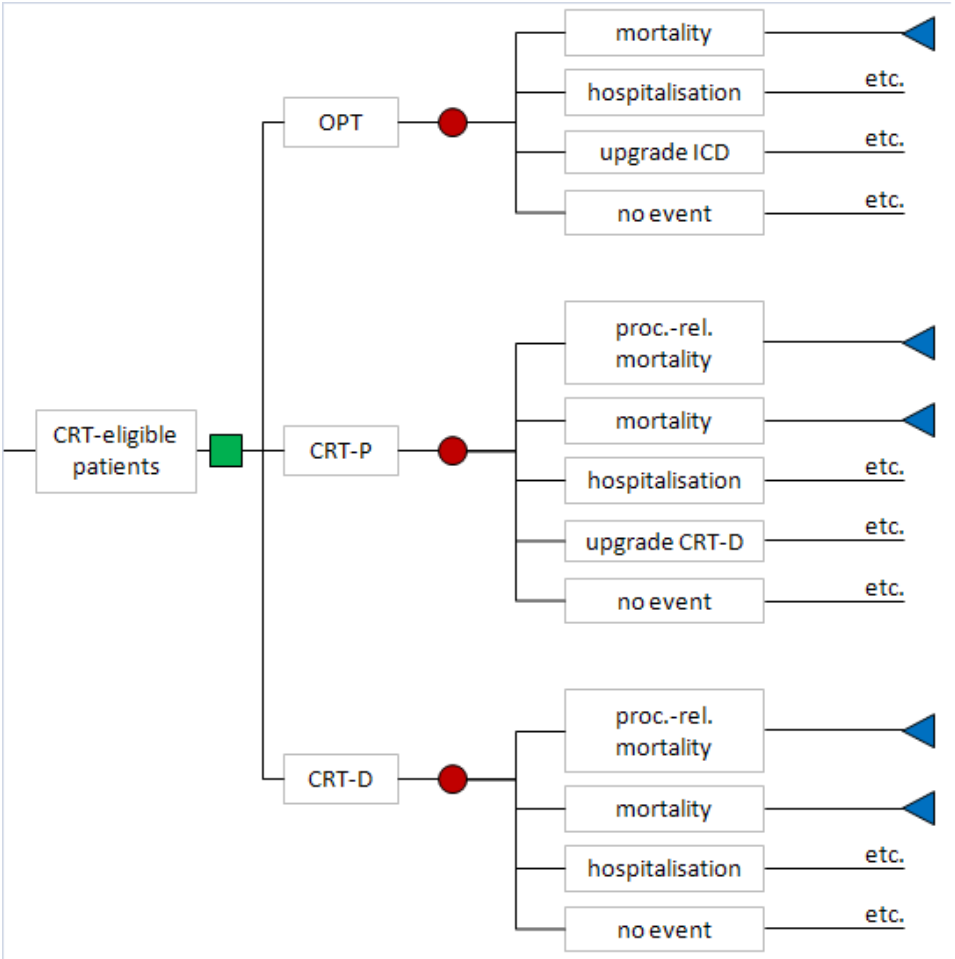


Figure 9.1.: CRT-P/D decision model

CRT: cardiac resynchronisation therapy; CRT-P: CRT in combination with a conventional pacemaker; CRT-D: CRT in combination with a conventional defibrillator; ICD: implantable cardioverter defibrillator. The green square is a choice node, the red dots are chance nodes and the blue triangles are end nodes.

9.1.6.1 Mortality (treatment effect and extrapolation)

Several approaches are used to model survival for the three alternative treatments. The choice of the base case will depend on how realistic the results of the models are. This will be checked by looking at mortality after one year, which is about 12.6% in the CARE-HF and 19% in the COMPANION trial (see Table 7.13), and the number of patients alive at very old ages (e.g. >105 years). The modelled approaches for mortality are as follows (also see Table 9.3):

1. Feldman et al.[66] used all-cause mortality data from the COMPANION trial to estimate exponential survival functions for each treatment group to establish the monthly probability of death. This was 0.017, 0.013 (p=0.059) and 0.011 (p=0.003) for the OPT, CRT-P, and CRT-D group, respectively (see Table 8.12). In fact, these are rounded numbers. Applying the reduced risk of 24% and 36% for CRT-P and CRT-D (see subsection 4.2.3), results in a monthly probability of 0.01292 and 0.01088, respectively. The uncertainty around these numbers was incorporated with a normal distribution. For CRT-P, the 97.05% (i.e. 1-0.059/2) value equalled 0.017. For CRT-D, this was the 99.9985% value (i.e. 1-0.003/2). Based on these data, we calculated the 95% CI for CRT-P and CRT-D related monthly mortality (see Table 9.1).
   In the COMPANION trial, for mortality, the median duration of follow-up was 14.8 months, 16.5 months, and 16.0 months, for the three groups, respectively.[25] Extrapolation starts after month 16 for the three groups in our model. Three extrapolation scenarios were applied:

   a) The monthly probability of death was kept constant as in the model of Feldman et al. (*mortality scenario 1*)
   b) The monthly probability of death was made time-dependent by adding the absolute increase in monthly mortality in the normal (age- and sex-adjusted) Belgian population (*mortality scenario* 2).
   c) The monthly probability of death was made time-dependent by increasing this probability proportionally in accordance with the proportional increase of the age- and sex-adjusted all-cause mortality of the Belgian population (*mortality scenario* 3).

These scenarios considered the effect of resynchronisation therapy on all-cause mortality. This is a robust approach since it is difficult to subclassify causes of death in patients with cardiovascular disease.[76]

2. The study of Bond et al.[70]/Fox et al.[6] approximated the rate of heart failure death and sudden cardiac death in patients receiving medical therapy using Weibull distributions ($S(t) = exp(-lambda \times t^{gamma}, H(t) = lambda \times t^{gamma}$ *or* $tp(t_u) = 1 - exp[H(t-u) - H(t)]$ with S(t) the survivor function, H(t) the cumulative hazard function and tp the transition probability).[77] The probability of death due to heart failure was characterised by the parameters lambda = 0.0027 and gamma = 1.21 (95%CI 1.14 to 1.28). For sudden cardiac death this was 0.0015 and 1.29 (95%CI 1.20 to 1.38), respectively. The gamma values larger than 1 imply that the probabilities of death from heart failure and sudden cardiac causes increase with each model cycle in people receiving OPT.[70] Fox et al. assumed that death from other causes was equivalent to the risk of such an event from the general population. We incorporated the original numbers from this UK study in this modelling scenario (Table 9.1). Total mortality was attained by adding heart failure mortality, sudden cardiac deaths and death from other causes. For modelling the treatment effect (tr.eff), the formula $tp(t_u) = 1 - exp\left[lambda \times (t-u)^{gamma} - lambda \times t^{gamma}\right]^{tr.eff}$,[77] is applied. The treatment effect on heart failure due to the device was modelled applying a hazard ratio of 0.68 (95%CI: 0.46 to 0.98) for both CRT-P and CRT-D. For sudden cardiac death this was 0.75 (95% CI: 0.45 to 1.18) for CRT-P and 0.44 (95%CI: 0.23 to 0.86) for CRT-D (Table 9.1).(*mortality scenario 4*)

3. Two other scenarios were built by applying the treatment effect of meta-analyses to the mortality risk of the optimal medical therapy group. Based on Lam et al.,[5] the odds ratio for all cause mortality was 0.67 (95%CI 0.5 to 0.9) for CRT-P (CARE-HF, COMPANION, MUSTIC, MIRACLE) and 0.64 (95%CI 0.46 to 0.9) for CRT-D (COMPANION). Both ratios were modelled using a log-normal distribution (Table 9.1). This treatment effect was applied to the survival of the OPT group from the time-dependent scenarios (i.e. mortality scenario 2 and 3) and is referred to as *mortality scenario 5 and 6*.

Finally, according to Fox et al., there were 21 perioperative deaths in 2757 patients (Table 9.1). This procedure-related mortality was modelled using a beta-distribution. We assumed that this probability is device independent. To avoid double counting, the mortality rate of the first year was adjusted in order to retain the same number of deaths after one year.

Table 9.1.: 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
Proportion male	67%	/	/	/	Companion
Mortality (monthly)					
- based on study Feldman et al. + three extrapolation scenarios after month 16.					
OPT	0,017	/	/	/	Feldman et al., 2005
CRT-P	0,01292	0,00868	0,01716	Normal	Feldman et al., 2005;
CRT-D	0,01088	0,00801	0,01375	Normal	COMPANION trial and own calculations.
- based on study Fox et al./Bond et al.					
OPT		lambda	gamma		
Probability of death due to *heart failure* (HF)	/	0,0027	1,21	Weibull	Fox et al., 2007 and
Probability of *sudden cardiac death* (SCD)	/	0,0015	1,29	Weibull	Bond et al., 2008
Gamma values					
HF	1,21	1,14	1,28	Normal	Fox et al., 2007 and
SCD	1,29	1,20	1,38	Normal	Bond et al., 2008
Annual death rates (events per 1000 people) due to *non-cardiac causes*		male	female		
65-74 years	/	15,9	11,7	/	Fox et al., 2007
75-84 years	/	46,0	33,9	/	Fox et al., 2007
85+	/	129,0	113,9	/	Fox et al., 2007
Treatment effect on HF					
CRT-P and CRT-D	0,68	0,46	0,98	Log-normal	Fox et al., 2007 and
Treatment effect on SCD					Bond et al., 2008
CRT-P	0,75	0,45	1,18	Log-normal	Fox et al., 2007 and
CRT-D	0,44	0,23	0,86	Log-normal	Bond et al., 2008
- based on Feldman et al. and meta-analyses.					
OPT	0,017	/	/	/	Feldman et al., 2005
Treatment effect					
CRT-P	0,67	0,50	0,90	Log-normal	Lam et al., 2007
CRT-D	0,64	0,46	0,9	Log-normal	Lam et al., 2007
Procedure related mortality					
		alpha	beta		
Perioperative deaths	0,76%	21	2736	Beta	Fox et al., 2007
Hospitalisations					
- based on study Feldman et al.					
Monthly probability of hospital admission					
OPT	0,117	/	/	/	Feldman et al., 2005
CRT-P	0,098	0,0707	0,1253	Normal	Feldman et al., 2005 and
CRT-D	0,097	0,0704	0,1236	Normal	own calculations
- based on study Fox et al./Bond et al.					
OPT					
Monthly probability of hospitalisation due to heart failure	0,0381	/	/	/	Fox et al., 2007 and Bond et al., 2008
Treatment effect					Fox et al., 2007 and
CRT-P & CRT-D	0,65	0,45	0,94	Log-normal	Bond et al., 2008
Length of stay					
Primo implantation	7,34	6,2	8,48	Normal	Belgian database
Replacement	4,47	3,53	5,41	Normal	Belgian database
Utility weights					
OPT	0,68	0,63	0,73	Beta	Cleland et al., 2005;
CRT-P	0,78	0,73	0,83	Beta	Calvert et al., 2005;
CRT-D	0,78	0,73	0,83	Beta	Feldman et al., 2005 and
Hospitalisation primo implantation or replacement	0,46	0,41	0,51	Beta	own assumptions.
Costs					
Primo implantation					Belgian database,
CRT-P	9.398 €	8.859 €	9.936 €	Normal	reimbursement tariffs and
CRT-D	23.380 €	22.842 €	23.919 €	Normal	own adaptions.
ICD	27.261 €	26.867 €	27.658 €	Gamma	KCE report ICDs
Replacement					Belgian database,
CRT-P	9.061 €	8.267 €	9.856 €	Normal	reimbursement tariffs and
CRT-D	21.905 €	21.111 €	22.700 €	Normal	own adaptions.
Hospitalisation	5.777 €	1.129 €	17.807 €	Gamma	Technical cel (APR-DRG 194 "heart failure")
Follow-up medication (monthly cost)	30,88 €	29,85 €	31,82 €	Beta for volumes	Belgian database (volumes) and BCFI
Follow-up visits (average monthly cost)	OPT	CRT-P	CRT-D	Beta for	
GP, cardiologist (ECG, echo, integrity check)	52,98 €	71,87 €	90,77 €	volumes	expert opinion
Cross-over/upgrade					
OPT - ICD	0,0015	-50%	+50%	Uniform	Bond et al., 2009
CRT-P - CRT-D	0,0005	-50%	+50%	Uniform	Bond et al., 2009

9.1.6.2 Hospitalisations

Hospitalisation rates are based on Feldman et al.[66] In their study they used hospital admission data of the COMPANION trial to estimate the monthly probability of hospital admission. This was 0.117, 0.098 (p=0.172) and 0.097 (p=0.141) for the OPT, CRT-P, and CRT-D group, respectively. The uncertainty around these numbers was incorporated with a normal distribution. For CRT-P, the 91.4% (i.e. 1-0.172/2) value equalled 0.117. For CRT-D, this was the 92.95% value (i.e. 1-0.141/2). Based on these values we calculated the 95% CI (see Table 9.1). In our model, we assumed these rates to remain the same over the full time horizon (*hospitalisation scenario 1*). This assumption is altered in a scenario analysis (subsubsection 9.1.9.2).

9.1.7 Costs

Unless otherwise stated, the year of costs reflects 2008 values in euros. The consumer price index (CPI) was used to adjust costs.

9.1.7.1 CRT-P/D implantation and replacement

The cost for primo CRT-P and CRT-D implantation is based on real-life data for Belgian CRT-P/D implantations during the period 2008-mid 2009. Based on data from 342 CRT-D primo implantations, the cost was on average €23,380 (95%CI of the mean 22,842 - 23,919), modelled as a normal distribution (based on the central limit theorem). We refer to Appendix C for further details. For CRT-P, we did not rely on the costs in our database since both populations are very different (see subsection 7.2.4), with the CRT-P population being older and with probably very different comorbidities. In our approach, to calculate the cost of CRT-P, the cost for CRT-D was reduced with a theoretically calculated price difference between CRT-D and CRT-P. Based on the 2010 reimbursement tariffs (see Table 3.2), the price for CRT-P is €7,187 (€4,544 + 2 x €571.15 + €1,500.70). Although the latter left ventricular lead is not reimbursed for CRT-P, it is part of the reimbursement question and therefore taken into account. For CRT-D this is €21,170 (€17,388 + €571.15 + (€1,320.98 + €2,098.7)/2 + €1500.7), assuming that 'ICD electrode 1' is used in half of all cases and 'ICD electrode 2' in the other half. This results in a difference of €13,983 between CRT-P and CRT-D. As such, the average cost for CRT-P in our model becomes €9,398 (95%CI of the mean €8,859 - 9,936).

A similar approach was used for replacement costs. Based on Belgian data (n = 121), the CRT-D replacement cost was €21,905 (95%CI of the mean €21,111 - €22,700). With a price difference between the CRT-P and CRT-D device (exclusive leads) of €12,844 (i.e. €17,388 - €4,544), this amounts to €9,061 (95%CI of the mean €8,267 - €9,856) for CRT-P.

Service life was mainly based on expert opinion in other studies. Feldman et al.[66] modelled replacement after 6 years for CRT-P and 4.5 years for CRT-D. Bond et al. and Fox et al.[6] included a service life of 6.5 years for CRT-P and 5.5 years for CRT-D. In our model, we averaged these numbers, i.e. 75 and 60 months for CRT-P and CRT-D, respectively. This was altered in scenario analyses (subsubsection 9.1.9.2).

9.1.7.2 Hospitalisations

The number of hospitalisations was described before (subsubsection 9.1.6.2). The cost per hospitalisation was based on data from the Belgian Technical Cell (www.tct.fgov.be). The cost for "APR-DRG 194 Heart Failure" was on average €5,529 (90%CI 1,233 - 14,132) based on data from more than 19,000 hospitalisations in the year 2007. This cost was included as a gamma distribution and adjusted to 2008 values (CPI 104.5% or on average €5,777).

9.1.7.3 Follow-up

Medication: The drugs taken before CRT primo implantation were analysed for the Belgian CRT population (Table 7.6). In our model, we assumed the amount and type of drugs taken are the same for the three groups since CRT should be given on top of optimal medical treatment. Even though the cost for an individual patient is the same over the three groups, there will be an incremental cost for the cohort since more people survive in the CRT-P/D groups.

The identified drugs, percentage of patients taking them in the Belgian CRT population, and their costs are presented in the following table. Costs are based on the cheapest alternative identified on the website of the Belgian Centre for Pharmacotherapeutic Information (www.bcfi.be, accessed November 2010). The percentage of users is included as a beta distribution with parameters reflecting the values from the Belgian CRT sample. The average monthly drug cost is €30.88 (95%CI 29.85 - 31.82). This cost is assigned to all survivors in the three treatment groups.

Table 9.2.: Costs for medical treatment

Drug	Units/ package	Price/ package	Non-refundable	DDD	Price/ DDD	Use CRT patients	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

DDD: defined daily dose. Antithrombotic agents were not included in this cost since they are not considered being part of optimal medical treatment of HF. For loop diuretics we assumed furosemide and bumetanide were taken in 50/50% of cases.

Visits: Part subsection 7.2.9 describes the ambulatory medical contacts during the first 6 months after CRT-P or CRT-D implantation, with on average about 8 GP visits and 2 visits to the cardiologist. Based on expert opinion, we assumed patients had yearly 4 cardiologist visits (Nomenclature 101032, €19.37) and a GP visit (Nomenclature 102594, €34.02) for the other 8 months of the year. This was modelled applying a beta distribution with the minimum and maximum $\pm 50\%$ above/under the average. For all patients, the cardiologist also performed an ECG (Nomenclature 475075, €16.94) and echo (Nomenclature 469814, €69.24). An integrity check was also performed for CRT-P (Nomenclature 475871, €56.68) and CRT-D (Nomenclature 475893, €113.36). As such, the monthly visit costs for OPT, CRT-P and CRT-D is €52.98 , €71.87 and €90.77, respectively.

9.1.7.4 Cross-over/Upgrade

A possibility for cross-over/upgrade was included in the model. Patients in the OPT group could receive an ICD and 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.[70]/Fox et al.[6] if they survived a serious arrhythmic event. Based on their model, we included an upgrade probability of 0.0015 and 0.0005 per month for the OPT and CRT-P group, respectively. 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 the KCE study on ICDs[21] and amounts to €27,261 (95%CI 26,867 - 27,658), included as a gamma distribution. 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. Our model included replacement costs for initial implantations at fixed time points. Replacement costs for upgrades were not included since small number of initial upgrades in combination with the applied mortality rates result in an even much smaller number of possible replaced upgrades. Therefore, this simplification will very likely not influence results. Also cross-over- or upgrade-related procedural deaths were not explicitly taken into account since we assume this is reflected in the intention-to-treat mortality rates.

9.1.8 Utilities

Our utility values are based on the study of Cleland et al.,[1] Calvert et al.[74] and Feldman et al.[66] These studies gathered QoL data in the CARE-HF and COMPANION trials.

Cleland et al.: In the CARE-HF publication, the NYHA class and QoL were assessed at 90 days using of the Minnesota Living with Heart Failure (MLWHF) questionnaire, a disease-specific QoL instrument, and the EQ-5D instrument, a generic QoL instrument. As compared with patients in the medical-therapy group, patients in the CRT group had a better quality of life at 90 days. The EQ-5D scores were 0.63 (SD 0.29) and 0.70 (SD 0.28) in the OPT and CRT group respectively. The difference of 0.08 (95%CI 0.04 to 0.12) was statistically significant ($p<0.001$).[1] Unfortunately, no measurement of QoL at baseline was reported. As a result it is not sure if this difference can be interpreted as an improvement.

Calvert et al.: The aim of this study was to assess the QoL of patients with heart failure, due to left ventricular dysfunction (NYHA class III or IV), taking optimal medical therapy using baseline QoL assessments from the CARE-HF trial, and to evaluate the appropriateness of using the EQ-5D in patients with heart failure. Their conclusion was that the EQ-5D appears to be an acceptable valid measure for use in patients with heart failure although further evidence of the responsiveness of this measure in such patients is required.[74] The authors also predict that CRT may potentially lead to a 0.1 increase in EQ-5D index score, which was based on the observed relationship between the EQ-5D index and MLWHF scores and the observed 13 point decrease in MLWHF score in the MUSTIC trial.[33]

Feldman et al.: This study made an economic evaluation based on the COMPANION trial. Participants in the COMPANION study completed the MLHFQ questionnaire at baseline (before implantation), month 3, and month 6. Although the survey was not specifically designed to measure utility, a previously published algorithm[78] was used to convert MLHFQ scores to preference weights. At baseline, month 3, and month 6, the utility weight was 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.[66] Thus, also in this study, the difference/improvement in this indirect measurement of QoL was about 0.1.

In our model, we assumed the baseline to be 0.68, i.e. the level after 3 months of OPT treatment in the COMPANION study, according to Feldman et al. We did not choose for the lower baseline level since it is assumed that all our patients already received optimal treatment (and QoL does not further improve) and CRT-P/D may be given on top of that. Secondly, we assume that the improvement for the CRT-P/D groups is 0.1, resulting in a utility weight of 0.78. To model a significant difference, these utility values were included as symmetric beta distributions with an assumed minimum and maximum value of 0.05 below and above the mean value.

Finally, for heart failure hospitalisation, we relied on the study of McAlister et al.[31] In their study, four health states were considered: NYHA functional class II, III, and IV heart failure and heart failure severe enough to require hospitalisation. Hypothetical scenarios were described to illustrate what patients would typically feel and experience if living with each of these health states. The standard gamble technique of eliciting preferences was used. Based on data of 90 respondents, mean utilities for each health state were 0.94 for NYHA class II,

0.84 for NYHA class III, and 0.74 for NYHA class IV heart failure. Results for the hospitalisation were 0.57. Based on this study, we assumed QoL for hospitalisation to be 0.17 to 0.27 lower than the baseline QoL of 0.68 (i.e. the difference between the weights of NYHA class III or IV and heart failure hospitalisation). This results in an average utility weight of 0.46 for hospitalisation. We applied this very rough assumption due to a lack of better direct generic estimates of QoL. This lower utility was only assigned during the hospital stay for the initial implant and replacements, which was on average 7.34 days and 4.47 days, respectively, (see **??**) in the Belgian CRT sample. For other hospitalisations, which do not occur at a predetermined moment in time, we assume that the impact on QoL is expected to be already implicitly reflected in the previously assumed QoL values of 0.68 for OPT and 0.78 for CRT-P/D.

9.1.9 Uncertainty

9.1.9.1 Probabilistic (sensitivity) analysis

The combined impact of uncertainty in the model's input parameters on the results was modelled probabilistically. The used distributions and parameters are mentioned above. 1,000 Latin Hypercube simulations were performed. Given that OPT, CRT-P and CRT-D are all possible policy options, a three-way cost-effectiveness analysis was undertaken. Outcomes are presented for expected survival time, incremental costs, incremental effects, and the incremental cost-effectiveness ratio (ICER). Results are shown on the cost-effectiveness plane and cost-effectiveness acceptability curves.

In our probabilistic sensitivity analysis, rank correlation coefficients are calculated between the output values (the ICERs) and the sampled input values to indicate the relative importance of variables (and their uncertainty) on results. This helps determining the importance of the uncertainty around different input parameters on results.

9.1.9.2 Scenario analyses

Some scenarios are already explained in the previous sections. We bring them together in this part, together with some additional scenarios. Table 9.3 gives an overview of all scenarios.

Mortality: In our initial description on mortality, several scenarios were already mentioned (subsubsection 9.1.6.1). One extra change is added: the monthly probability of death was reduced from 0.017 to 0.01 in the OPT group. As such, the one-year mortality is about 11.4%, i.e. close to the lower estimation of the mean annual mortality rate among patients allocated to the control group in recent large long-term trials, as mentioned by Nichol et al.,[62] which ranged from 11% to 20%. After month 16, the time-dependent increase in mortality was applied for the OPT group and the treatment effect of the CRT-P and CRT-D group was applied to the OPT mortality probabilities for the alternative treatments. (*mortality scenario 7 and 8*)

Hospitalisations: Three scenarios are modelled for hospitalisation rates. The first two scenarios are based on Feldman et al.[66] Details on hospitalisation rates are provided above (subsubsection 9.1.6.2). In the first scenario, we assumed the rates to remain the same over the full time horizon (*hospitalisation scenario 1*). In contrast, Feldman et al. preferred not to extrapolate these probabilities after month 24 and assumed an equal hospital admission rate of 0.089 for the three groups. This was modelled in an alternative scenario (*hospitalisation scenario 2*) (Table 9.3).

The third scenario is based on Bond et al.[70]/Fox et al.[6] They included a monthly probability of hospitalisation due to heart failure with medical therapy of 0.0381. The relative risk of hospitalisation due to heart failure with device (both CRT-P and CRT-D) was 0.65 (95% CI: 0.45 to 0.94), modelled as a log-normal distribution. We incorporated these values in an

alternative scenario and assumed these values to remain the same over the full time horizon(*hospitalisation scenario 3*).

Procedure-related mortality: In the base case scenario, procedure-related mortality was based on data from Fox et al.,[6] being 21 perioperative deaths in 2757 patients (0.76%). In an alternative scenario, this variable was set at 0.42% (13/3113) based on the AHRQ report.[61]

Service life: In the base case the average of the mentioned service life in two other studies was used. In scenario analyses, we included the original data of these two studies.[66,6] Another scenario with equal service life was also included.

Time horizon: In the base case scenario, a life time horizon was applied for this chronic disease. Since extrapolation is surrounded by great uncertainty, results are also presented for a 10-year time horizon.

Discount rate: In the base case scenario, the discount rate for costs and effects is 3% and 1.5%, respectively. In scenario analysis, these rates are changed with equal discounting for both costs and effects (0%, 3% and 5%) and only discounting of costs (3% and 5%).

Age: In the base case scenario, a COMPANION-like population was included. The mean age was 67 years. In Belgium, the average age for CRT-P and CRT-D patients at first implant (period 2008-2009) was on average 69 years. In the HTA report of Fox and colleagues, the mean age was 74 years, reflecting the patients in UK practice. It would have been interesting to examine the influence of changing age. It is no problem to change the time-dependent increase in mortality which relies on the Belgian life tables. However, we have no information about the influence on other input variables, such as initial mortality, QoL, and hospitalisations. Therefore, we preferred no to model this as it could not be supported by reliable data.

Table 9.3.: Overview modelled scenarios

Mortality
Three extrapolation scenarios (after month 16) on the input data from Feldman - *mortality scenario 1*: constant monthly probability of death - *mortality scenario 2*: time dependent monthly probability of death: add absolute increase in monthly mortality in the normal (age- and sex-adjusted) Belgian population. - *mortality scenario 3*: time dependent monthly probability of death: apply relative increase in monthly mortality in the normal (age- and sex-adjusted) Belgian population.
mortality scenario 4: Weibull survival function based on data from Fox et al., 2007 and Bond et al., 2008.
mortality scenario 5: Monthly probability of death for OPT group from mortality scenario 2 and treatment effect from meta-analyses (Lam et al., 2007). *mortality scenario 6*: Monthly probability of death for OPT group from mortality scenario 3 and treatment effect from meta-analyses (Lam et al., 2007).
mortality scenario 7: The baseline mortality risk of 0,017 is changed to 0,01 (with treatment effect from meta-analyses (Lam et al., 2007) and absolute increase in monthly mortality). *mortality scenario 8*: The baseline mortality risk of 0,017 is changed to 0,01 (with treatment effect from meta-analyses (Lam et al., 2007) and relative increase in monthly mortality).
Hospitalisation
hospitalisation scenario 1: Data from Feldman et al. on (all-cause) hospitalisation, extrapolated over the full time horizon. *hospitalisation scenario 2*: Data from Feldman et al., with monthly probability of hospital admission after month 24 of 0,089 for the three groups. *hospitalisation scenario 3*: Data from Fox et al., on hospitalisations due to heart failure.
Procedure-related mortality
Base case: 21 perioperative deaths in 2757 patients (Fox et al., 2007) *Scenario*: 13/3113 deaths (AHRQ report)
Service life
Base case: CRT-P: 75 months, CRT-D: 60 months *Scenario*: CRT-P: 6 years and CRT-D 4.5 years (Feldmann et al.); CRT-P: 6.5 years and CRT-D 5.5 years (Bond et al./Fox et al.); both 5 years.
Time horizon
Base case: lifetime *Scenario*: 10 years
Discount rate
Base case: 3% for costs and 1,5% for effects *Scenario*: 0%, 3% or 5% for both costs and effects and 0% for effects in combination with 3% or 5% for costs.

9.2 Results

Results of the economic evaluation are described in this part. In the base case, results for all mortality and hospitalisation scenarios are presented. For the sensitivity analysis, we rely on one of these scenarios to test the sensitivity of results for certain input variables (and the uncertainty surrounding them).

9.2.1 Base case (mortality scenarios)

Looking at the extrapolated survival curves (Figure 9.2), two scenarios are excluded as being unrealistic for the real-life situation. Mortality scenario 1, assuming a constant monthly probability of death, results in an overly optimistic survival at high ages. Of the initial cohort of 1000 67-year old patients, 1, 6 and 13 patients reach the age of 100 in the OPT, CRT-P and CRT-D group, respectively. At the age 105, still 3 and 7 patients are alive in the CRT-P and CRT-D group. Constant probabilities may be reasonable when comparing the results of the model with trial data for the first years. However, in the longer term, this provides rather counterintuitive results. Mortality scenario 4 is also excluded since the shape of the survival curves is unrealistic at the longer term (Figure 9.2). This is due to the addition of separate mortality curves (i.e. two Weibull functions for HF death and SCD and another function for non-cardiac deaths). Individually, they may have an acceptable shape, but adding

them together changes this. We still present results for these two scenarios (in light grey) but don't consider them further in this report.

In contrast, mortality scenario 2 and 3 incorporated an age-dependent extrapolation resulting in more realistic survival curves. With an absolute instead of a proportional increase in monthly mortality, according to the normal (age- and sex-adjusted) Belgian population, mortality scenario 2 is the most optimistic one of these two scenarios. Figure 9.2 shows the longer survival of patients in mortality scenario 2 versus 3. Mortality scenario 5-8 are all extensions of mortality scenario 2 or 3.

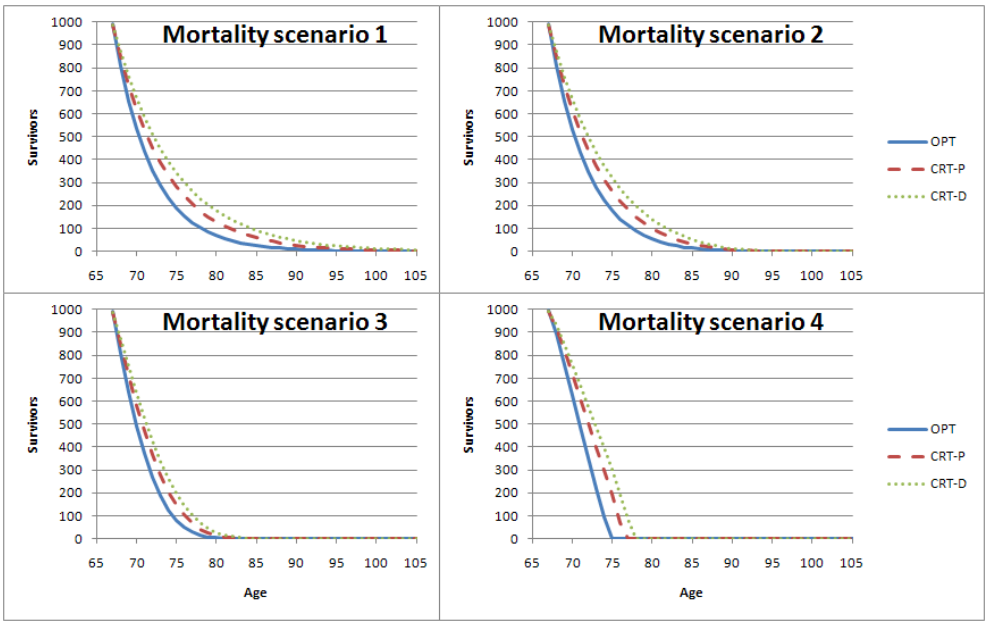


Figure 9.2.: Survival curves for mortality scenario 1-4

CRT-P: The remaining six mortality scenarios can be used to compare CRT-P with OPT. Mortality scenario 2 and 3 are based on COMPANION. Mortality scenario 2, for example, results in an undiscounted life expectancy of 4.6 years for the OPT group (Table 9.4). CRT-P increases the life expectancy with 1.31 years (95%CI -0.04 – 3.21). This difference improves and becomes significant when results of the meta-analysis are used (mortality scenario 5-8). For example, in the fifth scenario this is 1.83 years (95%CI 0.45 - 3.33). In scenario 7, with the lower base case mortality, this increases even further. Mortality scenarios 6 and 8 are the less optimistic age-dependent extrapolations of scenario 5 and 7, respectively.

Overall, for CRT-P, the average incremental cost ranges between €12,200 and €19,600 (Table 9.4). Whether or not this is statistically significant depends on the modelled mortality scenario. In combination with the discounted gain in life expectancy, this results in an average ICER of €10,900 to €15,000 per LYG for CRT-P vs. OPT. If life expectancy is adjusted for QoL, this improves further to €9,600 to €12,600 per QALY gained (Table 9.4).

CRT-D: Since the cost effectiveness of CRT-P vs. OPT is better than the cost effectiveness of CRT-D vs. OPT, CRT-P becomes the appropriate comparator for the more expensive CRT-D intervention. COMPANION is the only study that incorporated both CRT-P and CRT-D in the same study population in a randomised way. In this study, both intervention are compared with OPT, which allows an indirect comparison between CRT-P and CRT-D. Based on mortality scenario 2, CRT-D adds another 0.8 years (95%CI -1.40 – 2.95) on top of CRT-P. Currently, there is no evidence that this improvement would be significant. Mortality scenarios 5 to 8 are less reliable to compare CRT-D with CRT-P 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 has an influence on the reliability of the indirect comparison between CRT-P and CRT-D. These results are presented but not considered further. We also included (in read) the result if CRT-D is compared to OPT to show the influence on the results and thus the importance of applying the correct comparator. Since this is not the correct approach, these results are also not considered further.

Relying on the COMPANION study, the discounted life time incremental cost of CRT-D versus CRT-P is on average €30,900 in mortality scenario 2. In combination with the discounted life gain (8.41 months (95%CI -14.54 - 30.43)), this results in an average ICER of €44,000 per LYG (Table 9.4). Including QoL adjustments, this becomes €56,600 per QALY gained. In mortality scenario 3, ICERs are less favourable for CRT-D, i.e. €51,300 per LYG or €65,900 per QALY gained versus CRT-P.

The following figure (Figure 9.3) shows the cost-effectiveness plane for the most optimistic scenario (i.e. mortality scenario 2). The two figures on the left represent both CRT-P and CRT-D versus OPT (incremental effects expressed as LYG (top) and QALY gained (bottom)). On the right, CRT-P becomes the comparator for CRT-D. These figures clearly show the importance of considering CRT-P as a comparator for CRT-D. The 1000 simulated dots for CRT-D (in blue) are positioned less favourable if CRT-P is taken into account. We also remark that these are the results based on the COMPANION trial with insignificant improvements in mortality for CRT-P vs. OPT (as shown in Figure 9.3). However, based on the meta-analysis of Lam et al.,[5] this becomes significant (see Table 9.4, figure not shown). As mentioned above, there is no evidence that CRT-D improves survival significantly more than CRT-P.

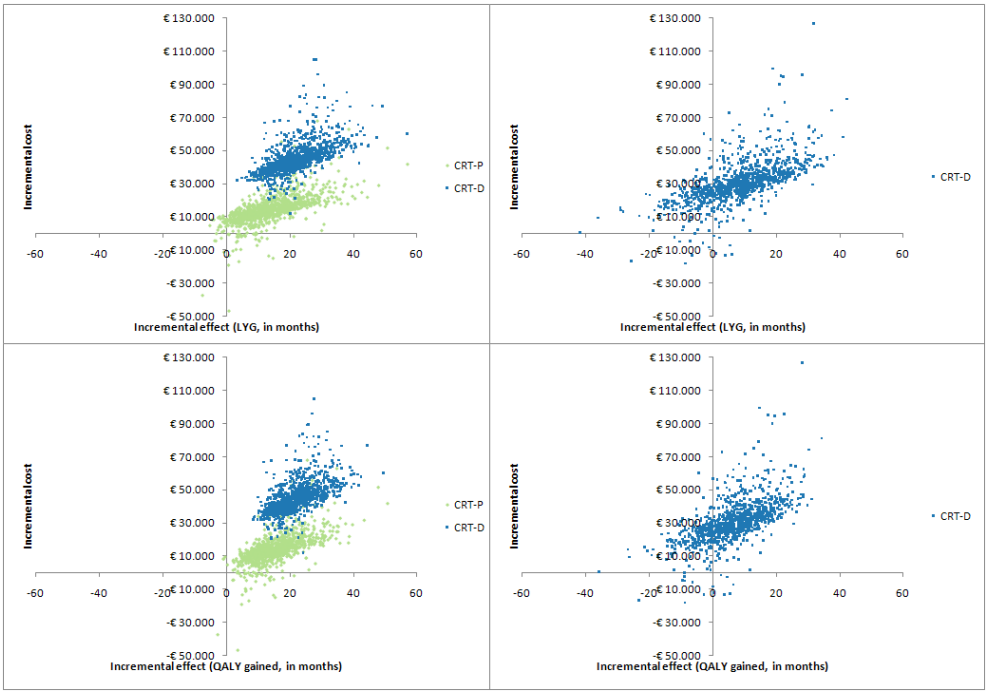


Figure 9.3.: CE-planes CRT-P/D versus OPT (left panel) and CRT-D versus CRT-P (right panel) (mortality scenario 2)

The following figure (Figure 9.4) shows the cost-effectiveness acceptability (CEA)-curves, which present the probability that a certain alternative is cost effective depending on the willingness to pay (WTP) for a QALY gained. The first two parts of this figure compare CRT-P vs. OPT and CRT-D vs. CRT-P. The last part compares all three alternatives at the same time. Again results are presented for mortality scenario 2.

Table 9.4.: IC (in €), IE (in months) and ICERs (€/LYG or €/QALY gained) for CRT-P/D depending on the modelled mortality scenario

mortality scenario		1	2	3	4	5	6	7	8
CRT-P vs OPT	IC	€ 16.910	€ 14.745	€ 12.151	€ 13.592	€ 18.691	€ 15.052	€ 19.646	€ 17.006
		-€ 1.496 € 44.243	-€ 1.935 € 36.008	-€ 1.081 € 27.885	€ 934 € 27.409	€ 3.066 € 43.148	€ 2.691 € 33.158	-€ 1.586 € 46.570	€ 526 € 39.835
	IE (LYG)	17,48	13,79	9,74	11,83	19,30	13,68	21,64	17,20
		-0,49 45,37	-0,43 33,59	-0,31 24,20	1,87 22,37	4,75 34,78	3,31 25,12	5,70 37,29	4,26 31,14
	IE (QALY)	18,91	15,77	11,58	13,64	20,06	14,65	24,48	19,24
		4,73 41,51	4,32 31,72	3,30 23,29	5,37 22,45	8,11 32,29	5,93 23,67	10,95 37,68	8,32 30,66
CRT-D vs OPT	IC	€ 51.181	€ 45.624	€ 37.977	€ 41.994	€ 45.237	€ 37.717	€ 51.970	€ 44.607
		€ 33.088 € 82.861	€ 29.821 € 68.108	€ 25.301 € 55.302	€ 26.003 € 65.766	€ 27.209 € 70.048	€ 23.806 € 56.962	€ 29.484 € 80.135	€ 25.900 € 68.228
	IE (LYG)	28,78	22,19	15,78	19,49	21,50	15,30	23,87	19,18
		11,86 52,52	9,75 38,03	6,82 27,64	6,60 32,71	4,74 39,38	3,30 28,72	5,68 41,59	4,25 35,43
	IE (QALY)	27,71	22,32	16,28	19,60	21,76	15,90	26,20	20,77
		14,05 46,97	11,89 35,42	8,69 26,22	9,30 30,52	8,16 35,53	6,12 26,26	11,08 40,42	8,42 33,30
CRT-D vs CRT-P	IC	€ 34.271	€ 30.879	€ 25.825	€ 28.402	€ 26.547	€ 22.666	€ 32.324	€ 27.602
		€ 5.087 € 71.009	€ 7.183 € 60.263	€ 7.373 € 48.617	€ 9.853 € 56.243	-€ 600 € 57.607	€ 1.807 € 46.949	€ 31 € 70.065	€ 1.066 € 59.106
	IE (LYG)	11,30	8,41	6,04	7,66	2,20	1,63	2,23	1,98
		-20,46 42,47	-14,54 30,43	-10,54 22,53	-5,42 21,17	-19,73 24,37	-14,86 18,20	-20,90 25,67	-17,80 22,23
	IE (QALY)	8,80	6,55	4,70	5,95	1,70	1,26	1,72	1,53
		-16,76 34,21	-12,26 24,82	-9,05 18,10	-4,68 17,71	-16,43 19,91	-11,82 14,43	-17,55 20,78	-14,78 17,85
ICER (LYG)	CRT-P vs OPT	*€ 11.608*	*€ 12.834*	*€ 14.970*	*€ 13.786*	*€ 11.623*	*€ 13.208*	*€ 10.895*	*€ 11.865*
	CRT-D vs OPT	€ 23.234	€ 26.638	€ 31.512	*€ 25.853*	*€ 25.249*	*€ 29.577*	*€ 26.125*	*€ 27.904*
		€ 14.173 € 41.276	€ 16.531 € 46.931	€ 18.883 € 56.923					
	CRT-D vs CRT-P	*€ 36.390*	*€ 44.080*	*€ 51.339*	*€ 44.489*	*€ 144.628*	*€ 167.143*	*€ 173.750*	*€ 166.990*
ICER (QALY)	CRT-P vs OPT	*€ 10.733*	*€ 11.219*	*€ 12.589*	*€ 11.954*	*€ 11.180*	*€ 12.332*	*€ 9.630*	*€ 10.607*
	CRT-D vs OPT	€ 23.304	€ 25.639	€ 29.386	*€ 26.936*	*€ 26.905*	€ 30.874	*€ 23.804*	*€ 25.775*
		€ 15.286 € 38.505	€ 16.920 € 41.385	€ 18.865 € 46.609	€ 17.722 € 44.165	€ 16.875 € 48.954	€ 18.888 € 57.489		
	CRT-D vs CRT-P	*€ 46.721*	*€ 56.615*	*€ 65.941*	*€ 57.271*	*€ 187.479*	*€ 216.672*	*€ 225.848*	*€ 216.807*
Life expectancy (undiscounted)	OPT	4,86 years	4,60 years	3,60 years	3,96 years	4,60 years	3,60 years	7,08 years	5,30 years
	CRT-P	6,59 years	5,90 years	4,49 years	5,04 years	6,43 years	4,85 years	9,20 years	6,92 years
		5,01 8,78	4,72 7,41	3,69 5,53	4,09 6,05	5,24 7,68	4,04 5,73	7,88 10,52	5,87 8,03
	CRT-D	7,73 years	6,71 years	5,04 years	5,75 years	6,64 years	5,00 years	9,43 years	7,11 years
		6,22 9,69	5,67 7,95	4,33 5,93	4,57 7,04	5,27 8,09	4,06 6,03	7,91 10,91	5,90 8,40
	CRT-P vs OPT	1,73 years	1,31 years	0,89 years	1,08 years	1,83 years	1,25 years	2,12 years	1,62 years
		-0,05 4,59	-0,04 3,21	-0,03 2,22	0,17 2,04	0,45 3,33	0,30 2,31	0,55 3,68	0,40 2,96
	CRT-D vs CRT-P	1,14 years	0,80 years	0,55 years	0,71 years	0,21 years	0,15 years	0,22 years	0,19 years
		-2,12 4,35	-1,40 2,95	-0,97 2,05	-0,50 1,96	-1,90 2,36	-1,37 1,68	-2,06 2,54	-1,73 2,13

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 benefit.

The CEA-curves show that OPT is the preferred option if the WTP for a QALY gained is less than €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 (third part in Figure 9.4). If this willingness is more than €30,000, the probability that OPT is cost effective 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 a cost effective alternative. The fact that there is still a probability that CRT-P is cost effective at these high WTP threshold illustrates the uncertainty around the incremental benefit of CRT-D versus CRT-P.

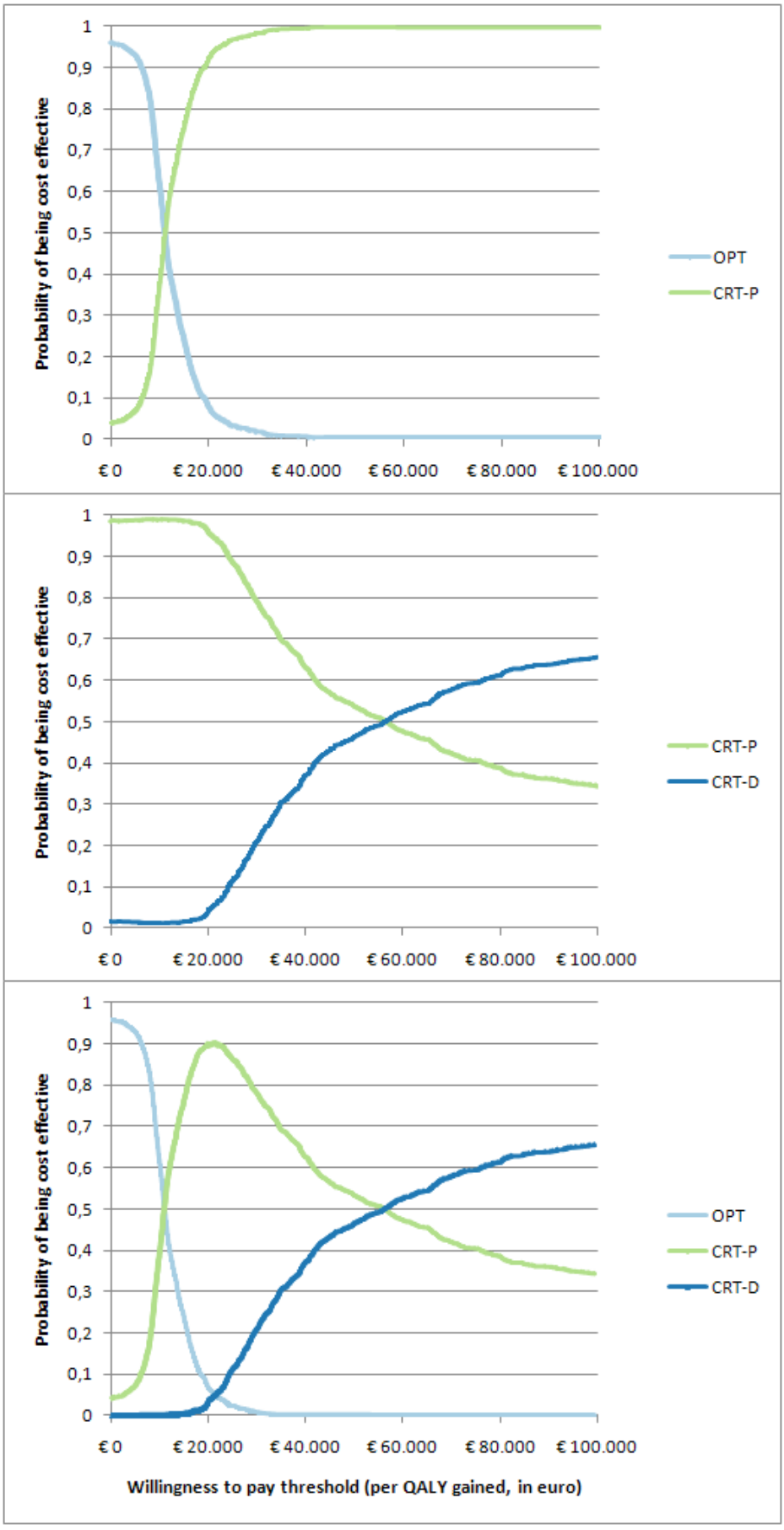


Figure 9.4.: CEA-curves CRT-P vs. OPT, CRT-D vs. CRT-P and for the three alternatives together (mortality scenario 2)

9.2.2 Sensitivity analyses

9.2.2.1 Scenario analyses

The results for the three modelled hospitalisation scenarios are presented in the following table (Table 9.5). The ICERs for CRT-P vs. OPT are not influenced a lot. This is the same for CRT-D vs. CRT-P, which is mainly because the modelled changes apply to both the CRT-P and CRT-D group. As such, incremental costs between both groups remain rather unchanged.

Table 9.5.: IC (in €), IE (in months) and ICERs (€/LYG or €/QALY gained) for CRT-P/D depending on the modelled hospitalisation scenario

mortality scenario 2				
hospitalisation scenario		1	2	3
CRT-P vs OPT	IC	€ 14.745	€ 17.361	€ 11.932
		-€ 1.935 € 36.008	€ 7.418 € 36.036	€ 3.513 € 19.955
	IE (LYG)	13,79	13,79	13,79
		-0,43 33,59	-0,43 33,59	-0,43 33,59
	IE (QALY)	15,77	15,77	15,77
		4,32 31,72	4,32 31,72	4,32 31,72
CRT-D vs OPT	IC	€ 45.624	€ 48.187	€ 40.115
		€ 29.821 € 68.108	€ 36.899 € 70.269	€ 31.159 € 49.508
	IE (LYG)	22,19	22,19	22,19
		9,75 38,03	9,75 38,03	9,75 38,03
	IE (QALY)	22,32	22,32	22,32
		11,89 35,42	11,89 35,42	11,89 35,42
CRT-D vs CRT-P	IC	€ 30.879	€ 30.826	€ 28.183
		€ 7.183 € 60.263	€ 14.088 € 53.032	€ 19.363 € 38.624
	IE (LYG)	8,41	8,41	8,41
		-14,54 30,43	-14,54 30,43	-14,54 30,43
	IE (QALY)	6,55	6,55	6,55
		-12,26 24,82	-12,26 24,82	-12,26 24,82
ICER (LYG)	CRT-P vs OPT	*€ 12.834*	*€ 15.111*	*€ 10.386*
	CRT-D vs OPT	€ 26.638	€ 28.217	€ 23.716
		€ 16.531 € 46.931	€ 17.539 € 47.266	€ 14.988 € 41.253
	CRT-D vs CRT-P	*€ 44.080*	*€ 44.004*	*€ 40.231*
ICER (QALY)	CRT-P vs OPT	*€ 11.219*	*€ 13.210*	*€ 9.079*
	CRT-D vs OPT	€ 25.639	€ 27.133	€ 22.724
		€ 16.920 € 41.385	€ 18.426 € 40.825	€ 15.437 € 34.885
	CRT-D vs CRT-P	*€ 56.615*	*€ 56.518*	*€ 51.671*

Table 9.6 presents the result for the six discount rate scenarios. They are all applied to the most optimistic mortality scenario in combination with the first hospitalisation scenario. The impact on incremental costs and effects are as expected (i.e. increase if discount rate decreases and vice versa). The impact on the ICER depends on the combination of both discount rates for costs and effects. The most favourable ICERs are identified for the fourth scenario with a rate of 5% for costs and no discounting for effects. Overall, ICERs remain favourable for CRT-P vs. OPT. The averages range between €10,300 to €15,400 per LYG and between €9,200 and €12,900 per QALY gained). For CRT-D vs. CRT-P average ICERs range between €35,500 and €54,600 per LYG and €45,600 and €70,100 per QALY gained.

Table 9.6.: Discount rate scenarios (IC (in €), IE (in months) and ICERs (€/LYG or €/QALY gained))

mortality scenario 2		E: 1,5%	E: 0%	E: 0%	E: 0%	E: 3%	E: 5%
hospitalisation scenario 1		C: 3%	C: 0%	C: 3%	C: 5%	C: 3%	C: 5%
discount rate scenario		1	2	3	4	5	6
CRT-P vs OPT	IC	€ 14.745	€ 17.349	€ 14.745	€ 13.483	€ 14.745	€ 13.483
		-€ 1.935 € 36.008	-€ 2.345 € 45.318	-€ 1.935 € 36.008	-€ 1.732 € 31.749	-€ 1.935 € 36.008	-€ 1.732 € 31.749
	IE (LYG)	13,79	15,69	15,69	15,69	12,21	10,49
		-0,43 33,59	-0,47 38,57	-0,47 38,57	-0,47 38,57	-0,39 29,49	-0,34 25,10
	IE (QALY)	15,77	17,58	17,58	17,58	14,25	12,58
		4,32 31,72	4,72 36,03	4,72 36,03	4,72 36,03	3,97 28,30	3,66 24,47
CRT-D vs OPT	IC	€ 45.624	€ 52.854	€ 45.624	€ 42.046	€ 45.624	€ 42.046
		€ 29.821 € 68.108	€ 34.156 € 84.150	€ 29.821 € 68.108	€ 27.491 € 61.815	€ 29.821 € 68.108	€ 27.491 € 61.815
	IE (LYG)	22,19	25,34	25,34	25,34	19,59	16,78
		9,75 38,03	11,03 43,79	11,03 43,79	11,03 43,79	8,69 33,30	7,52 28,25
	IE (QALY)	22,32	25,10	25,10	25,10	20,00	17,47
		11,89 35,42	13,23 40,19	13,23 40,19	13,23 40,19	10,83 31,35	9,55 27,12
CRT-D vs CRT-P	IC	€ 30.879	€ 35.505	€ 30.879	€ 28.563	€ 30.879	€ 28.563
		€ 7.183 € 60.263	€ 5.920 € 72.371	€ 7.183 € 60.263	€ 7.208 € 54.003	€ 7.183 € 60.263	€ 7.208 € 54.003
	IE (LYG)	8,41	9,65	9,65	9,65	7,38	6,28
		-14,54 30,43	-16,79 35,38	-16,79 35,38	-16,79 35,38	-12,71 26,69	-10,74 22,67
	IE (QALY)	6,55	7,52	7,52	7,52	5,75	4,89
		-12,26 24,82	-14,13 28,52	-14,13 28,52	-14,13 28,52	-10,63 21,56	-9,19 18,35
ICER (LYG)	CRT-P vs OPT	*€ 12.834*	*€ 13.269*	*€ 11.277*	*€ 10.312*	*€ 14.494*	*€ 15.417*
	CRT-D vs OPT	€ 26.638	€ 26.891	€ 23.387	€ 21.646	€ 30.107	€ 32.443
		€ 16.531 € 46.931	€ 17.058 € 47.663	€ 14.389 € 41.532	€ 12.974 € 39.036	€ 18.867 € 52.656	€ 20.049 € 57.572
	CRT-D vs CRT-P	*€ 44.080*	*€ 44.128*	*€ 38.379*	*€ 35.501*	*€ 50.202*	*€ 54.573*
ICER (QALY)	CRT-P vs OPT	*€ 11.219*	*€ 11.841*	*€ 10.064*	*€ 9.202*	*€ 12.415*	*€ 12.859*
	CRT-D vs OPT	€ 25.639	€ 26.328	€ 22.850	€ 21.124	€ 28.551	€ 30.135
		€ 16.920 € 41.385	€ 17.605 € 42.656	€ 15.013 € 36.998	€ 13.478 € 33.714	€ 18.844 € 45.746	€ 19.481 € 48.102
	CRT-D vs CRT-P	*€ 56.615*	*€ 56.673*	*€ 49.289*	*€ 45.593*	*€ 64.479*	*€ 70.099*

For the remaining modelled scenarios (Table 9.7), the most important results is the impact of the time window. If the time horizon is reduced from life time to a 10-year time horizon, the ICER for CRT-D deteriorates. The average ICER increases from €56,000 per QALY gained to €86,000 per QALY gained. However, this result is misleading since our model includes replacement costs for initial implantations at fixed time points and CRT-D devices are assumed to be replaced after 5 years versus 75 months for CRT-P. With a 10-year time horizon, the CRT-D group has one more replacement than the CRT-P group. Applying the same service life for the CRT-P group (i.e. scenario 'service life 3' in Table 9.7) and looking at a 10 year time horizon, the results change as follows: CRT-P vs. OPT: IC decreases from €16.400 to €13.800, IE decreases from 15.76 to 11.76 months and the ICER increases from €12.500 to €14.100. For CRT-D vs. CRT-P: IC goes from €29.200 to €26.100, IE decreases from 6.55 to 4.07 months, and ICER increases from €53.500 to €76.900.

For the other scenarios, the impact on the ICER of CRT-D versus CRT-P is rather limited. For the procedure related mortality this may be somewhat misleading for the comparison of CRT-P vs. OPT since the model includes a correction for double counting (i.e. the first-year mortality rate was kept at the same level). As such, the influence of changing procedure related mortality is limited to the first year in the model. For CRT-D vs. CRT-P the influence is minimal since the model incorporates the same procedure related mortality for both procedures. As a result, the impact on incremental effects remains limited. Only if this mortality rate would be different between both procedures, incremental effects and thus ICERs would be influenced.

9.2.2.2 Probabilistic sensitivity analyses

The probabilistic sensitivity analysis shows which parameters (including their surrounding uncertainty) contribute most to the uncertainty around the expected ICER. The calculation of correlation coefficients is only reliable if the simulated dots are situated in the same quadrant of the cost-effectiveness plane. This is because a positive ICER can be situated in both the first and third quadrant and a negative ICER in the second or fourth quadrant. As such, ranking the ICERs situated in different quadrants is not useful if this difference is not taken into account. In mortality scenario 2, only the CRT-D vs. OPT comparison is completely situated in the first quadrant. Therefore, we calculated the correlation coefficients for this comparison (while as mentioned before CRT-P and not OPT is the justified comparator on the cost-efficiency frontier for CRT-D). The results of the probabilistic sensitivity analysis are illustrated in Figure 9.5. Only input parameters whose coefficient of correlation exceeds 0.1 are plotted.

In the upper part, the results for the QoL-adjusted ICER are shown. Both the change in monthly probability of death and hospitalisation with CRT-D were the most influential input parameters. Uncertainty in the QoL for CRT-D patients was also strongly (negatively) correlated with the uncertainty around the ICERs with higher estimates of the utilities being associated with lower (better) ICERs (upper part Figure 9.5). This was vice versa for the QoL related to OPT. The importance of the monthly probability of death becomes higher if results are not adjusted for QoL (lower part Figure 9.5). It may be strange that the cost for the implant has no high correlation coefficient. However, the correlation coefficient incorporates at once both the importance of a variable for the outcome and the uncertainty surrounding this variable. For example, if a variable is fixed, no correlation coefficient can be calculated. The cost for the implantation was well-known (based on Belgian data) and was modelled as a normal distribution around the mean, which results in a relatively small 95% CI. As a result, the correlation coefficient was relatively low because of the small variation in this input parameter. In contrast, the cost for hospitalisations were less certain and had a very wide confidence interval (see Table 9.1). As a result, the correlation coefficient for hospitalisations is higher. However, it is clear that important changes in the prices of the devices would have a major impact on the cost effectiveness of the interventions.

Table 9.7.: Sensitivity analyses on time horizon, service life and procedure-related mortality (IC (in €), IE (in months) and ICERs (€/LYG or €/QALY gained))

mortality scenario 2 hospitalisation scenario 1 Scenario			10 year time horizon	service life 1	service life 2	service life 3	proc. related mortality
CRT-P vs OPT	IC	€ 14.745	€ 11.750	€ 15.020	€ 14.495	€ 16.416	€ 14.756
		-€ 1.935 € 36.008	-€ 2.732 € 27.116	-€ 1.623 € 36.293	-€ 2.221 € 35.749	-€ 280 € 37.736	-€ 1.902 € 36.023
	IE (LYG)	13,79	9,18	13,79	13,79	13,79	13,81
		-0,43 33,59	-0,32 20,87	-0,43 33,59	-0,43 33,59	-0,43 33,59	-0,41 33,60
	IE (QALY)	15,77	11,77	15,77	15,77	15,76	15,79
		4,32 31,72	3,67 21,56	4,31 31,72	4,32 31,72	4,31 31,71	4,32 31,72
CRT-D vs OPT	IC	€ 45.624	€ 40.868	€ 48.246	€ 43.503	€ 45.624	€ 45.636
		€ 29.821 € 68.108	€ 26.815 € 57.899	€ 32.293 € 71.207	€ 27.683 € 66.190	€ 29.821 € 68.108	€ 29.843 € 68.158
	IE (LYG)	22,19	14,40	22,19	22,19	22,19	22,21
		9,75 38,03	6,80 23,17	9,75 38,03	9,75 38,03	9,75 38,03	9,78 38,05
	IE (QALY)	22,32	15,83	22,31	22,32	22,32	22,33
		11,89 35,42	9,06 23,70	11,89 35,41	11,89 35,43	11,89 35,42	11,91 35,44
CRT-D vs CRT-P	IC	€ 30.879	€ 29.119	€ 33.226	€ 29.008	€ 29.208	€ 30.879
		€ 7.183 € 60.263	€ 9.475 € 50.594	€ 9.680 € 62.669	€ 5.412 € 58.051	€ 5.225 € 58.292	€ 7.177 € 60.270
	IE (LYG)	8,41	5,22	8,41	8,41	8,41	8,41
		-14,54 30,43	-8,36 18,51	-14,54 30,43	-14,54 30,43	-14,54 30,43	-14,54 30,44
	IE (QALY)	6,55	4,06	6,54	6,55	6,55	6,55
		-12,26 24,82	-7,09 15,30	-12,27 24,81	-12,27 24,83	-12,25 24,84	-12,26 24,82
ICER (LYG)	CRT-P vs OPT	*€ 12.834*	*€ 15.355*	*€ 13.073*	*€ 12.617*	*€ 14.289*	*€ 12.826*
	CRT-D vs OPT	€ 26.638	€ 35.611	€ 28.182	€ 25.390	€ 26.638	€ 26.615
		€ 16.531 € 46.931	€ 21.927 € 62.320	€ 17.617 € 49.689	€ 15.645 € 44.883	€ 16.531 € 46.931	€ 16.529 € 46.800
	CRT-D vs CRT-P	*€ 44.080*	*€ 66.913*	*€ 47.430*	*€ 41.409*	*€ 41.694*	*€ 44.080*
ICER (QALY)	CRT-P vs OPT	*€ 11.219*	*€ 11.979*	*€ 11.430*	*€ 11.028*	*€ 12.499*	*€ 11.218*
	CRT-D vs OPT	€ 25.639	€ 31.451	€ 27.129	€ 24.436	€ 25.639	€ 25.627
		€ 16.920 € 41.385	€ 20.022 € 48.508	€ 18.094 € 43.128	€ 15.838 € 39.770	€ 16.920 € 41.385	€ 16.914 € 41.362
	CRT-D vs CRT-P	*€ 56.615*	*€ 86.089*	*€ 60.960*	*€ 53.155*	*€ 53.472*	*€ 56.612*

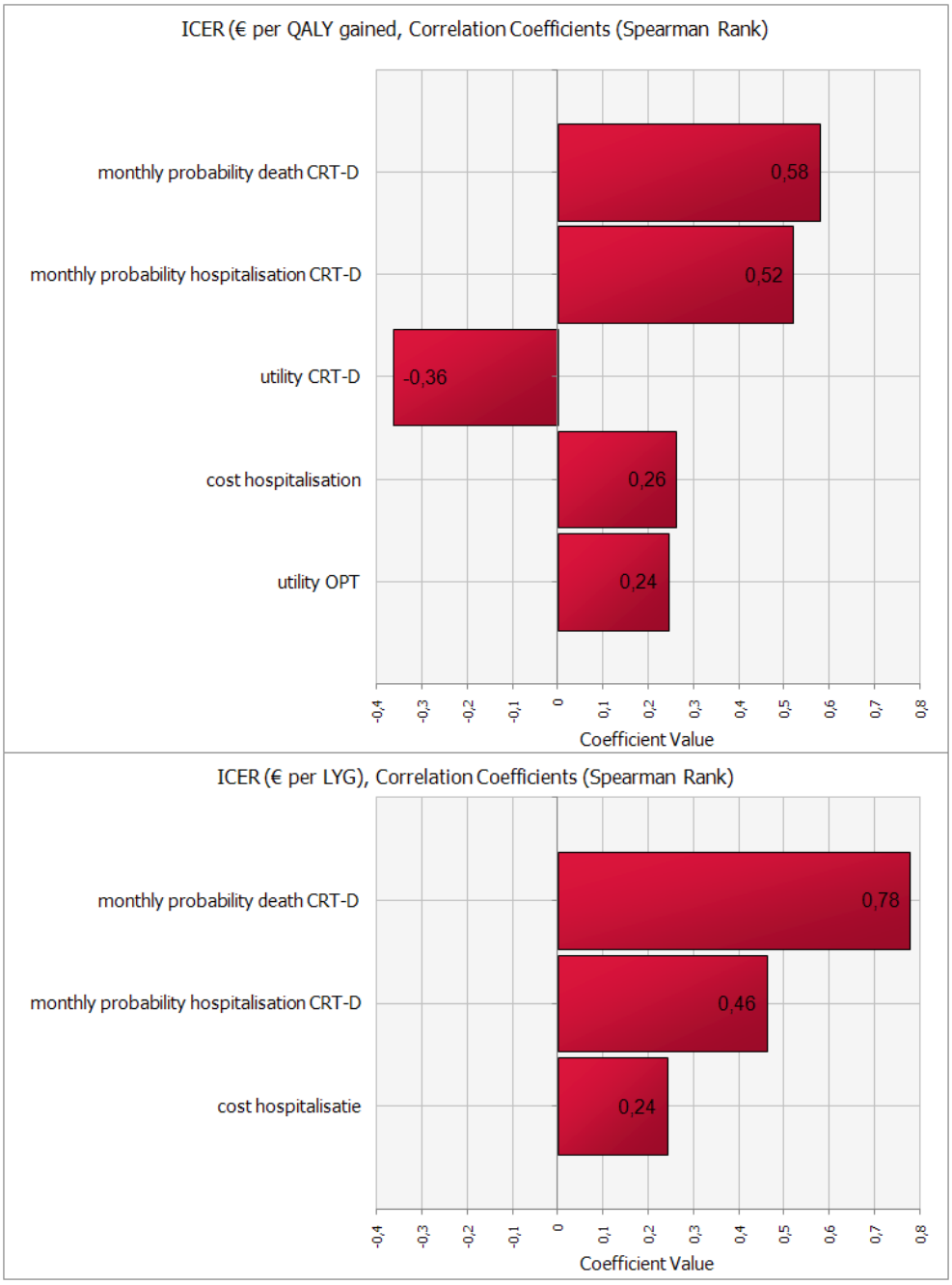


Figure 9.5.: Probabilistic sensitivity analysis

10 Budget impact

We estimated the number of eligible patients in Belgium to be on average 680 (95%CI 435-962) or 850 (95%CI 560-1201), depending on the underlying assumptions (seechapter 12). For our budget impact analysis, we assume that 850 new implants per year are possible in Belgium and this number remains constant through the years. The budget impact was calculated yearly for every new cohort of patients and was calculated until a steady-state was reached.

All costs are based on the cost-effectiveness model. Similar as in the previous part, we present the results based on mortality scenario 2. This time, for budget impact, both the full cost and incremental budget impact are calculated. Costs are not discounted. For the yearly budget of OPT, the cost categories were hospitalisation, follow-up (see subsubsection 9.1.7.3) and cross-over to ICD. For the CRT-P group this was CRT-P implantation, CRT-P replacement, hospitalisation, follow-up and upgrade from CRT-P to CRT-D. Finally, for CRT-D this was CRT-D implantation, CRT-D replacement, hospitalisation, and follow-up. All input variables have an underlying uncertainty. However, to keep the presentation of results clear, we calculated the budget impact with a fixed cohort of 850 patients in combination with the average cost (based on 1000 Latin-hypercube simulations) for all cost categories. In this part, we present the aggregated costs of all these categories. Details of all subcategories are available in appendix (Appendix D).

In 2011, the CRT-P and CRT-D cohorts cost about €7.6 and €19.6 million more, respectively, than the OPT group. When the first implants are replaced (i.e. in our model in 2017 for CRT-P and 2016 for CRT-D), this extra budget impact increases to more than €14 million for CRT-P and about €34 million for CRT-D.

The yearly budget increases stepwise due to the accumulated costs of (still living) patients treated/implanted in the preceding years and costs for a yearly new cohort of patients (Figure 10.1). Depending on the modelled mortality scenario, a steady state is reached in 2026 (mortality scenario 2) or 2021 (mortality scenario 3). The calculated budget impact is higher in mortality scenario 2 and it takes longer before it reaches a steady state due to the more optimistic survival extrapolation. In it's steady state, the total budget impact is about €31, €50, and €79 million for OPT, CRT-P and CRT-D, respectively. This means an extra effort of about €19 or €48 million versus OPT, depending on the choice of CRT-P or CRT-D, respectively. This is lower if a more rapid increase in the time-dependent mortality rate is modelled (mortality scenario 3). However, the trend is about the same with a much higher budgetary effort for CRT-D in comparison to CRT-P.

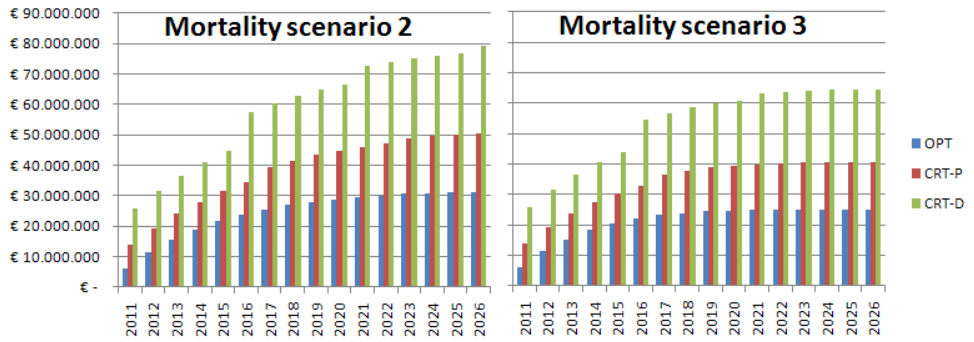


Figure 10.1.: Budget impact CRT-P/D

KEY POINTS

Cost-effectiveness

- **Assuming constant mortality rates results in unrealistic survival in the long term. Including an age-dependent survival curve is necessary to model a credible survival function in the long term.**
- **The modelled life expectancy of about 5 years in the OPT group shows that the considered population has a relatively bad prognosis.**
- **The cost-effectiveness of CRT-P versus OPT is on average between €10,900 and €15,000 per LYG and between €9,600 and €12,600 per QALY gained.**
- **From an economic point of view (i.e. working on the cost-efficiency frontier), CRT-D should not be compared to OPT, but to CRT-P.**
- **The cost-effectiveness of CRT-D versus CRT-P is on average higher than €44,000 per LYG and €57,000 per QALY gained. These results are based on a treatment effect that on average is better for CRT-D versus CRT-P, i.e. a decrease in mortality of 36% versus 24%, respectively. However, it is not shown that CRT-D performs significantly better than CRT-P. If (future evidence would show that) the treatment effect is not (much) better for CRT-D versus CRT-P, CRT-D's ICERs would be much more unfavourable.**
- **Based on several sensitivity analyses, the ICERs for CRT-P vs. OPT are rather robust for modelled changes. In case of CRT-D, changes in mortality gain vs. CRT-P and a shorter time horizon result in more unfavourable ICERs.**
- **Based on efficiency arguments, CRT-P can be recommended for our target population of NYHA III and IV patients. The cost-effectiveness of CRT-D versus CRT-P is rather questionable.**

Budget impact

- **The budgetary effort is more than just the cost for the device.**
- **The budgetary effort increases over the years: In the first year, the CRT-P and CRT-D cohorts cost about €7.6 and €19.6 million more, respectively, than the OPT group. When the first implants are replaced (i.e. after >5 years), this extra budget impact increases to more than €14 million for CRT-P and about €34 million for CRT-D. In the steady state, this is an extra budgetary effort of more than €19 million or €48 million for CRT-P and CRT-D, respectively, versus OPT.**

11 Discussion of the health-economic evaluations

In chapter 8, a review was done of the economic literature. All identified cost-effectiveness studies were performed abroad. Since costs and resource use may vary highly from country to country, no conclusions could be drawn for the Belgian context solely based on the literature review. In chapter 9, a Belgian cost-effectiveness model was therefore developed. The role of the economic literature review lied mainly in presenting how different authors structured their models and estimated the input variables and how results differed in function of the assumptions.

11.1 General limitations of the trials

All identified economic evaluations, including our own model, are subject to a number of common limitations. Firstly, a major limitation is the short-term follow-up of the trials. Given this short follow-up, evaluations are either done on short-term horizon, not accounting all costs and benefits of the treatment, either they are done on long-term (as in our model), but then crucial assumptions are made on extrapolation of mortality, quality of life and costs of the treatment options. None of the existing trials has long enough follow-up, for instance, to address device replacement costs.

Secondly, the economic evaluations are limited by the external validity of the trial results. One major limitation is that only experienced providers participated in the trials.[61] Therefore, it is possible that the complication rates are not generalisable to other, less experienced, provider settings. If this is the case, then the results of the economic models are biased in favour of the CRT treatments. Similar, it is not clear how average crude late device related serious adverse events are reported in the trialschapter 6. Again, not including this in the economic evaluation would (incorrectly) favour CRT.

Furthermore, the majority of heart failure patients in the CRT trials were receiving optimal drug therapy including ACE inhibitors and beta-blockers, which is not reflective of real world clinical practice in Belgium (see chapter on Belgian practice).

Another limitation on the external validity of the trials is that they excluded patients with an indication for an ICD,[6] which does not reflect the real-world situation.

For other limitations of the trial results, we refer to the chapter on clinical effectiveness.

11.2 Model structure and inputs

11.2.1 Comparators

We aimed to assess the cost-utility for three treatment alternatives for patients with heart failure: OPT, CRT-P and CRT-D. Given that CRT-P appears to have a better cost-effectiveness ratio compared to OPT than CRT-D, the relevant comparator for assessing the cost-effectiveness of CRT-D, which is (non-significantly) better than CRT-P, is therefore CRT-P, not OPT. The comparator chosen obviously may have a large impact on the resulting ICER. Feldman et al.[66] for instance compared both CRT-P and CRT-D with OPT, but did not compare CRT-D with CRT-P directly. By comparing CRT-D with OPT, it is clear that this biases results and leads to a higher comparative advantage than when compared with CRT-P. The ICER of CRT-D

compared to OPT as reported by Feldman et al. was $43,000 per QALY, whereas the ICER compared to CRT-P would have resulted in $172,000 per QALY (own calculations based on published results from Feldman et al.[66]). It is clear that from an economic point of view, working on the cost-efficiency frontier may have a large impact on the ICERs and may alter conclusions. This is the case for the evaluation of CRT-D.

Furthermore, based on medical arguments, it could be argued that CRT-D should be compared to conventional ICD treatment. However, from an economic point of view, ICD is not a cost-effective intervention in primary prevention (Figure 11.1 and references[21,79]), and it does not make sense to quantify the efficient use of resources based on a non-efficient alternative. In a previous KCE report,[21] the ICER of ICD was found to be €71,400 (40,200 – 134,600) per QALY gained compared to OPT in the most favourable scenario, and €132,100 (71,600 – 261,500) per QALY gained in the worst-case scenario. The average ICERs are indicated on the following figure. Given that the ICER of ICD compared to OPT appears higher than both the ICER of CRT-P and CRT-D compared to OPT, ICD is excluded from the cost-efficiency frontier by extended dominance (assuming that the effectiveness of ICD is not higher than that of CRT-D). Therefore, from an economic point of view, CRT-P is the justified comparator for CRT-D and not ICD.

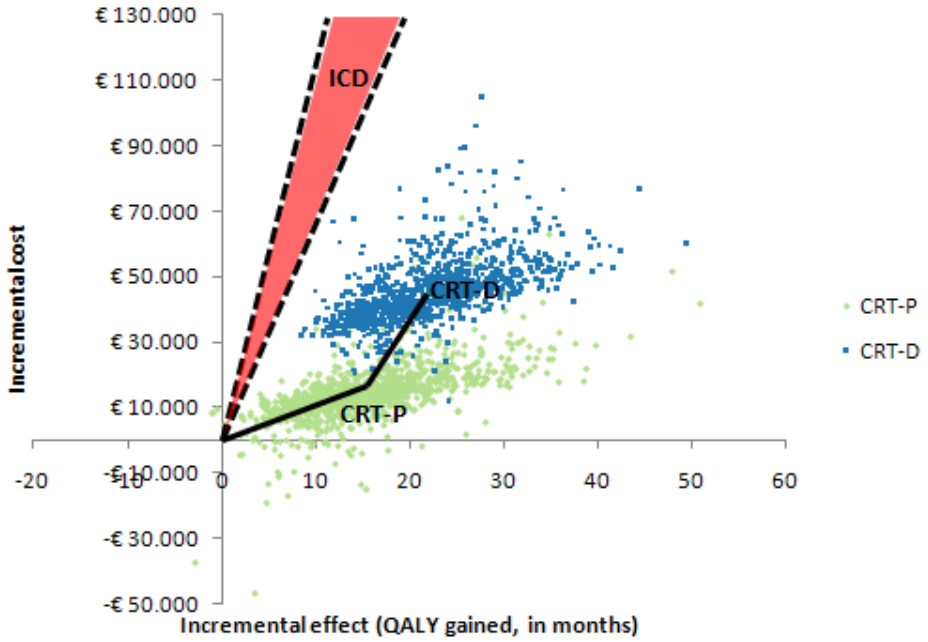


Figure 11.1.: Cost-effectiveness plane for CRT-P, CRT-D (and ICD)

11.2.2 Mortality

The annual mortality rate used in our model was 19 %, based on the outcome of the COMPANION trial, and about 11% in alternative scenarios (*mortality scenario 7 and 8*). In CARE-HF this was 12.6% and Nichol et al.[62] mention that large long-term trials (assessing pharmacological treatment in patients with LV dysfunction after MI, advanced chronic heart failure or chronic heart failure), show annual mortality rates ranging from 11% to 20% for OPT patients. Although comparable (but at the high end) with of mortality rates in other CRT trials it is unsure whether these data are generalisable outside the clinical trial setting.

As longer-term follow-up data are lacking, mortality rates of the trial were furthermore extrapolated using different functions. The extrapolation methods were checked for their fit

with the short term trial mortality rates, and their face validity in terms of how long patients were living. As such we avoided patients living up to for instance 112 years, which was the case if monthly mortality rates were kept constant. We based our analysis on all-cause mortality, since it is difficult to distinguish causes of death in patients with cardiovascular disease.[62] This is in contrast to for instance Bond et al.[70]/Fox et al.[6] where mortality was subclassified in death resulting from worsening heart failure, a sudden cardiac event, other (non-cardiac) causes and postoperative death (for initial and consequent operations).

The results of a meta-analysis show that CRT-P performs significantly better than OPT. Similarly, the COMPANION study shows a significant reduction in mortality for CRT-D versus OPT. However, from an economic point, CRT-P is the correct comparator for CRT-D. There is currently no trial that shows that CRT-D performs significantly better than CRT-P. If the effect on mortality would be relatively small, than the cost effectiveness of the more expensive CRT-D intervention becomes very questionable.

11.2.3 Hospitalisations

Whereas some other models also distinguish between different types of hospitalisations, such as hospitalisation due to heart failure, due to arrhythmia, due to lead dislodgement and infections, we did not make such a distinction in the base scenario. Peri-procedural complications linked to the implantation, other than mortality, were not separately considered in our model and were assumed to be implicitly included in the cost of the initial implantation.

Given that no separate cost data is available for the different types of hospitalisations in Belgium, we based our analysis on an overall hospitalisation rate and an average hospitalisation cost. As no better data were readily available, the hospitalisation cost for all hospitalisations in the APR-DRG 194 group in the year 2007 was taken as a proxy. We are aware however that the hospitalisations in this APR-DRG also include hospitalisations which are not relevant for this economic evaluation. Besides the base scenario we also considered a scenario with hospitalisation due to heart failure only.

The scenario with all-cause hospitalisations may include non-disease related hospitalisations and may possibly overestimate the costs for survivors in the model. However, given that this is the case for all three treatment options, the impact on incremental costs may rather be limited. In contrast, hospitalisation due to heart failure, i.e. the third hospitalisation scenario, may underestimate costs since it is not clear if e.g. device-related hospitalisations are included in this category. As mentioned in the patient issues chapter 6, adverse events related to CRT-P and CRT-D can be substantial and may be higher in real-world situations than in controlled trial settings. If CRT-P and CRT-D related adverse events would seem to be higher than modelled, cost-effectiveness results would deteriorate.

11.2.4 Utilities

Furthermore, all evaluations are limited in the way how improvement in QoL was included, since utility studies are scarce, subject to a number of limitations, and result in considerable variation both in terms of absolute utility values and incremental changes. The studies either only include utility values for part of the relevant health states, either they are not derived from a general public sample, either they measure utility values for the different NYHA classes rather than for the different treatment groups directly. Such indirect utility determination approach however cannot be considered optimal as its validity depends on a double link, firstly the link between the treatment and outcome (in terms of NYHA class, which is a subjective measure for functional disability) and secondly between NYHA class and quality of life. Such indirect determination therefore bears an increased risk of inaccuracy.

Some models based utility values on different sources for utility values. This approach is also questionable as utility values may differ considerably between studies and may better

reflect the incremental effects of treatments rather than the absolute utility values for a given treatment option. However, even the incremental effect changes considerably depending on which study is taken (see Figure 8.2). When results from different studies are combined, however, incremental changes are theoretically calculated and therefore unreliable. In our model, we have aimed to address these issues by taking direct utility measures based on a single source,[67] except for the utility for hospitalisation. This latter health state however does not have a major impact on the model results since it was only included for the initial and device replacement hospitalisations (since QoL during the other hospitalisations is assumed to be reflected in the general utility values). Using a different source for hospitalisations therefore is not considered a major issue in this model.

Calvert[74] furthermore showed that the EQ-5D appears to be an acceptable valid measure for use in patients with heart failure. This further motivated the use of direct EQ-5D utility values in our model.

A common limitation of the utility values used in all models (including our own model) is that they were assumed the same for CRT-D as for CRT-P related events, given that no separate utility values are available. Patients with CRT-D however may have a lower quality of life due to shocks of the defibrillator.[21,68] This assumption therefore likely has a favourable impact on the ICER of CRT-D.

Another limitation of the utility values we used is that they are assumed to remain constant for the lifetime time horizon. It is known however, that QoL varies in function of a person's age, and therefore one can question this assumption. The impact of how the utilities are extrapolated into the future may however not be very large, as when the same assumption is taken consistently in all treatment options, the incremental difference (which eventually determines the ICER) is likely to be rather small. Nevertheless, our assumptions on constant utilities are on the optimistic side for the CRT treatments. Looking at other models, extrapolation of utilities is done in different ways. Yao (2007)[3] e.g. assumed continuing constant monthly transition probabilities between NYHA classes on the long term. Caro (2006)[2] on the other hand argued that this is not consistent with the CARE-HF trial where improvements in NYHA class took mostly place shortly after CRT implantation and remained relatively stable throughout the further study period. Bond (2009)[70] also modeled no further change in NYHA class after 18 months.

11.2.5 Pharmaceuticals

In some of the discussed models, pharmaceutical costs were excluded for the reason that there are no significant differences in consumption of pharmaceuticals between the treatment groups. This may be true for an individual, however, it is not correct when comparing the OPT, CRT-P and CRT-D groups since mortality is different over the three groups. In our model, pharmaceutical costs are therefore included, since patients in the CRT group live longer and are thus likely to consume more pharmaceuticals in the long run. Similar, GP and cardiologist visits (including integrity checks) increase disease-related follow-up costs and should be included in the model since they have an impact on incremental costs.

11.2.6 Device longevity

Annual replacement probability from start as applied by McAlister[61] and Nichol[62]does not appear to be very logical; Replacements occur normally within a certain time frame. this implies that the annual replacement probability remains very low during the first years, to increase suddenly sharply to almost 100% after e.g. 5 or 6 years. Industry may argue that service life improves with newer models being introduced. For example, Yao et al. assume a longer service life for CRT-D (7 years) than CRT-P (6 years). Such optimistic assumptions should be better supported by evidence. As long as this is not the case, more conservatively device longevity estimates should be used.

11.2.7 Cardiac transplantation

The possibility of cardiac transplantation was not included in our model mainly since it occurs rather seldom. Furthermore, the procedure appears to be associated with long-term complications which would need to be included as well.[62]

11.2.8 Uncertainty

In our analysis we have aimed to reflect uncertainty by fitting and choosing the most appropriate distributions for different parameters in the decision model. We used Beta distributions for (transition) probabilities and utilities, log-normal distributions for treatment effects (see Table 9.1 for a full overview). In the discussed models from abroad, sometimes rather inappropriate distributions were applied. McAlister (2004)[61] and Nichol (2004)[62] for instance used a triangular distribution for utilities. A triangular distribution is defined by a mode, a lower and upper limit. Real-life data, including utility data, however do not tend to follow triangular distributions. With asymmetric triangular distributions, furthermore, the mode does not equal the mean, whilst often mistakenly the mean is used to determine the mode.

11.3 Patient subgroups

It would have been interesting to examine the influence of changing age. It is no problem to change the time-dependent increase in mortality which relies on the Belgian life tables. However, we have no information about the influence on other input variables, such as initial mortality, QoL, and hospitalisations. Therefore, we preferred no to model this as it could not be supported by reliable data.

Finally, there are no trials for NYHA class I/II patients that compare CRT-P and CRT-D with optimal medical therapy and gather information on hard endpoints. Therefore, it is not possible to make a reliable cost-effectiveness calculation for this population. Recently, there has been a publication on the cost-effectiveness of CRT in NYHA class I/II patients.[80] This publication, however, did not make a difference between the much more expensive CRT-D and cheaper CRT-P intervention. As discussed before, this is of major importance for the calculated cost-effectiveness of CRT-D. Furthermore, the general comparator is indicated as optimal medical therapy, but all patients in fact received an implant. In less than 10% of these patients no ICD was implanted and the left ventricular pacing function was switched off. Currently, there is no evidence on hard endpoints to support a reliable economic evaluation of CRT-P and CRT-D.

Part IV.

Organisational issues

12 Expected future use of CRT in Belgium

12.1 Recent Belgian studies in heart failure patients

In this chapter, we estimate the future need for CRT devices in Belgium. Our model is based on Belgian data from two recently published studies. One study aimed to determine the incidence of HF in Belgium, based on general practice.[7] A second study aimed to evaluate in patients hospitalised with NYHA III-IV HF, the prevalence of CRT candidates, the actual use of CRT and potential clinical reasons for not using CRT in eligible CRT candidates.[8]

In the general practitioners (GP) study, data were prospectively collected during a 2-year period by a nationwide network of a sample of GPs (sentinel practices). All adult patients for whom the diagnosis of HF was clinically suspected for the first time were registered. Patients were included in the study if the diagnosis of HF was confirmed after 1 month. The yearly adult sentinel population was estimated to be 143,705 or almost 1.8% of the Belgian adult population. In total, 754 patients were suspected to have HF during the 2 years of the registration. The diagnosis of HF was confirmed after 1 month for 557 patients or 74% of all recorded patients. The median age of the patients with confirmed HF was 79 years (SD 12.6). The median age of the female patients was 82 years (SD 11.7) and the median age of the male patients was 76 years (SD 12.9). From their data, the authors estimated that in Belgium yearly 15,643 new patients of HF are diagnosed (95% CI: 13,861 to 17,590; PI in Figure 12.1). At the time of the diagnosis, only few in patients were classified as NYHA I (3%). Most of the patients were classified as NYHA III (50%), 27% as NYHA IV and 20% as NYHA II. Six months after the initial diagnosis, mortality was 19%, with no differences between men and women. After 6 months, 25.6% of the survivors were in NYHA II, 45.2% in NYHA class III and 25.2% in NYHA IV (Table 12.1).

Table 12.1.: NYHA class at 1 and 6 months after diagnosis (confirmed cases)

	Patients with diagnosis confirmed at 1 month		Patients alive at 6 months	
	n	%	n	%
NYHA I	11	2,0	18	4,0
NYHA II	112	20,1	115	25,6
NYHA III	280	50,3	203	45,2
NYHA IV	154	27,6	113	25,2
	557	100,0	449	100,0

Source: Devroey et al.[7] (additional numeric data obtained from the author)

The hospital based study was founded on the data from a prospective HF registry conducted in 2 hospitals in Belgium in 2008.[8] Data were available from 322 consecutive patients who were admitted on cardiology wards in 2 hospitals. Mean age of the patients was 76 SD 11 years, 57 % of them were male. In total, 79 patients (25% of the population) had LVEF $\leq$35% and QRS$\geq$120 ms. Of these 79 potential CRT candidates, 18 patients (23%) received CRT during hospitalisation or during the 6 months following discharge, indicating that 6% of the total population was treated with a new CRT device. Of these, approximately one quarter received a CRT-P and three quarters a CRT-D. Potential CRT candidates who were not treated with CRT were older (76 SD 10 vs 68 SD 13 years), had a smaller QRS (146 SD 27 vs 167 SD 23 ms) and had more frequently a history of CAD (75% vs 44%).

12.2 Scenario based on general practice

In the first scenario we assume that patients who are considered for CRT treatment will have their HF diagnosis first made by a GP (Figure 12.1). In the GPs study, the yearly incidence of HF in the Belgian population was estimated to be 15,643 (95% CI: 13,861 to 17,590; P1 in Figure 12.1). It represents the "Incident HF" number in the model. This figure is comparable with the incidence rate of 1.63 per 1000 inhabitants registered in the Intego network, a computerised voluntary network of GPs in Flanders. [a]

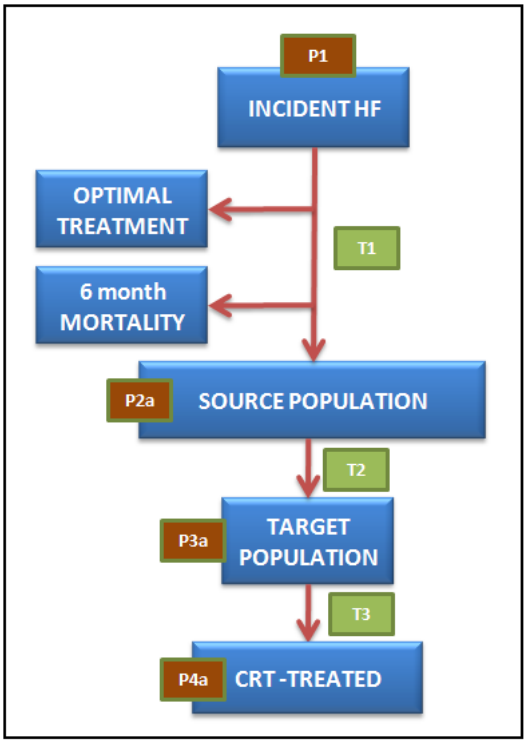


Figure 12.1.: Scenario based on the incidence of HF, diagnosed by a sample of Belgian general practitioners.[7]

From the original cohort, 431/557 (77.4%) (T1) patients is alive and in NYHA class II, III or IV after six months. Applying these proportions (with their distributions) to the yearly incident HF population yields an estimate of 12105 (95%CI 10828 – 13466) (P2a) NYHA class II-IV patients under optimal treatment. These patients constitute the source population in the model. Not all patients with severely symptomatic HF are suitable candidates for CRT treatment. According to current knowledge, HF patients that most probably will benefit from CRT have severe systolic left ventricular dysfunction (LVEF$\leq$35%), electrocardiographic signs of cardiac dyssynchrony (QRS width >120 ms), and are in sinus rhythm. From the Belgian hospital based study mentioned above, 79/322 (24.5%) (T2) of the source population is estimated to meet these guidelines (we assume that the proportion from this study in NYHA class III-IV applies to NYHA class II patients as well).[8] Applying these proportions (with their distributions) to the source population, yields a yearly target population 2969 (95%CI 2417 – 3555) (P3a) potential CRT candidates per year. In the same study, 18/79 (22.8%) (T3) of eligible patients eventually were treated with a CRT. Taking into account these numbers in the model yields a yearly estimate of 676 (95%CI 435 – 962) (P4a) new CRTs.

a. www.zorg-en-gezondheid.be/Cijfers/Zorgaanbod-en-verlening/Artsen/Chronische-aandoeningen–incidentie-en-prevalentie/ and www.intego.be.

12.3 Scenario based on hospital practice

A second scenario starts from the observed number of hospitalisations for HF in Belgium as indicated by the mandatory Belgian register of Minimal Clinical Data. In the year 2008, 18123 unique patients were hospitalised because of HF as a primary diagnosis were registered in Belgium (Figure 12.2) (on a total population of 10,584,534 in 2007). Since CRT implantation is not used as an acute therapeutic intervention, we define the source population in this scenario by subtracting the patients that die in-hospital. In the MCD data, in-hospital mortality amounts to 15.7% (2840/18123) (T4). This yields a source population of 15282 (95%CI 15089 – 15484) (P2b).

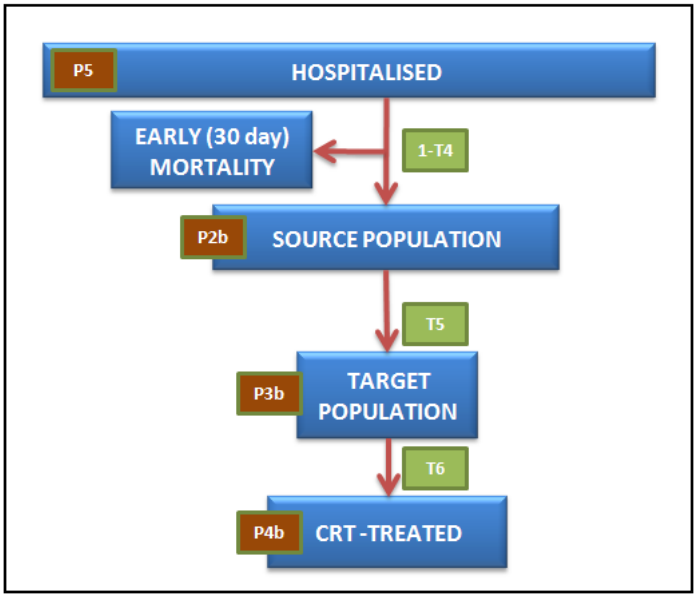


Figure 12.2.: Scenario based on observed hospitalisations for HF in Belgium.[8]

Applying the hospital based data retrieved from Desutter[8] (T2 and T3) yields a target population of 3749 (95%CI 3152 – 4371) (P3b) and a CRT-treated number of patients of 853 (95%CI 560 - 1201) (P4b). These numbers are higher than those obtained in the first scenario. This may be related to the fact that Minimal Clinical Data are collected for billing purposes and are not intended for being used as clinical information. On the other hand, patients that are treated with CRT but that have not been hospitalised for HF prior to the CRT implantation, are not considered in this model.

As described in a previous chapter, yearly CRT implantation rates in Belgium numbered 522 for primo implantations and 187 for replacements in 2008/2009. The observed primo implantation rates lie at the lower estimate side obtained by our models. The demand for CRT may increase in forthcoming years as a consequence of the results of recent trials that demonstrate a beneficial effect of CRT in patients with only mild or moderate HF symptoms (NYHA class II). On the other hand, a component of these potential future patients may already have been receiving a CRT because of off-label use of CRT. This is demonstrated in a European CRT survey in 140 centres from 13 European countries between November 2008 and June 2009.[17] Out of 2438 patients in whom a CRT device was implanted, 23% were in atrial fibrillation, 22% were in NYHA class I/II and 17% had an ejection fraction of more than 35%.

As can be inferred from the scenarios described above, the proportion of patients from the target population that eventually receives CRT treatment has an enormous impact on the estimation of the future use of the CRT devices. This proportion may vary widely and is

largely dependent on patients' and physicians' preferences, their belief in modern technology, age, co-morbid conditions, life expectancy, organisational issues and cost considerations.

KEY POINTS

- **Based on recent Belgian data in HF patients, a crude estimation of the yearly number of new NYHA II, III and IV patients amounts to a CRT target population of 3000 to 3800 patients.**
- **The proportion of patients from the target population that eventually will receive cardiac resynchronisation therapy may vary widely and is dependent on patients' and physicians' preferences, their belief in modern technology, age, co-morbid conditions, life expectancy, organisational issues and cost considerations. Based on real world Belgian data, we assume that yearly 680 to 850 new patients will receive CRT.**

13 CRT-P or CRT-D?

As discussed earlier, CRT therapy can be delivered in its basic version known as CRT-P, or in an extended version where it is combined with an ICD and is then known as CRT-D. The rationale to combine CRT and ICD therapy in one patient is related to the fact that HF patients are at high risk for life threatening arrhythmias, potentially leading to sudden cardiac death.

13.1 The defibrillation component

Conventional ICDs are indicated in the secondary prevention of sudden death in patients with documented life threatening ventricular arrhythmias, irrespective of NYHA class. In primary prevention their effectiveness has been documented in NYHA class II/III patients with a left ventricular ejection fraction $\leq$35%, and in NYHA class I patients with an ischaemic cardiomyopathy and an ejection fraction of $\leq$30%. ICD is contra-indicated in NYHA class IV or in patients with an expected survival of less than one year.[21]

Although the absolute risk of dying due to cardiac arrest or due to HF both increase with the functional degree of HF, there is a disproportionally higher risk of progressive HF death in highly symptomatic patients. Conversely, cardiac arrest represents the major cause of death in mildly symptomatic patients, a group of patients in whom an ICD has been demonstrated to offer the greatest benefit.[46,81] There are no randomised trials that directly compared the clinical effectiveness of ICD in primary prevention in NYHA class II versus III however, and current guidelines do not make a distinction between NYHA class II/III in their recommendations for ICD therapy (appendix).

The potential contribution of device based treatment in patients with left ventricular systolic dysfunction is summarised and schematically outlined in Figure 13.1.

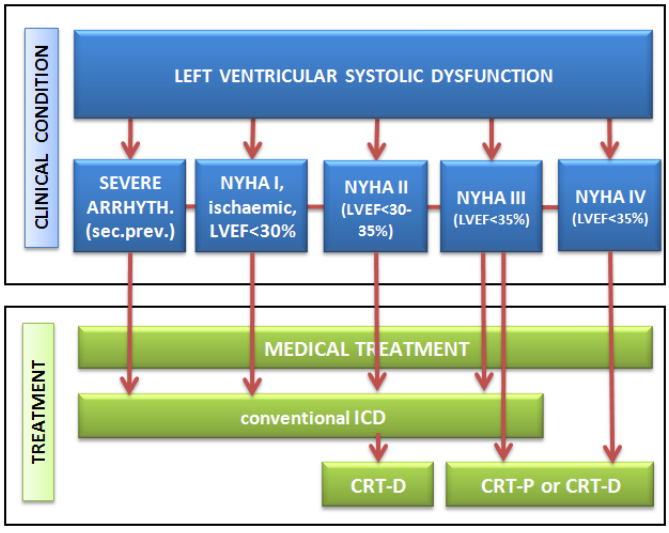


Figure 13.1.: Device-based treatment of patients with left ventricular systolic dysfunction (Source: KCE. Horizontal lines connecting NYHA classes indicate that over time, patients may move from one class to another. Sec. prev.:secondary prevention. Arrows point towards device treatment supported by scientific evidence.)

13.2 The resynchronisation component

As far as CRT is concerned, randomised trials have shown that CRT-P and CRT-D prolong life and reduce hospitalisations for HF when added to optimal medical therapy in subsets of patients with NYHA class III/IV HF. This has been best documented in medical therapy refractory patients with symptomatic chronic HF, who were in sinus rhythm, who had a severely depressed systolic heart function (ejection fraction ≤ 35%) and intraventricular conduction delays. In these trials, NYHA class IV patients represented a minority of patients (15% in COMPANION[25] and 6% in CARE-HF[1] of the study population.

The methods used to assign a given NYHA class to patients was not elaborated in the trials, but some necessary clinical characteristics were specified in the study protocol. In COMPANION, patients had to be hospitalised for the treatment of HF in the preceding 12 months.[25] In CARE-HF, eligible patients should have had HF for at least six weeks, but those who had a major cardiovascular event in the previous six weeks were excluded.[1] Based on these elements, recently issued clinical guidelines have restricted the use for CRT in NYHA class IV patients to "ambulatory NYHA class IV" patients defined as: "NYHA class IV patients that have had no scheduled or unscheduled admission for HF during the month preceding the CRT implantation and who have a life expectancy of at least 6 months".[12]

No trials have compared CRT-P with optimal medical therapy in patients with only mild symptoms of HF (NYHA class I/II). Trials in these patient groups enrolled mostly NYHA class II patients with an established indication for a conventional ICD, and randomised them to ICD-only or CRT-D. In the most recently published trial, a survival benefit was shown in patients treated with a CRT-D over those treated with an ICD-only.[51]

The effect of CRT on overall hospitalisations is not fully clear. Data from the earlier trials do not allow to establish the long term effect of CRT on all-cause hospital admissions. In the most recently published trial, the proportion of patients that were hospitalised at least once during follow-up was similar in both study groups (56.3% in the ICD-only group versus 57.0% in the CRT-D group).[51]

A direct comparison of CRT-P versus CRT-D has never been performed and it is still a matter of debate whether CRT-D confers a survival benefit over CRT-P.[82,?] In the COMPANION trial, patients were randomised to medical treatment, to CRT-P or to CRT-D. The risk of the combined end point of death from, or hospitalisation for HF was reduced by 34% in the CRT-P group (P<0.002) and by 40% in the CRT-D group (P<0.001 for the comparison with the medical-therapy group). A CRT-P reduced the risk of death from any cause by 24% (P=0.059), and a CRT-D reduced the risk by 36% (P=0.003).[25] In a Bayesian network meta-analysis of 12 trials, the effect on all-cause mortality was calculated when adding CRT-D to optimal treatment as compared to optimal treatment alone, to CRT-P and to ICD-only.[5] It was found that CRT-D therapy reduces the number of deaths by one third compared with medical therapy alone. However, there was insufficient evidence to show the superiority of CRT-D therapy over CRT-P. The authors argue that the routine use of CRT-D in all patients eligible for both treatments, on the basis that it may prolong survival over CRT-P or ICD alone, is not appropriate.

KEY POINTS

- **In the primary prevention of sudden cardiac death, conventional ICDs are indicated in subgroups of HF patients in NYHA class II/III. They are contra-indicated in NYHA class IV.**
- **In comparison with an optimal medical treatment, both CRT-P and CRT-D have an additional beneficial effect in subgroups (ejection fraction $\leq$35%, QRS $\geq$120ms) of patients with NYHA class III/IV. It is not clear whether CRT-D performs better than CRT-P in these patients.**
- **In NYHA class II patients CRT-D has an added benefit over conventional ICD treatment. The role played by CRT-P in NYHA class II patients has not been established.**
- **Practising cardiologists are facing a dilemma in NYHA class II patients that are suitable candidates for conventional ICD treatment. Clinical trials have shown that in some of those patients, CRT-D therapy performs better than a conventional ICD.**

14 Regulatory considerations

Whereas Belgium holds a top position in the number of conventional PM implants per million inhabitants in Europe since decades, this is not the case for ICD or CRT devices.[10] EUCOMED (an international association of manufacturers and suppliers of medical technology) provides data on its website (www.eucomed.org) of PM and ICD sales per million inhabitants in 16 European countries for the years 2004 through 2008. Data related to conventional CRT sales in 2005-2008 are depicted in Table 14.1. In contrast to conventional PMs, the Belgian CRT sales numbers provided by EUCOMED are superior to those from IMA as described in a previous chapter (Table 7.2). The reason for this difference is not clear and it is not known if sales data from other countries are different from official implantation numbers as well.

These EUCOMED data indicate that Belgium has a relatively high number of CRT-P and a low number of CRT-D sales as compared to other Western European countries. Adding both 2008 numbers shows that with 85 CRTs per million inhabitants per year, Belgium and France rank seventh among 16 West-European countries in CRT sales rate. Whereas Belgium is a top implanter of conventional PMs, its CRT implantation rate is average compared to other Western European countries. This behavioural difference in the Belgian PM versus CRT practice may be related to the fact that, in contrast to conventional PM therapy, CRT practice has been restricted so far (i.e. no reimbursement for the left ventricular lead in CRT-P and CRT-D limited to ICD-accredited centres).

Table 14.1.: Sales of CRT-P and CRT-D per million inhabitants in selected European countries, 2005-2008

	CRT-P				CRT-D				CRT-P + CRT-D
	2005	2006	2007	2008	2005	2006	2007	2008	2008
AUSTRIA	32	26	29	29	32	42	57	68	97
BELGIUM	46	47	46	46	26	28	40	39	85
DENMARK	43	37	36	33	32	43	50	59	92
FINLAND	15	14	11	14	5	13	20	25	39
FRANCE	33	32	31	33	25	38	47	52	85
GERMANY	15	15	15	13	55	70	84	103	116
GREECE	10	10	8	7	8	12	17	28	35
IRELAND	16	7	3	3	29	8	31	37	40
ITALY	29	26	26	26	73	93	114	134	160
NETHERLANDS	35	32	29	25	53	72	87	94	119
NORWAY	25	25	27	23	18	21	24	22	45
PORTUGAL	9	9	9	11	18	22	27	31	42
SPAIN	9	12	11	12	16	19	25	27	39
SWEDEN	37	54	50	54	21	30	37	38	92
SWITZERLAND	14	16	15	17	29	38	45	51	68
UK	20	23	30	32	18	35	39	47	79
WESTERN EUROPE*	23	25	25	25	38	52	63	74	99
RATIO BEL/W.EU.	2,00	1,88	1,84	1,84	0,68	0,54	0,63	0,53	0,86

Source: EUCOMED website (www.eucomed.org). *Average Western European numbers obtained from van Veldhuisen.[83]

The fact that the CRT-D implantation rate in Belgium is relatively low in a European context may be consequential to the fact that the reimbursement of ICDs in primary prevention

is legally limited and hence physicians may have opted for implanting a CRT-P in patients in whom they otherwise would have considered a CRT-D. Obviously, this holds true only for cardiologists working in an ICD accredited centre. The relatively high number of CRT-Ps may also be related to the almost unrestricted access for hospitals to CRT-P implantations. The overall relatively low CRT implantation rate most probably is also impacted by the fact that the left ventricular lead was not reimbursed until July 1, 2007, when it was accepted for reimbursement in combination with CRT-D only.

The implantation of a CRT device is more demanding than that of a conventional PM or ICD, because of the technical skills involved in the positioning of the left ventricular lead. In some patients, it may be impossible to reach an appropriate stimulation site of the left ventricle through the coronary sinus. In these cases, the lead can be stitched on the outer side of the heart ("epicardial") via an additional surgical incision through the chest wall, involving the help of a cardiac surgeon.

The technical complexity of CRT insertion is illustrated by the reporting of a substantial number of failed implantations, as well as a high number of procedure related complications in clinical trials. The MADIT-CRT trial, of the 1089 patients who were assigned to the CRT-D group, 11 (1.0%) did not receive any device at all, and 82 patients who were assigned to the CRT-D group (7.5%) received an ICD-only because of technical difficulties in positioning the CRT pacing lead.[40] Of the 1079 CRT-D patients that were included in the safety endpoint, 7.9% experienced procedure related complications versus 5.5% in the ICD-only group (Table 5.3).[40] In the CRT-D group in RAFT, a left ventricular lead was successfully implanted in 841 patients (94.7%), in 802 during an initial attempt and in 39 during a subsequent attempt.[51]

In the CARE-HF trial, the implantation success rate was 95.9%. The individual centre experience was shown to be the only factor that predicted a higher procedural success. If arbitrarily set at less or at more than 10 CRT implants per year, more experienced centres had a 90% success rate at first attempt, compared with 82% in the less experienced.[53]

From the US NCDR (National Cardiovascular Data Registry) ICD Registry a volume / complications relationship was established among more than 300,000 patients who underwent an ICD implantation between January 2006 and December 2008.[84] The annual ICD procedure volume per hospital varied widely, with a median of 57 patients/year. The adjusted odds of any adverse event after ICD implantation (including CRT-D but excluding epicardial lead placements) were significantly higher in the lowest-volume quartile ($\leq$24 patients per year) compared with the highest-volume. Remarkably for CRT-Ds the odds ratio for the lowest quartile compared with the highest quartile was not statistically significant, but the inverse trend relationship between hospital annual ICD volume and outcome was significant when tested over all 4 quartiles of volume. The inverse volume / outcome relationship was unaffected by an adjustment for baseline characteristics (patient, operator and hospital characteristics). The authors concluded that high-volume hospitals are more likely to have better outcomes as a result of their greater experience.

In another study from the same database, the incidence of acute lead dislodgements and its consequences were analysed.[85] Acute lead dislodgement occurred in 1.2% of patients. This was more common in patients with NYHA class IV HF, atrial fibrillation or a CRT-D device and in patients undergoing implants by non-electrophysiology-trained implanters. Moreover, patients who had suffered an acute dislodgement were at higher risk for adverse events later on. They were five times more likely to have a cardiac arrest, tamponade, pneumothorax, or infection than those who did not, and were twice as likely to die in hospital.

In the 2007 ESC guidelines for CRT, experts "strongly propose a minimum case load of at least 20 CRT implantations per year".[86] Applying this number to recent Belgian data indicates that 15 out of 23 ICD accredited centres meet this lower limit, whereas none of the cardiac care program P or the cardiac care program E hospitals reaches this level.

Part V.

Patient issues

The prolongation of life and the decreased number of HF hospitalisations conferred by CRT treatment come at a cost for patients because of device and procedure related complications and hospitalisations. Patients in whom CRT is considered should be well informed on the benefits they can reasonably expect from the intervention and of the limitations of this mode of therapy. Successful left ventricular lead insertion may be impossible in up to 8.5% of patients.[40] Major complications related to the implantation of the left ventricular lead occurs in up to 10% of patients.[38]

Randomised trials have shown an increased life expectancy in eligible HF patients after successful CRT implantation, as well as a favourable effect on a number of HF events. However, most patients presenting with clinical HF are no candidates for CRT treatment. This is related to the fact that CRT is beneficial only in drug refractory patients with chronic *systolic* HF (low ejection fraction) who are in sinus rhythm and show an intraventricular conduction delay. HF typically is a disease of the elderly. In the Belgian GPs study, the median age of patients at diagnosis was 79 years.[7] Very elderly patients with multiple co-comorbidities and a poor life expectancy may not be appropriate candidates for CRT treatment, even if they meet guideline criteria, and many of them will eventually not receive such a device. In the Belgian hospital based study, less than a quarter of eligible patients eventually received CRT.[8]

In NYHA class II and III patients the question rises whether one opts for ICD-only, CRT-P or CRT-D. It is currently not known if CRT-D offers an additional benefit to CRT-P by reducing the risk for sudden cardiac arrest, although many cardiologists may opt for CRT-D because they believe it does.

In HF patients with severely incapacitating symptoms, the question may rise whether the prevention of sudden death is what they really want. Patients with advanced HF may find a death due to a ventricular arrhythmia more appealing than that due to recurrent pulmonary oedema or low output failure.[21] CRT postpones the occurrence of symptoms to HF but prognosis remains bleak and most of these patients will die because of HF. Half of patients carrying a diagnosis of HF will die within 4 years, and in patients with severe HF more than 50% will die within a year.[9] The average patient hospitalised with HF and low ejection fraction is more than 75 years old and has at least 2 comorbidities. The 1-year mortality rate for this population is in the range of 30% to 50%.[11] As argued by Cubbon, frank discussions are needed with patients with NYHA class III/IV symptoms, those aged over 75 years, and those with extremely poor ventricular function about how and where they might like to die.[87]

Part VI.

Discussion

14.1 The technology

A cardiac resynchronisation therapy device, in its basic configuration represented as CRT-P, is a pacemaker that is specially designed for the treatment of HF. Basically, it is a conventional pacemaker connected to the right atrium and the right ventricle that can stimulate the left ventricle via a third electrode as well. It can also incorporate a conventional implantable cardioverter defibrillator (ICD) resulting in a device that can (1) perform resynchronisation therapy and (2) deliver a shock in case cardiac arrest occurs. In this configuration, the system is known as CRT-D.

The basic functionalities of the cardiac devices described in the present report are summarised in Table 14.2.

Table 14.2.: Basic functionalities of cardiac stimulatory devices

	CONVENTIONAL DEVICES		CARDIAC RESYNCHRONISATION THERAPY	
	BRADYCARDIA PACEMAKER	IMPLANTABLE DEFIBRILLATOR (ICD)	CRT-P	CRT-D
INCREASES HEART RATE IN CASE OF BRADYCARDIA	√	√	√	√
DELIVERS SHOCK IN CASE OF FATAL ARRHYTHMIA		√		√
AIMED AT IMPROVING CONTRACTILE FUNCTION			√	√

14.2 The evidence

In clinical trials studying cardiac resynchronisation therapy, HF patients in NYHA class I or IV were only poorly represented and hence, the evidence from these trials is mostly applicable to patients in NYHA class II or III. However, differentiating NYHA class II and III in patients has been criticised because of its subjective nature. In one study, it was shown that the classification of HF patients into NYHA class II or III by doctors was little different than allocating them by chance.[13,14] These difficulties may hamper the external validity of the clinical trials.

14.2.1 In patients with NYHA class III (and IV)

Randomised trials have shown that CRT-P and CRT-D prolong life when added to optimal medical therapy in subsets of patients with NYHA class III/IV HF.[25,1] This has been best documented in drug-refractory patients with symptomatic chronic HF who were in sinus rhythm, who had a severely depressed systolic heart function (ejection fraction$\leq$35%) and intraventricular conduction delays (QRS>120 ms).

Our modelling with the data from the largest of these trials in combination with Belgian demographic data revealed that in NYHA class III/IV patients, CRT-P increases longevity with on average 1.31 (95%CI -0.04 to 3.21) years compared to optimal treatment. Likewise, the addition of a defibrillator function to CRT-P (i.e. CRT-D) in those patients would prolong life with on average 0.80 (95%CI -1.40 to 2.95) years. In this study the survival benefit for CRT-P was not significant but in meta-analyses this gain became a significant 1.83 (95%CI 0.45 to 3.33) years.

A direct comparison of the performance of CRT-P vs. CRT-D against optimal medical therapy has never 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.

Compared to optimal medical therapy, CRT reduces the number of hospital admissions for HF. The treatment effect of CRT on all-cause hospitalisations is not fully clear since hospitalisations due to device failure in most trials have not been clearly documented. Improvements in health related QoL were shown by using the Minnesota Living With HF (MLWHF) and the EQ-5D scales with both CRT-P and CRT-D in NYHA class III patients.[6,25]

14.2.2 In patients with NYHA class II (and I)

No trials have been performed to compare CRT-P and/or CRT-D with optimal medical therapy in patients with only mild symptoms of HF (NYHA class I/II). Three large trials comparing CRT-D with ICD have been published, mostly including NYHA class II patients.[38,40,51] In two of them, including patients with a fairly low mortality risk, no mortality benefit could be documented.[40,38] In the most recently published study that recruited patients at higher mortality risk than in the previous studies, a benefit in terms of all-cause mortality was demonstrated.[51]

It remains to be established if CRT-P performs differently than CRT-D as compared to optimal medical treatment.

We did not model mortality data for NYHA I/II patients because of insufficient data.

CRT-D compared to ICD reduced the subsequent need for hospitalisation because of HF. The effect on overall hospitalisation rate is not clear.

14.2.3 Adverse effects of CRT

To patients cardiac resynchronisation therapy comes at a cost of complications and hospitalisations related to the device and the implantation procedure. From meta-analyses of NYHA III/IV trials, it can be concluded that almost 10% of attempted first implantations result in failure while peri-operative death is almost 1%. In the COMPANION trial, moderate or severe adverse events related to the procedure occurred in 8 to 10% of patients.[25] In RAFT, over a mean follow-up of 40 months, the proportion of patients that were hospitalised because of device related complications was 20.0% in the CRT-D group and 12.2% in the ICD-only group.[51] Although device related complications are concentrated in the first days and weeks after the procedure, late problems are by no means uncommon. In MADIT-CRT, the incidence rate of late serious device related events was three- to fourfold higher than the incidence rate of non-fatal HF events (which is the target for CRT treatment).[40]

14.3 The guideline

In August, 2010, a focused update of 2007/2008 European guidelines[19,86] became available.[12] For NYHA class III/IV patients, a class IA recommendation for CRT reads as follows: "CRT-P/CRT-D is recommended to reduce morbidity and mortality in patients who are in sinus rhythm, in NYHA class III/IV and with an ejectionfraction $\leq$35% and a QRS duration $\geq$ 120 ms whilst being optimally treated. Class IV patients should be ambulatory, i.e. no admissions for HF during the last month and a reasonable expectation of survival of > 6 months."

The most salient feature of this guideline update was its upgrading of the recommendation for cardiac resynchronisation therapy in NYHA class I/II patients. It adds the following class IA recommendation: "CRT *preferentially by CRT-D* is recommended to *reduce morbidity* or to *prevent disease progression* in patients with heart failure, who are in sinus rhythm and are in NYHA class II with an ejection fraction$\leq$35% and a QRS duration $\geq$ 150 ms, while being optimally treated medically". This recommendation is reportedly supported by evidence from three randomised trials: MIRACLE ICD II,[47] REVERSE,[38,39] and MADIT-CRT.[40] Critical

analysis of these trials however reveals that they do not provide hard data to support this claim. More specific, no answer is given to the following questions:

- Is CRT-D preferable to CRT-P? No trials have investigated the clinical effectiveness of CRT-P versus standard therapy in NYHA II patients.
- Does CRT reduce morbidity? In MADIT-CRT, overall serious events, observed at any time during the trial, occurred in similar proportions in ICD-only patients (59.7%) and in CRT-D patients (60.4%).
- Does CRT prevent disease progression? Surrogate endpoints such as ejection fraction or echocardiographic measures were favourably affected by CRT-D versus ICD-only treatment, but it is not clear to what extent this is beneficial to patients. In their comments, the guideline editors themselves stipulate that "further studies are needed to determine whether reverse left ventricular modelling leads to better long-term clinical outcomes".[12]

In November 2010, the results of the RAFT trial in NYHA class I/II HF patients became available.[51] In contrast to previous studies in patients with only mild HF symptoms, survival improved with CRT-D as compared to ICD-only. Probably, this stems from the fact that RAFT recruited patients with a higher baseline risk. As far as morbidity data are concerned, results from RAFT showed a decrease in the need for hospitalisations because of HF (19.5% versus 26.1%). However, the number of patients hospitalised at least once during the entire study period was similar in both study groups.

14.4 The cost

Based on clinical evidence, a cost-utility analysis was performed from the perspective of the health care payer, including both payments out of the government's health care budget as well as patients' co-payments.

For the treatment effect, the results of the COMPANION trial were initially applied. This is the only trial that compares CRT-P as well as CRT-D versus optimal standard therapy, which allows to make an indirect comparison between CRT-P and CRT-D. This study mainly includes NYHA class III patients. Based on the results of the COMPANION trial and a rather optimistic lifetime extrapolation, a mortality reduction of 24% (p=0.059) for CRT-P versus optimal standard therapy results in a discounted quality-adjusted life gain of 15.8 months (4 to 32). For CRT-D versus optimal standard therapy this is 22.3 months (12 to 35), when applying the 36% (p = 0.003) reduction in mortality. Based on this model, the difference between CRT-P and CRT-D is 6.6 (-12 to 25) quality-adjusted life months, which is not statistically significant. The results for CRT-P versus optimal standard therapy improve (and become more significant) if the modeled treatment effect is based on the results of a meta-analysis (which is only available for CRT-P).

The incremental discounted life time costs for CRT-P versus optimal standard therapy were €14.700 (-1.900 to 36.000). For CRT-D versus CRT-P this was €30.900 (7.200 to 60.300). This results in an ICER of about €11.200 per QALY gained for CRT-P versus optimal standard therapy and about €57.000 per QALY gained for CRT-D versus CRT-P (Figure 14.1). This difference in cost-effectiveness is mainly determined by the threefold higher device price for a CRT-D versus a CRT-P. It should be noticed that the ICER of CRT-D versus CRT-P increases considerably if a shorter 10-year time horizon is applied.

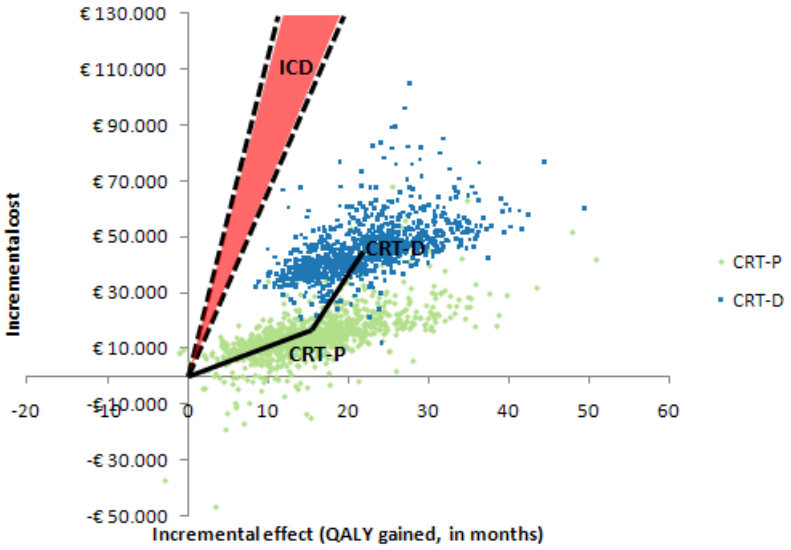


Figure 14.1.: Cost-effectiveness plane for CRT-P, CRT-D (and ICD) (Source: KCE.)

It could be argued that in the previous reasoning, CRT-D should be compared to conventional ICD treatment instead of optimal standard therapy. However, from an economic point of view, conventional ICD therapy is not a cost-effective intervention in primary prevention (Figure 14.1 and references[21,79]), and it does not make sense to quantify the efficient use of resources based on a non-efficient alternative. Therefore, from an economic point of view, CRT-P is the justified comparator for CRT-D and not ICD. Finally, there are no trials for NYHA class I/II patients that compare CRT-P and CRT-D with optimal medical therapy and gather information on hard endpoints. Therefore, it is not possible to make a reliable cost-effectiveness calculation for this population.

14.5 The Belgian practice

EUCOMED data indicate that Belgium has relatively high CRT-P and relatively low CRT-D sales as compared to other Western European countries. Adding the 2008 EUCOMED CRT-P and CRT-D sales numbers shows that with 85 CRTs per million inhabitants per year, Belgium together with France rank 7th among 16 West-European countries in CRT sales rate. Whereas Belgium is a top implanter of conventional PMs, its CRT implantation rate is intermediate as compared to other Western European countries. This behavioural difference in the Belgian PM versus CRT practice may be related to the fact that, in contrast to conventional PM therapy, CRT practice has been restricted so far by legally limiting the use of CRT-D in ICD accredited centres, and by the absence of a reimbursement of the left ventricular lead.

Based on Belgian data from two recently published studies we estimated the future need for CRT devices in Belgium.[7,8] Depending on a scenario that started from GP or hospitalised patients, and included NYHA class II, III and IV, a yearly target population between 3000 and 3800 new CRT implantations was obtained. In the hospital based study,[8] 22.8% of these target patients eventually were treated with a CRT. Applying this proportion to the target population would yield an estimated yearly number of new CRT devices of 680 (95%CI 435-962) and 850 (95%CI 560-1201) respectively. The 2008 primo implantation rate in Belgium was 531 units and lies at the lower end of these estimates. Obviously this number to a large extent is dependent on the proportion of target patients that eventually are treated with the device. This proportion may vary widely and has a large impact on the estimation of the future use of the CRT devices. It is dependent on physicians' preferences, patient values, age,

co-morbid conditions, life expectancy, organisational issues and cost considerations. Our budget impact analyses reaches a steady state in 2021. Based on an assumed yearly cohort of 850 new patients, the total budget impact is €20 million for optimal medical treatment, €38 million for CRT-P and €54 million for CRT-D. This means an extra yearly budgetary effort of €18 million or €34 million, depending on the choice of CRT-P or CRT-D.

The implantation of a CRT device is more demanding than that of a conventional pacemaker or ICD, especially because of the technical skills involved in the positioning of the left ventricular lead. In the MADIT-CRT trial, 8.5% of patients assigned to CRT-D implantation did not receive the device.[40] In the patients assigned to CRT-D in RAFT, a left ventricular lead was successfully implanted in 90.3% of patients during the initial attempt. It was successful in another 4.4% during a subsequent attempt.[51] Because of the technical skills required to successfully execute a CRT implantation, and the potential for serious complications, ESC guidelines "strongly propose a minimum case load of at least 20 CRT implantations per year".[86] In 2008, the yearly CRT implantation rates in Belgium numbered 531 for primo implantations, and 187 for replacements. Eighty percent of all CRT implantations took place in an ICD-accredited hospital. Only 15 out of 23 ICD-accredited centres met the lower ESC limit, whereas none of the cardiac care program P, nor the cardiac care program E hospitals reached this level. Given the huge costs involved and the specific skills required to successfully execute a CRT implantation, an efficient organisation and planning of CRT therapy is imperative.

14.6 The conclusion

The effectiveness of CRT-P and CRT-D is best supported by clinical trial evidence for drug-refractory NYHA class III patients in sinus rhythm with severe systolic dysfunction and electrocardiographic signs of intraventricular conduction delay. In these patients, CRT prolongs life and reduces the need for *HF related hospitalisations*. In the worst-off NYHA class II patients ("RAFT-type patients") it has been shown that CRT-D prolongs life as compared to conventional ICDs. It has not been clearly demonstrated that cardiac resynchronisation therapy reduces the *overall hospitalisation rate* of HF patients as compared to standard medical therapy.

The implantation of a CRT device requires specific skills from the implanting physician. Even in experienced hands, more than one implantation attempt is needed in up to 10% of patients and in some of them, a correct positioning of the left ventricular lead never succeeds. Although device related complications are concentrated in the first days and weeks after the procedure, late problems are common. Both patients and physicians have to balance the benefits and risks of CRT.

The most recently published practice guideline strongly recommends cardiac resynchronisation therapy in NYHA class III and NYHA class II patients. For the latter, the guideline imposes more stringent intraventricular conduction delay criteria ($\geq$ 150 ms in NYHA II versus $\geq$ 120 ms in NYHA class III). Nevertheless, we found insufficient scientific data to support the assignment of a class IA label to this recommendation in NYHA class II patients.

Modelling data from a clinical trial revealed that treatment with a CRT-P in NYHA class III patients results in a quality-adjusted life gain of 16 months (4 to 32) compared with an optimal medical therapy. From the same model, we found an additional quality adjusted life gain from CRT-D compared with CRT-P treatment of 7 months (-12 to 25), which is not statistically significant. The incremental cost-effectiveness ratio (ICER) of CRT-P versus optimal standard therapy is about €11.200 per QALY gained and about €57.000 per QALY gained for CRT-D versus CRT-P. This difference in cost-effectiveness is mainly determined by the threefold higher device price for a CRT-D versus a CRT-P.

In Belgium, conventional defibrillators are reimbursed for primary prevention in patients with heart failure and a severely depressed left ventricular contractile function. In a previous

study, we have shown that in these patients ICD therapy is clinically effective though not cost-effective.[21,79] In July 2009, the Agreement Council decided to limit the yearly number of reimbursed ICD primo implants (including conventional ICDs and CRT-D alike) to 1300, of which no more than 40% would be accepted for primary prevention.

A number of patients currently considered for conventional ICD treatment may derive additional benefit from treatment with CRT-D. In this respect, practising cardiologists when confronted with NYHA class II patients, are facing a dilemma because clinical trials have shown that CRT-D therapy performs better than a conventional ICD. On the other hand, trial data have not shown that CRT-D therapy performs better than CRT-P, yet treatment with a CRT-D induces more device related complications and is less cost-effective. Modelling trial data on NYHA class III patients and real world Belgian patients data indicate that, even if CRT-D would confer a survival benefit over CRT-P, this would come at an additional cost of €57,000 per QALY gained.

Part VII.

Appendices

A Clinical guidelines

A.1 Clinical guidelines for ICD therapy

Because ICD therapy is a component of CRT-D, clinical GLs on ICD therapy are briefly reviewed here. In 2006, the ACC, the AHA and the ESC jointly issued "GLs for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death".[20] They were partly updated in the US "2008 GL for device-based therapy of cardiac rhythm abnormalities".[11] In Belgium, an agreement has been made between the RIZIV/INAMI and representatives of the Belgian electrophysiologists on the reimbursable clinical indications for ICD therapy. The most recent agreement has been endorsed on July 12, 2010.

A summary table with the major indications for ICD therapy are depicted inTable A.1. It can be inferred from this table that the indications that are currently accepted in Belgium for ICD reimbursement largely correspond to international GLs. However, in Belgium an upper limit of 1300 reimbursable ICD primo implants per year is legally imposed. A maximum of 40% (520) of these are accepted for primary prevention.

A.2 Clinical guidelines for CRT

Comprehensive clinical guidelines (GLs) on cardiac pacing have been published in 2007 by the European European Society of Cardiology (ESC)[86] and in 2008, jointly by the American College of Cardiology (ACC), the American Heart Association (AHA) and the Heart Rhythm Society (HRS). The latter was formerly known as the North American Society of pacing and Electrophysiology (NASPE).[11] The European 2007 GL constitutes the first ever GL issued by the ESC on cardiac pacing. The US 2008 GL represents the most recent of a consecutive series of pacing GL updates, issued in 2002, 1998, 1991, 1984 in 1974 respectively. The 1998 edition was the first to touch upon heart failure as a potential indication for pacemaker therapy. It considered symptomatic drug-refractory dilated cardiomyopathy with prolonged PR interval as a potential indication for dual-chamber pacing. It mentioned that preliminary data on biventricular pacing suggested a possible improvement in symptoms in patients with dilated cardiomyopathy, but regarded this pacing mode still as investigational. The 2002 US GL update on the other hand assigned a recommendation class IIa (indicating "it is reasonable") to "biventricular pacing in medically refractory, symptomatic NYHA class III or IV patients with idiopathic dilated or ischaemic cardiomyopathy, prolonged QRS interval (greater than or equal to 130 ms), LV end-diastolic diameter greater than or equal to 55 mm, and ejection fraction less than or equal to 35%". This recommendation was based on two prospective randomised trials: MUSTIC[33] and MIRACLE.[22]

Practice GLs related to the treatment of HF have been issued separately from GLs for device-based cardiac therapy. The most recent GL on heart failure, issued by the ESC was published in 2008.[19] A "Focused Update on device therapy in heart failure" was released on-line in August 2010.[12] In April 2009, the ACC/AHA jointly issued a focused update of the 2005 GL for the diagnosis and management of heart failure. An update of the American GL is anticipated for 2011/2012.

Table A.1.: Guidelines for ICD therapy: indications and contra-indications

#	JOINT US/EU 2006 ICD GL	LOE	US 2008 updated ICD GL	LOE	BELGIAN 2010 ICD REIMBURSEMENT	PRIM/ SEC
1	In patients with CHD or NICM with sustained unstable VT or	IA	id.		Cardiac arrest. Syncope or near-syncope due to spontaneous VT.	S
2			In patients with structural heart disease and spontaneous sustained VT, whether stable or unstable.	IB		S
3			In patients with CHD and nonsustained VT, LVEF<40% and inducible VT/VF.	IB	In patients with CHD and nonsustained VT, LVEF<40% and inducible VT/VF.	S
4	In patients with CHD with LVEF ≤30-40% and NYHA II/III.	IA	In patients with CHD with LVEF ≤35% and NYHA II/III.	IA	In patients with CHD with LVEF ≤35% and NYHA II/III.	P
5	In patients with NICM with LVEF ≤30-35% and NYHA II/III.	IB	In patients with NICM with LVEF ≤35% and NYHA II/III.	IB	In patients with NICM with LVEF ≤35% and NYHA II/III.	P
6	In patients with CHD with LVEF ≤30-35% and NYHA I.	IIaB	In patients with CHD with LVEF ≤30% and NYHA I.	IA	In patients with CHD with LVEF ≤30% and NYHA I.	P
7	In patients with CHD or NICM and normal or near-normal LVEF and recurrent sustained VT.	IIaC	id.	IIaC		S
8	In patients with NICM with LVEF ≤30-35% and NYHA I.	IIbC	id.	IIbC		P
9	In patients with NICM with significant LV dysfunction and unexplained syncope.	IIaC	id.	IIaC	In patients with NICM with unexplained syncope and non-inducible arrhythmia.	S
10			Unexplained syncope and inducible VT/VF.	IB	Unexplained syncope and advanced structural heart disease with inducible VT/VF.	S
11			Unexplained syncope and advanced structural heart disease.	IIbC		S
12	Miscellaneous syndromes (primary prevention).					
CONTRA-INDICATIONS						
1	NYHA class IV patients or contraindications for ICD not specifically mentioned in this GL		ICD therapy is not indicated for NYHA IV patients who are not candidates for cardiac transplantation or CRT-D (i.e. *ambulatory* class IV)*.	IIIC	NYHA class IV	
2			ICD therapy is not indicated for patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantation criteria specified in the Class I, IIa, and IIb recommendations.	IIIC	Life expectancy < 1 year	
3			Miscellaneous			

Classes of recommendations and levels of evidence (LOE) see **??**. Patients are expected to receive optimal medical therapy and have a reasonable expectation of survival with a good functional status for more than 1 year. * "Ambulatory NYHA class IV as defined previously (subsection 1.2.2) and discussed in chapter on CRT. PRIM/SEC: use in primary (P) or secondary (S) prevention.

A.2.1 European guidelines for CRT

The guideline This guideline was published in August 2010 by the Committee for Practice Guidelines (CPG), a committee of the European Society of Cardiology (ESC) and was intended to be an update of the previous guidelines on CRT and pacing.[12,19] This clinical practice guideline considered the most recent evidence and included in its evidence several meta-analyses. In this chapter we will focus on its conclusions that are specifically relevant for patients in NYHA functional classes III and IV.

The guideline concerns different aspects of CRT but the scope of part two of this guideline is the effectiveness of CRT with either CRT-P or CRT-D in patients with heart failure in NYHA function class III/IV despite optimal pharmacological treatment, LVEF $\leq$ 35%, sinus rhythm (SR), left ventricular (LV) dilatation, and QRS duration of $\geq$ 120 or $\geq$ 130 ms, and uses the most recent clinical trial evidence with the intention to come to evidence-based conclusions.

Traditionally, these recommendations are based on the outcomes in the cohort of patients described by the inclusion criteria in the protocols of RCTs. But, since the characteristics of patients actually included in a trial sometimes differ substantially from the eligibility criteria, the Guideline Task Force members favoured restricting the applicability of these recommendations to the clinical profile and outcomes of the actually enrolled cohort rather than on the strict eligibility criteria, trying to represent a more accurate interpretation of the evidence provided by a trial's result.

Although it was stated that the guideline is evidence based, the specific search strategies are not specified and it is unclear whether a specific search strategy was used. However, given the large number of knowledgeable experts involved in the drafting of this guideline, it seems unlikely that major trials would have been overlooked. Probably more worrysome, the inclusion criteria for studies were unclear and some manifest mistakes crept into the data and the evidence tables as will be detailed further on.

Studies included The main studies included in this updated guideline are:
- MIRACLE,[22] and MIRACLE ICD,[24]
- COMPANION trial: CRT with or without ICD: combined endpoints of all-cause mortality and rehospitalisation for HF lowered by 35-40% although this endpoint was mainly driven by lower rehospitalisation rates (76%) and not by lower all-cause mortality,[25]
- CARE-HF: examining only CRT-P and showing less unplanned (first) rehospitalisations for worsening HF by 52% and unplanned (first) hospitalisations for major CVD events by 39%,[1]
- CARE-HF extension study.[26]

However, the COMPANION and CARE-HF trials were mistakenly described in this guideline update as double blind trials while these were clearly not blinded for the treating physicians and the patients themselves (see further in this chapter in the detailed description of studies). The MIRACLE and MIRACLE ICD trials, however, were real double blind trials where all patients had a device implanted prior to randomisation and with proper concealment of therapy for patients, treating physicians and nursing staff.

Main results

Mortality In COMPANION (see subsection 4.2.3), CRT-D was associated with a significant decrease in all-cause mortality (relative risk reduction 36 %, p=0.003), while the 24 % relative risk reduction in all-cause mortality associated with CRT-P was nearly statistically significant (p=0.059). A limitation of COMPANION was the absence of prespecified analysis to compare CRT-D and CRT-P, precluding demonstration of the superiority of one CRT strategy over the other. In CARE-HF (see subsection 4.2.4), where only CRT-P was assessed, a 36 % relative reduction in the risk of death (p<0.002) was observed after a mean follow-up time

of 29 months in the original trial. In the CARE-HF extension study, a relative risk reduction of 40% ($p<0.0001$) was observed, mainly due to a marked reduction in HF-related deaths.

Morbidity The authors report that in the COMPANION trial, CRT with or without an ICD lowered the combined endpoint of *all-cause mortality and hospitalisation for HF* by 35–40% (whichever event occurred first), mainly driven by the 76% lower rate of hospitalisations. However, this statement appears to be an incorrect interpretation of the original article that stated that CRT-D or CRT-P lowered the combined risks of rates of *death from HF or hospitalisation for HF* (a secondary end point) by 40% and 34% respectively.

In CARE-HF, CRT-P lowered the proportion of first unplanned hospitalisations for worsening HF by 52%, and the number of first unplanned hospitalisations for major cardiovascular events by 39%.

The COMPANION study also enrolled 217 NYHA class IV patients.[88] Patients were required to have had no scheduled or unscheduled admissions for HF during the last month and are termed *ambulatory class IV patients* and having a life expectancy of >6 months. Post hoc (unplanned) analysis found that time to all-cause mortality or first all-cause hospitalisation was significantly improved by both CRT-P and CRT-D as compared with optimal medical treatment. No significant benefit was observed on all-cause mortality. The 2-year all-cause mortality rates were 55% and 45% with CRT-D and CRT-P, respectively, compared with 62% in the control group. A significant functional improvement was also documented. Therefore, the authors conclude that these data support the use of CRT to improve morbidity (but not mortality) in ambulatory class IV patients.

The MIRACLE ICD study[47] and one large meta-analysis[5] support the choice of a CRT-D in patients in NYHA class III/IV, with LVEF of $\leq$ 35%, QRS width of $\geq$ 120 ms with a conventional indication for an ICD.

Quality of life Quality of life was not formally addressed in this clinical practice guideline update.

Adverse events Adverse events were not formally addressed in this clinical practice guideline update.

Impact of CRT on cardiac function and structure The authors of the updated guideline report a consistent finding in randomised trials with up to 6 months of follow-up of an up to 15% absolute reduction in LV end-diastolic diameter and an up to 6% increase in LVEF following CRT.[89,1] In the CARE-HF study, the mean reduction in LV end-systolic volume was 18% at 3 months and 26% after 18 months of CRT. Similarly, the mean LVEF increase was 3.7% at 3 months increasing to 6.9% at 18 months. The authors believe that these observations provide consistent evidence of a substantial, progressive, and sustained reverse remodelling effect conferred by CRT.

Recommendations A synoptic table juxtaposing the recommendations from the original 2007 GL and the 2010 update, along with the corresponding classes of recommendations and the levels of evidence, is provided in Table A.2.

The most important changes compared to the previous guideline in this update are:
- LV dilatation no longer required in the recommendation,
- Class IV patients should be ambulatory,
- Reasonable expectation of survival with good functional status for >1 year for CRT-D,
- Evidence is strongest for patients with typical LBBB,
- Similar level of evidence for CRT-P and CRT-D.

Conclusions The assessment of the evidence in this guideline, and therefore the recommendations, are to a large extent an opinion based product of a consensus process rather than a strict scientific assessment of available evidence. Evidence was not used systematically but seems to have been chosen to illustrate specific elements of the consensus. Therefore, we used this document mainly as an up-to-date reference source for recent studies and meta-analyses, rather than as a systematic assessment of efficacy or effectiveness.

A.2.2 US 2008 guideline for CRT

There are no major differences between the US and the European GLs. The US guideline for the first time introduced an additional NYHA class, "ambulatory NYHA class IV", which was later used in the 2010 European guideline update as well.[11]

In contrast to its European 2007 counterpart, the US guideline also provides recommendations on CRT in patient in NYHA class I or II. It stipulates that CRT may be considered for patients with LVEF less than or equal to 35% and with NYHA functional Class I or II symptoms who are receiving optimal recommended medical therapy when they are undergoing implantation of a permanent pacemaker or an ICD with anticipated frequent ventricular pacing. A class of recommendation III ("should not be administered") was assigned to CRT for asymptomatic patients with reduced LVEF in the absence of other indications for pacing and for patients whose functional status and life expectancy are limited predominantly by chronic noncardiac conditions.

In March 2010, an FDA meeting was held to discuss a Boston Scientific's PMA application to request approval for an expansion of the indications for the company's CRT-D devices, based on the MADIT-CRT study.[40] The FDA panel voted in favour of the proposed indication expansion towards (1) mild heart failure (NYHA Class II) with EF $\leq$30% and QRS duration $\geq$130ms and (2) asymptomatic heart failure (NYHA Class I) of ischaemic origin with EF $\leq$30% and QRS duration $\geq$130ms. The panel added two conditions to the approval: only patients with left bundle branch block and stable sinus rhythm were eligible for CRT and furthermore, a post approval study with a meaningful comparator group had to be set up to assess the predictive values of subgroups and safety.

Table A.2.: European Society of Cardiology 2007 and 2010 guidelines on CRT

#		ESC 2007 GLs	LOE	ESC 2010 UPDATE	LOE
1	HF NYHA class III/IV	CRT-P for HF pts who remain symptomatic in NYHA III–IV despite OPT, with LVEF ≤35%, LV dilatation, normal sinus rhythm and QRS ≥120 ms	IA	CRT-P/CRT-D is recommended to reduce morbidity and mortality in NYHA III/IV, LVEF ≤35%, QRS ≥120 ms, SR, OPT. *Class IV patients should be ambulatory*, i.e. no admissions for HF during the last month and a reasonable expectation of survival >6 months. For CRT-D, survival of >1 year with good functional status is required.	IA
2		CRT-D is an acceptable option for abovementioned pts who have an expectancy of survival with a good functional status for more than 1 year	IB		
3	HF plus indication for ICD	HF pts with a Class I indication for an ICD who are symptomatic in NYHA III–IV despite OPT, with LVEF ≤ 35%, LV dilatation, QRS ≥120 ms	IB		
4	HF plus bradycardia-PM indication	CRT in HF pts with NYHA III–IV,LVEF ≤35%, LV dilatation and a concomitant indication for permanent pacing	IIaC	CRT-P/CRT-D to reduce morbidity in NYHA III/IV, LVEF ≤35%, QRS ≥120 ms	IB
				CRT-P/CRT-D should be considered to reduce morbidity in NYHA III/IV, LVEF ≤35%, QRS <120 ms	IIaC
				CRT-P/CRT-D to reduce morbidity in NYHA II, LVEF ≤35%, QRS <120 ms	IIbC
5	HF plus atrial fibrillation	HF pts who remain symptomatic NYHA III–IV despite OPT, with low LVEF ≤35%, LV dilatation, permanent AF and indication for AV junction ablation.	IIaC	CRT-P/CRT-D to reduce morbidity in NYHA III/IV, LVEF ≤35%, QRS >130 ms in PM dependency induced by AV nodal ablation	IIaB
				CRT-P/CRT-D to reduce morbidity in NYHA III/IV, LVEF ≤35%, QRS >130 ms in slow ventricular rate and frequent (>94%) pacing	IIaC
6	LV dysfunction NYHA class II	NA		CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression in NYHA II, LVEF ≤35%, QRS ≥150 ms, SR, OPT	IA

B Belgian practice appendix

B.1 CRT identification numbers

IMA data were selected for each patient that presented one of the following code between January 1, 2005 and June 30, 2009.

CRT-P numbers 106006000651 126003000076 126003000112 106007000251 126003000103 126003000067 106006000432 126003000015 126003000051 106006000457 126003000024 106006000511 126003000042 106006000685 126003000085 106006000475 126003000033 106006000703 126003000094 106006000581 126003000051

Plugged CRT-D numbers 120003000013 120003000022 120003000031 120003000047 120003000056 120003000065 120003000074 120003000083 120003000092 120003000101 120003000117 120003000126 120003000135 120003000144 120003000153 120003000162 120003000171 120003000187 120003000196 120003000205 120003000214 120003000223 120003000232 120003000241 120003000251 120003000257 120003000266 120003000275 120003000284 120003000293 120003000302 120003000311 120003000327 120003000336 120003000345 120003000354 120003000363 120003000372 120003000381 120003000397 120003000406 120003000415 120003000424 120003000433 120003000442 120003000451 120003000467 120003000476 120003000485 120003000494 120003000503 120004000015 120004000024 120004000033 120004000042 120004000051 120004000067 120004000076 120004000085 120004000094 120004000103 120004000112 120004000121 120004000137 120004000146 120004000155

Full-feature CRT-D numbers 120005000017 120005000026 120005000035 120005000044 120005000053 120005000062 120005000071 120005000087 120005000096 120005000105 120005000114 120005000123 120005000132 120005000141 120005000157 120005000166 120005000175 120005000184 120005000193 120005000202 120005000211 120005000227 120005000236 120005000245 120005000254 120005000263 120005000272 120005000281 120005000297 120005000306 120005000315 120005000324 120005000333 120005000342 120005000351 120005000367 120005000376 120005000385 120005000394 120005000403 120005000412 120005000421 120005000437 120005000446 120005000455 120005000464 120005000473 120005000482 120005000491 120005000507 120006000012 120006000021 120006000037 120006000046 120006000055 120006000064 120006000073 120006000082 120006000091 120006000107 120006000116 120006000125 120006000134 120006000143 120006000152

Supplement for CRT-D upgrading 120007000014 120007000023 120007000032 120007000041 120007000057 120007000066 120007000075 120007000084 120007000093 120007000102 120007000111 120007000127 120007000136 120007000145 120007000154 120007000163 120007000172 120007000181 120007000197 120007000206 120007000215 120007000224 120007000233 120007000242 120007000251 120007000267 120007000276 120007000285 120007000294 120007000303 120007000312 120007000321 120007000337 120007000346 120007000355 120007000364 120007000373 120007000382 120007000391 120007000407 120007000416 120007000425 120007000434 120007000443 120007000452 120007000461 120007000477 120007000486 120007000495 120007000504 120008000016 120008000025 120008000034 120008000043 120008000052 120008000061 120008000077 120008000086 120008000095 120008000104 120008000113 120008000122 120008000131 120008000147 120008000156

B.2 Hospitalisation daily lump-sums

Table B.1.: Hospitalisation daily lump-sums

NIHDI Code	Label French	Label Dutch
768025	Hospitalisation - partie variable sur base des factures introduites: hôpitaux aigus - forfait par jour	Ziekenhuisverpleging - variabel gedeelte op basis van ingediende facturen : acute ziekenhuizen - bedrag per dag
768106	Hospitalisation - partie variable sur base des factures introduites: services Sp autres que palliatifs - forfait par jour	Ziekenhuisverpleging - variabel gedeelte op basis van ingediende facturen : Sp-diensten andere dan palliatieve - bedrag per dag
768121	Hospitalisation - partie variable sur base des factures introduites: hôpitaux psychiatriques (720,***,**) - forfait par jour	Ziekenhuisverpleging - variabel gedeelte op basis van ingediende facturen : psychiatrische ziekenhuizen (720,***,**) - bedrag per dag
768143	Hospitalisation - partie variable sur base des factures introduites: services palliatifs Sp - forfait par jour	Ziekenhuisverpleging - variabel gedeelte op basis van ingediende facturen : palliatieve Sp-diensten - bedrag per dag
768165	Hospitalisation - partie variable sur base des factures introduites: centres pour brûlés - forfait par jour	Ziekenhuisverpleging - variabel gedeelte op basis van ingediende facturen : centra voor brandwonden - bedrag per dag

B.3 Pseudo-codes recorded by device: primo-implantations and replacements

Table B.2.: Pseudo-codes recorded by device: primo-implantations and replacements

Stadium	NIHDI Ambul. Code	NIHDI Hospit. code	Label French	Label Dutch
Primo-implantation	684530	684541	Premier stimulateur cardiaque implantable, y compris l'adaptateur	Eerste implanteerbare hartstimulator, inclusief adaptor
Primo-implantation	691633	691644	Conventions - Défibrillateurs cardiaques implantables : Défibrillateur cardiaque implantable	Overeenkomsten - Implanteerbare hartdefibrillatoren : Implanteerbare hartdefibrillator
Replacement	684655	684666	Renouvellement prématuré du stimulateur cardiaque (article 35, § 11, 4° de la nomenclature)	Voortijdige hernieuwing van de hartstimulator (artikel 35, § 11, 4° van de nomenclatuur)
Replacement	691655	691666	Conventions - Défibrillateurs cardiaques implantables : Défibrillateur cardiaque implantable de remplacement	Overeenkomsten - Implanteerbare hartstimulatoren : Implanteerbare vervangingshartdefibrillator
Replacement	684375	684386	Stimulateur cardiaque de remplacement, y compris l' adaptateur	Vervangingshartstimulator, inclusief adaptor
Regularisation	785072		Régularisations - Implants et défibrillateurs cardiaques implantables	Regularisaties - Implantaten en implanteerbare hartdefibrillatoren

B.4 CRT system integrity checks

Table B.3.: CRT system integrity checks

NIHDI Ambul. code	NIHDI Hospit. code	Label French	Label Dutch
475856	475860	Contrôle de la qualité et/ou reprogrammation d'un stimulateur cardiaque, chambre simple (SSI), avec interrogation de la mémoire et mesure du seuil de stimulation et de sensibilité, avec protocole et tracés	Controle van de deugdelijkheid en/of herprogrammatie van een eenkamerpacemaker (SSI), met ondervraging van het geheugen en meting van de stimulatie- en gevoeligheidsdrempel, met protocol en tracés
475871	475882	Contrôle de la qualité et/ou reprogrammation d'un stimulateur cardiaque, chambre double (D.D.D.), avec interrogation de la mémoire et mesure du seuil de stimulation et de sensibilité, avec protocole et tracés	Controle van de deugdelijkheid en/of herprogrammatie van een tweekamerpacemaker (DDD), met ondervraging van het geheugen en meting van de stimulatie- en gevoeligheidsdrempel, met protocol en tracés
475893	475904	Contrôle de la qualité et/ou reprogrammation d'un défibrillateur cardiaque, avec mesure du seuil de stimulation et de sensibilité, avec évaluation de la performance du défibrillateur, avec protocole et tracés	Controle van de deugdelijkheid en/of herprogrammatie van een hartdefibrillator, met meting van de stimulatie- en gevoeligheidsdrempel en met evaluatie van de performantie van de defibrillator, met protocol en tracés

B.5 Contacts (consultations and visits by GP and specialists)

Table B.4.: Contacts (consultations and visits by GP and SP)

NIHDI Ambul. code	Label French	Label Dutch
101010	Consultation au cabinet du médecin généraliste avec droits acquis	Raadpleging in de spreekkamer van de algemeen geneeskundige met verworven rechten
101032	Consultation au cabinet du médecin généraliste agréé	Raadpleging in de spreekkamer van de erkende huisarts
101076	Consultation au cabinet du médecin généraliste agréé accrédité	Raadpleging in de spreekkamer van de geaccrediteerde erkende huisarts
102093	Consultation, à son cabinet, du médecin spécialiste en cardiologie, y compris un rapport écrit éventuel	Raadpleging, in de spreekkamer, van de geneesheer, specialist voor cardiologie, inclusief eventueel schriftelijk verslag
102594	Consultation, à son cabinet, du médecin accrédité spécialiste en cardiologie, y compris un rapport écrit éventuel	Raadpleging, in de spreekkamer, van de geaccrediteerde geneesheer, specialist voor cardiologie, inclusief een eventueel schriftelijk verslag
103014	Consultation du médecin spécialiste appelé par écrit par le médecin généraliste agréé traitant ou par le médecin généraliste avec droits acquis traitant, au domicile du malade, avec rapport écrit par le médecin spécialiste	Consult van de geneesheer-specialist, schriftelijk geroepen door de behandelende erkende huisarts of door de behandelende algemeen geneeskundige met verworven rechten bij een zieke thuis, met schriftelijk verslag van de geneesheer specialist
103036	Honoraires du médecin appelé en consultation : s'il s'agit d'un médecin de médecine générale	Honorarium van de ter consult bijgeroepen geneesheer : indien het om een algemeen geneeskundige gaat
103051	Consultation du médecin spécialiste appelé par écrit par le médecin généraliste agréé traitant ou par le médecin généraliste avec droits acquis traitant, auprès du malade résidant en maison de repos ou en maison de repos et de soins, comme définies dans l'intitulé qui précède les prestations 103913 et 104112, avec rapport écrit par le médecin spécialiste. La présence simultanée des deux médecins n'est obligatoire que dans le cas où celle-ci est demandée dans la demande écrite	Consult van de geneesheer-specialist, schriftelijk geroepen door de behandelende erkende huisarts of door de behandelende algemeen geneeskundige met verworven rechten bij een zieke verblijvend in een rustoord voor bejaarden of in een rust- en verzorgingstehuis, zoals gedefinieerd in de hoofding voorafgaand aan de verstrekkingen 103913 en 104112, met schriftelijk verslag van de geneesheer specialist. De aanwezigheid van beide geneesheren samen is slechts vereist in de gevallen waarin dit gevraagd wordt in de schriftelijke aanvraag

NIHDI Ambul. code	Label French	Label Dutch
103073	Consultation du médecin spécialiste appelé par écrit par le médecin traitant, auprès du malade séjournant en résidence communautaire, momentanée ou définitive de personnes handicapées, avec rapport écrit par le médecin spécialiste appelé. La présence simultanée des deux médecins n'est obligatoire que dans le cas où celle-ci est demandée dans la demande écrite	Consult van de geneesheer-specialist, schriftelijk geroepen door de behandelende arts bij een zieke verblijvend in een instelling waar gehandicapten tijdelijk of definitief verblijven, met schriftelijk verslag van de bijgeroepen geneesheer specialist. De aanwezigheid van beide geneesheren samen is slechts vereist in de gevallen waarin dit gevraagd wordt in de schriftelijke aanvraag
103110	Visite au domicile du malade, par le médecin généraliste avec droits acquis	Bezoek, bij de zieke thuis, door de algemeen geneeskundige met verworven rechten
103132	Visite, au domicile du malade, par le médecin généraliste agréé	Bezoek, bij de zieke thuis, door de erkende huisarts
103213	Visite par le médecin généraliste avec droits acquis à plusieurs bénéficiaires à leur résidence ou domicile commun, à l'occasion d'un même déplacement : deux bénéficiaires, par bénéficiaire	Bezoek door de algemeen geneeskundige met verworven rechten bij verscheidene rechthebbenden in hun gemeenschappelijke woonplaats of gemeenschappelijk huis, bij eenzelfde reis : twee rechthebbenden, per rechthebbende
103235	Visite par le médecin généraliste avec droits acquis à plusieurs bénéficiaires à leur résidence ou domicile commun, à l'occasion d'un même déplacement : trois bénéficiaires ou plus, par bénéficiaire	Bezoek door de algemeen geneeskundige met verworven rechten bij verscheidene rechthebbenden in hun gemeenschappelijke woonplaats of gemeenschappelijk huis, bij eenzelfde reis : drie rechthebbenden of meer, per rechthebbende
103316	Visite par le médecin généraliste avec droits acquis dans un établissement où séjournent des enfants, des convalescents ou des handicapés (séjour de jour, séjour de nuit, séjour de jour et de nuit) : à un bénéficiaire	Bezoek door de algemeen geneeskundige met verworven rechten in een instelling waar kinderen, herstellenden of gehandicapten verblijven (dagverblijf, overnachting, dagverblijf en overnachting) : bij één rechthebbende
103331	Visite par le médecin généraliste avec droits acquis dans un établissement où séjournent des enfants, des convalescents ou des handicapés (séjour de jour, séjour de nuit, séjour de jour et de nuit) : à deux bénéficiaires, à l'occasion d'un même déplacemen	Bezoek door de algemeen geneeskundige met verworven rechten in een instelling waar kinderen, herstellenden of gehandicapten verblijven (dagverblijf, overnachting, dagverblijf en overnachting) : bij twee rechthebbenden, bij eenzelfde reis, per rechthebbende

NIHDI Ambul. code	Label French	Label Dutch
103353	Visite par le médecin généraliste avec droits acquis dans un établissement où séjournent des enfants, des convalescents ou des handicapés (séjour de jour, séjour de nuit, séjour de jour et de nuit) : à trois bénéficiaires ou plus, à l'occasion d'un même déplacement, par bénéficiaire	Bezoek door de algemeen geneeskundige met verworven rechten in een instelling waar kinderen, herstellenden of gehandicapten verblijven (dagverblijf, overnachting, dagverblijf en overnachting) : bij drie rechthebbenden of meer, bij eenzelfde reis, per rechthebbende
103412	Visite par le médecin généraliste agréé à plusieurs bénéficiaires à leur résidence ou domicile commun, à l'occasion d'un même déplacement : deux bénéficiaires, par bénéficiaire	Bezoek door de erkende huisarts bij verscheidene rechthebbenden in hun gemeenschappelijke woonplaats of gemeenschappelijk huis, naar aanleiding van een zelfde reis : twee rechthebbenden, per rechthebbende
103434	Visite par le médecin généraliste agréé à plusieurs bénéficiaires à leur résidence ou domicile commun, à l'occasion d'un même déplacement : trois bénéficiaires ou plus, par bénéficiaire	Bezoek door de erkende huisarts bij verscheidene rechthebbenden in hun gemeenschappelijke woonplaats of gemeenschappelijk huis, naar aanleiding van een zelfde reis : drie rechthebbenden of meer, per rechthebbende
103515	Visite par le médecin généraliste agréé dans un établissement où séjournent des enfants, des convalescents ou des handicapés (séjour de jour, séjour de nuit, séjour de jour et de nuit) : à un bénéficiaire	Bezoek door de erkende huisarts in een instelling waar kinderen, herstellenden of mindervaliden verblijven (verblijf overdag, verblijf 's nachts, verblijf overdag en 's nachts) : bij één rechthebbende
103530	Visite par le médecin généraliste agréé dans un établissement où séjournent des enfants, des convalescents ou des handicapés (séjour de jour, séjour de nuit, séjour de jour et de nuit) : à deux bénéficiaires, à l'occasion d'un même déplacement, par bénéficiaire	Bezoek door de erkende huisarts in een instelling waar kinderen, herstellenden of mindervaliden verblijven (verblijf overdag, verblijf 's nachts, verblijf overdag en 's nachts) : bij twee rechthebbenden, naar aanleiding van een zelfde reis, per rechthebbende
103552	Visite par le médecin généraliste agréé dans un établissement où séjournent des enfants, des convalescents ou des handicapés (séjour de jour, séjour de nuit, séjour de jour et de nuit) : à trois bénéficiaires ou plus, à l'occasion d'un même déplacement, par bénéficiaire	Bezoek door de erkende huisarts in een instelling waar kinderen, herstellenden of mindervaliden verblijven (verblijf overdag, verblijf 's nachts, verblijf overdag en 's nachts) : bij drie rechthebbenden of meer, naar aanleiding van een zelfde reis, per rechthebbende
103611	Visite effectuée au domicile du malade entre 18 heures et 21 heures	Bezoek, tussen 18 en 21 uur afgelegd bij de zieke thuis
103633	Visite effectuée au domicile du malade, la nuit, entre 21 heures et 8 heures	Bezoek, 's nachts tussen 21 en 8 uur afgelegd bij de zieke thuis
103655	Visite effectuée le week-end, du samedi à 8 heures au lundi à 8 heures, au domicile du malade	Bezoek, tijdens het weekeind, van zaterdag 8 uur tot maandag 8 uur, afgelegd bij de zieke thuis

NIHDI Ambul. code	Label French	Label Dutch
103670	Visite au domicile du malade effectuée au cours d'un jour férié, c'est-à-dire depuis la veille de ce jour férié à 21 heures jusqu'au lendemain de ce même jour à 8 heures	Bezoek bij de zieke thuis, afgelegd op een feestdag, dat wil zeggen vanaf daags voor die feestdag om 21 uur tot daags na die feestdag om 8 uur
103751	Visite par le médecin spécialiste en pédiatrie à plusieurs bénéficiaires à leur résidence ou domicile commun, à l'occasion d'un même déplacement : deux bénéficiaires, par bénéficiaire	Bezoek door de geneesheer, specialist voor kindergeneeskunde bij verscheidene rechthebbenden in hun gemeenschappelijke woonplaats of gemeenschappelijk huis, bij eenzelfde reis : twee rechthebbenden,per rechthebbende
103913	Visite effectuée par le médecin généraliste agréé à un malade dans un établissement pouvant porter en compte une intervention forfaitaire telle que prévue dans les arrêtés ministériels des 19 mai 1992 et 5 avril 1995 concernant respectivement les maisons de repos et de soins et les maisons de repos pour personnes âgées : à un bénéficiaire	Bezoek door de erkende huisarts, bij de zieke in een inrichting die een forfaitaire tegemoetkoming zoals voorzien in de ministeriële besluiten van 19 mei 1992 en 5 april 1995 met betrekking tot respectievelijk de rust- en verzorgingstehuizen en de rustoorden voor bejaarden, in rekening kan brengen : bij één rechthebbende
103935	Visite effectuée par le médecin généraliste agréé à un malade dans un établissement pouvant porter en compte une intervention forfaitaire telle que prévue dans les arrêtés ministériels des 19 mai 1992 et 5 avril 1995 concernant respectivement les maisons de repos et de soins et les maisons de repos pour personnes âgées : à deux bénéficiaires, à l'occasion d'un même déplacement, par bénéficiaire	Bezoek door de erkende huisarts, bij de zieke in een inrichting die een forfaitaire tegemoetkoming zoals voorzien in de ministeriële besluiten van 19 mei 1992 en 5 april 1995 met betrekking tot respectievelijk de rust- en verzorgingstehuizen en de rustoorden voor bejaarden, in rekening kan brengen : bij twee rechthebbenden, bij eenzelfde reis, per rechthebbende
103950	Visite effectuée par le médecin généraliste agréé à un malade dans un établissement pouvant porter en compte une intervention forfaitaire telle que prévue dans les arrêtés ministériels des 19 mai 1992 et 5 avril 1995 concernant respectivement les maisons de repos et de soins et les maisons de repos pour personnes âgées : à trois bénéficiaires ou plus, à l'occasion d'un même déplacement, par bénéficiaire	Bezoek door de erkende huisarts, bij de zieke in een inrichting die een forfaitaire tegemoetkoming zoals voorzien in de ministeriële besluiten van 19 mei 1992 en 5 april 1995 met betrekking tot respectievelijk de rust- en verzorgingstehuizen en de rustoorden voor bejaarden, in rekening kan brengen : bij drie rechthebbenden of meer, bij eenzelfde reis, per rechthebbende

NIHDI Ambul. code	Label French	Label Dutch
104112	Visite effectuée par le médecin généraliste avec droits acquis à un malade dans un établissement pouvant porter en compte une intervention forfaitaire telle que prévue dans les arrêtés ministériels des 19 mai 1992 et 5 avril 1995 concernant respectivement les maisons de repos et de soins et les maisons de repos pour personnes âgées : à un bénéficiaire	Bezoek door de algemeen geneeskundige met verworven rechten bij de zieke in een inrichting die een forfaitaire tegemoetkoming zoals voorzien in de ministeriële besluiten van 19 mei 1992 en 5 april 1995 met betrekking tot respectievelijk de rust- en verzorgingstehuizen en de rustoorden voor bejaarden in rekening kan brengen : bij één rechthebbende
104134	Visite effectuée par le médecin généraliste avec droits acquis d'un malade dans un établissement pouvant porter en compte un intervention forfaitaire telle que prévue dans les arrêtés ministériels des 19 mai 1992 et 5 avril 1995 concernant respectivement les maisons de repos et de soins et les maisons de repos pour personnes âgées : à deux bénéficiaires, à l'occasion d'un même déplacement, par bénéficiaire	Bezoek door de algemeen geneeskundige met verworven rechten bij de zieke in een inrichting die een forfaitaire tegemoetkoming zoals voorzien in de ministeriële besluiten van 19 mei 1992 en 5 april 1995 met betrekking tot respectievelijk de rust- en verzorgingstehuizen en de rustoorden voor bejaarden in rekening kan brengen : bij twee rechthebbenden, bij eenzelfde reis, per rechthebbende
104156	Visite effectuée par le médecin généraliste avec droits acquis à un malade dans un établissement pouvant porter en compte une intervention forfaitaire telle que prévue dans les arrêtés ministériels des 19 mai 1992 et 5 avril 1995 concernant respectivement les maisons de repos et de soins et les maisons de repos pour personnes âgées : à trois bénéficiaires ou plus, à l'occasion d'un même déplacement, par bénéficiaire	Bezoek door de algemeen geneeskundige met verworven rechten bij de zieke in een inrichting die een forfaitaire tegemoetkoming zoals voorzien in de ministeriële besluiten van 19 mei 1992 en 5 april 1995 met betrekking tot respectievelijk de rust- en verzorgingstehuizen en de rustoorden voor bejaarden in rekening kan brengen : bij drie rechthebbenden of meer, bij eenzelfde reis, per rechthebbende
104215	Visite effectuée par le médecin généraliste agréé au domicile du malade entre 18 heures et 21 heures	Bezoek door de erkende huisarts tussen 18 en 21 uur afgelegd bij de zieke thuis
104230	Visite effectuée par le médecin généraliste agréé au domicile du malade, la nuit, entre 21 heures et 8 heures	Bezoek door de erkende huisarts 's nachts tussen 21 en 8 uur afgelegd bij de zieke thuis
104252	Visite effectuée par le médecin généraliste agréé le week-end, du samedi à 8 heures au lundi à 8 heures, au domicile du malade	Bezoek door de erkende huisarts tijdens het weekend, van zaterdag 8 uur tot maandag 8 uur, afgelegd bij de zieke thuis
104274	Visite au domicile du malade effectuée par le médecin généraliste agréé au cours d'un jour férié, c'est-à-dire depuis la veille de ce jour férié à 21 heures jusqu'au lendemain de ce jour à 8 heures	Bezoek bij de zieke thuis, afgelegd door de erkende huisarts op een feestdag, dat wil zeggen vanaf daags vóór die feestdag om 21 uur tot daags na die feestdag om 8 uur

NIHDI Ambul. code	Label French	Label Dutch
104355	Consultation du médecin généraliste agréé appelé par un médecin au domicile du malade	Consult van een erkende huisarts bij de zieke thuis door een geneesheer aangevraagd
104370	Visite effectuée par le médecin généraliste agréé à un patient palliatif à domicile	Bezoek door de erkende huisarts thuis bij een palliatieve patiënt
104392	Visite effectuée entre 18 heures et 21 heures, par le médecin généraliste agréé à un patient palliatif à domicile	Bezoek door de erkende huisarts tussen 18 en 21 uur thuis bij een palliatieve patiënt
104414	Visite effectuée la nuit, entre 21 heures et 8 heures, par le médecin généraliste agréé à un patient palliatif à domicile	Bezoek door de erkende huisarts 's nachts tussen 21 en 8 uur thuis bij een palliatieve patiënt
104436	Visite effectuée le week-end, du samedi à 8 heures au lundi à 8 heures, par le médecin généraliste agréé à un patient palliatif à domicile	Bezoek door de erkende huisarts tijdens het weekeind van zaterdag 8 uur tot maandag 8 uur, thuis bij een palliatieve patiënt
104451	Visite effectuée au cours d'un jour férié, c'est-à-dire depuis la veille de ce jour férié à 21 heures jusqu'au lendemain de ce jour à 8 heures, par le médecin généraliste agréé à un patient palliatif à domicile	Bezoek door de erkende huisarts op een feestdag, dat wil zeggen vanaf daags voor die feestdag om 21 uur tot daags na die feestdag om 8 uur bij een palliatieve patiënt
104510	Visite effectuée par le médecin généraliste avec droits acquis au domicile du malade entre 18 heures et 21 heures	Bezoek door de algemeen geneeskundige met verworven rechten tussen 18 en 21 uur afgelegd bij de zieke thuis
104532	Visite effectuée par le médecin généraliste avec droits acquis au domicile du malade, la nuit, entre 21 heures et 8 heures	Bezoek door de algemeen geneeskundige met verworven rechten 's nachts tussen 21 en 8 uur afgelegd bij de zieke thuis
104554	Visite effectuée par le médecin généraliste avec droits acquis le week-end, du samedi à 8 heures au lundi à 8 heures, au domicile du malade	Bezoek door de algemeen geneeskundige met verworven rechten tijdens het weekeind van zaterdag 8 uur tot maandag 8 uur, afgelegd bij de zieke thuis
104576	Visite au domicile du malade effectuée par le médecin généraliste avec droits acquis au cours d'un jour férié, c'est-à-dire depuis la veille de ce jour férié à 21 heures jusqu'au lendemain de ce jour à 8 heures	Bezoek bij de zieke thuis, afgelegd door de algemeen geneeskundige met verworven rechten op een feestdag, dat wil zeggen vanaf daags vóór die feestdag om 21 uur tot daags na die feestdag om 8 uur
104650	Consultation du médecin généraliste avec droits acquis appelé par un médecin au domicile du malade	Consult van de algemeen geneeskundige met verworven rechten bij de zieke thuis door een geneesheer aangevraagd
104672	Visite effectuée par le médecin généraliste avec droits acquis à un patient palliatif à domicile	Bezoek door de algemeen geneeskundige met verworven rechten, thuis bij een palliatieve patiënt

NIHDI Ambul. code	Label French	Label Dutch
104694	Visite effectuée, entre 18 heures et 21 heures, par le médecin généraliste avec droits acquis à un patient palliatif à domicile	Bezoek door de algemeen geneeskundige met verworven rechten, tussen 18 en 21 uur thuis bij een palliatieve patiënt
104716	Visite effectuée la nuit, entre 21 heures et 8 heures, par le médecin généraliste avec droits acquis à un patient palliatif à domicile	Bezoek door de algemeen geneeskundige met verworven rechten, 's nachts tussen 21 en 8 uur thuis bij een palliatieve patiënt
104731	Visite effectuée le week-end, du samedi à 8 heures au lundi à 8 heures, par le médecin généraliste avec droits acquis à un patient palliatif à domicile	Bezoek door de algemeen geneeskundige met verworven rechten, tijdens het weekeind van zaterdag 8 uur tot maandag 8 uur thuis bij de palliatieve patiënt
104753	Visite effectuée au cours d'un jour férié, c'est-à-dire depuis la veille de ce jour férié à 21 heures jusqu'au lendemain de ce jour à 8 heures, par le médecin généraliste avec droits acquis à un patient palliatif à domicile	Bezoek door de algemeen geneeskundige met verworven rechten, op een feestdag, dat wil zeggen vanaf daags voor die feestdag om 21 uur tot daags na die feestdag om 8 uur thuis bij de palliatieve patiënt

B.6 GP and specialists qualification codes

Table B.5.: Qualification codes from the IMA database 2008-2009

Qualification	code	label
GP	1 - 9	General practitioner
Geriatrician	18	geriatry trainee
Internist	58	Internal medicine trainee
Geriatrician	573	Internal medicine, geriatry and endocrino-diabetology
Internist	580	Internal medicine specialist
Geriatrician	581	Internal medicine specialist, holder of geriatry title
Internist	582	Internal medicine and in vitro nuclear medicine specialist
Internist	583	Internal medicine specialist, holder of endocrino-diabetology title
Internist	584	Internal medicine specialist, holder of F & P title
Internist	589	Internal medicine specialist, holder of urgency title
Cardiologist	591	Internal medicine and cardiology specialist
Cardiologist	730	Cardiology specialist
Cardiologist	734	Cardiology and F & P specialist
Cardiologist	739	Internal medicine specialist, holder of cardiology title
Internist	983	Internal medicine and nuclear medicine specialist, holder of endocrino-diabetology title
Internist	985	Internal medicine and nuclear medicine specialist

B.7 Identifying hospital episodes in IMA-AIM reimbursement data

To calculate the length of stay and the reimbursements per hospital episode, the following algorithm was used.

1. Sort data set by patient ID and reimbursement date of hospital "lump sum per diem" (one of RIZIV-INAMI nomenclature codes as described in Table B.1).
2. Add to each reimbursement date of hospital "lump sum per diem" an end date calculated as $date_{reimbursement} + N_{days}$ where N_{days} = number of days recorded in the IMA-AIM data.
3. Merge adjacent reimbursement episodes: $(end_{n+1} - start_n) \leq 1$.
4. Hospital episodes in which one of the CRT implant RIZIV-INAMI nomenclature codes was found, was marked as the index hospitalisation.

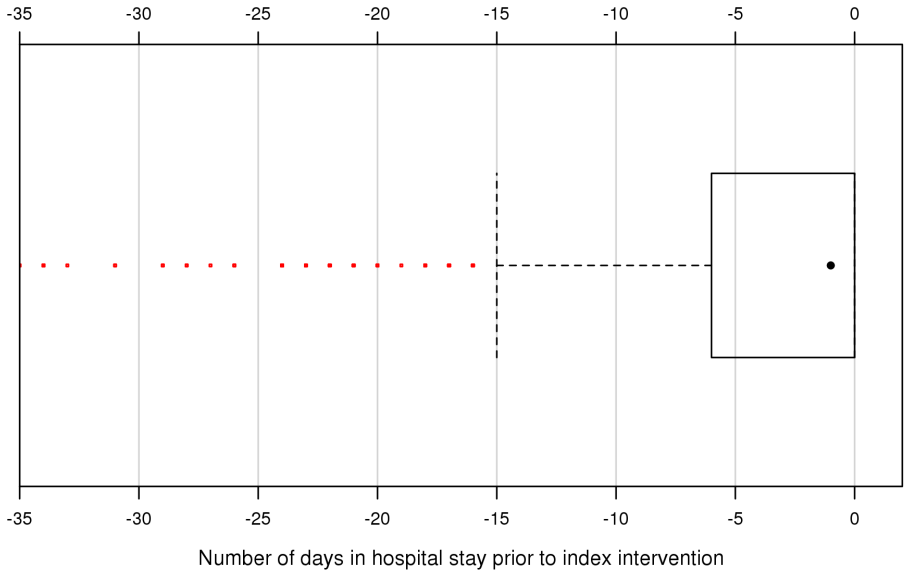
C Modelling appendix

C.1 Hospital episodes in IMA-AIM reimbursement data

To calculate the length of stay and the reimbursements per hospital episode, the algorithm described in section B.7 was adjusted. Figure Figure C.1 shows the distribution of the number of days a patient was hospitalised prior to the day the CRT was implanted. Based on this analysis, we chose to exclude, for reasons of clinical relevance, all days in the hospital stay prior to the CRT implant according to the following rule

$$if\ (date_{intervention} - date_{start} > 1)\ then\ date_{start} = (date_{intervention} - 1)$$

Figure C.1.: Distribution of the number of days prior to CRT implant (extreme values ≤ -36 are not shown [2.5% of data])



A further change to the length of stay for the hospital episodes was the adjustment of the length of stay for the CRT-P hospital episodes to a level similar to the CRT-D hospital episodes. This adjustment attenuates the effect of possible confounders influencing the length of stay (e.g. age). The adjustment was effected per hospital episode according to the following rule

$$LOS_{CRT-P}\ adjusted = LOS_{CRT-P} \times \frac{mean\ LOS_{CRT-D}}{mean\ LOS_{CRT-P}} = LOS_{CRT-P} \times 0.930\ldots$$

where LOS =length of stay of the hospital episode

C.2 Reimbursed items in hospital episodes

All selected RIZIV-INAMI nomenclature codes (see appendix Appendix B) reimbursed between the start date and end date of the hospital episode were taken into account.

In Belgium, hospital per diem costs are covered by 2 distinct systems of public health funding. A major part is covered through fixed monthly hospital payments but these are not registered in the IMA-AIM data. Additional remuneration consists of a lump sum billed each day of the hospital stay, for which the data are available in the IMA-AIM data. We replaced these lump sums by the 100% hospital lump sum per diem calculated as the actual per diem prices[a] available per hospital, per year, per semester and per type of stay (see table Table B.1 in appendix Appendix B) multiplied by the number of invoiced days for the hospital stay.

The total lump sum per diem per hospital episode was adjusted in a similar way to the length of stay (see section C.1 above). The lump sum per diem adjustment was effected per hospital episode according to the following rule

$$LSPD_{CRT-P}\ adjusted = LSPD_{CRT-P} \times \frac{mean\ LSPD_{CRT-D}}{mean\ LSPD_{CRT-P}} = LSPD_{CRT-P} \times 0.994\ldots$$

where $LSPD = \sum$ lump sum per diem of the hospital episode

a. as published by RIZIV–INAMI (http://www.riziv.be)

D Budget impact appendix

The following tables show the disaggregated calculation of the budget impact for both the OPT, CRT-P and CRT-D cohort (an assumed yearly 850 patients).

Yearly cohort of 850 patients		Average costs of the cohort in the follow-up year															
year	Cost categories	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
2011	OPT hospitalization	6.228.829 €	5.068.100 €	4.111.090 €	3.328.411 €	2.687.406 €	2.163.855 €	1.737.134 €	1.390.594 €	1.109.229 €	880.968 €	695.833 €	546.339 €	426.164 €	330.361 €	253.953 €	193.404 €
	OPT follow-up	773.169 €	629.091 €	510.300 €	413.148 €	333.581 €	268.594 €	215.626 €	172.611 €	137.686 €	109.352 €	86.372 €	67.816 €	52.899 €	41.007 €	31.523 €	24.007 €
	OPT upgrade ICD	376.983 €	306.733 €	248.813 €	201.443 €	162.648 €	130.962 €	105.135 €	84.162 €	67.133 €	53.318 €	42.113 €	33.066 €	25.792 €	19.994 €	15.370 €	11.705 €
	OPT total cost	7.378.982 €	6.003.923 €	4.870.202 €	3.943.002 €	3.183.635 €	2.563.410 €	2.057.896 €	1.647.367 €	1.314.048 €	1.043.639 €	824.318 €	647.221 €	504.855 €	391.362 €	300.846 €	229.116 €
2012	OPT hospitalization		6.228.829 €	5.068.100 €	4.111.090 €	3.328.411 €	2.687.406 €	2.163.855 €	1.737.134 €	1.390.594 €	1.109.229 €	880.968 €	695.833 €	546.339 €	426.164 €	330.361 €	253.953 €
	OPT follow-up		773.169 €	629.091 €	510.300 €	413.148 €	333.581 €	268.594 €	215.626 €	172.611 €	137.686 €	109.352 €	86.372 €	67.816 €	52.899 €	41.007 €	31.523 €
	OPT upgrade ICD		376.983 €	306.733 €	248.813 €	201.443 €	162.648 €	130.962 €	105.135 €	84.162 €	67.133 €	53.318 €	42.113 €	33.066 €	25.792 €	19.994 €	15.370 €
	OPT total cost		7.378.982 €	6.003.923 €	4.870.202 €	3.943.002 €	3.183.635 €	2.563.410 €	2.057.896 €	1.647.367 €	1.314.048 €	1.043.639 €	824.318 €	647.221 €	504.855 €	391.362 €	300.846 €
2013	OPT hospitalization			6.228.829 €	5.068.100 €	4.111.090 €	3.328.411 €	2.687.406 €	2.163.855 €	1.737.134 €	1.390.594 €	1.109.229 €	880.968 €	695.833 €	546.339 €	426.164 €	330.361 €
	OPT follow-up			773.169 €	629.091 €	510.300 €	413.148 €	333.581 €	268.594 €	215.626 €	172.611 €	137.686 €	109.352 €	86.372 €	67.816 €	52.899 €	41.007 €
	OPT upgrade ICD			376.983 €	306.733 €	248.813 €	201.443 €	162.648 €	130.962 €	105.135 €	84.162 €	67.133 €	53.318 €	42.113 €	33.066 €	25.792 €	19.994 €
	OPT total cost			7.378.982 €	6.003.923 €	4.870.202 €	3.943.002 €	3.183.635 €	2.563.410 €	2.057.896 €	1.647.367 €	1.314.048 €	1.043.639 €	824.318 €	647.221 €	504.855 €	391.362 €
2014	OPT hospitalization				6.228.829 €	5.068.100 €	4.111.090 €	3.328.411 €	2.687.406 €	2.163.855 €	1.737.134 €	1.390.594 €	1.109.229 €	880.968 €	695.833 €	546.339 €	426.164 €
	OPT follow-up				773.169 €	629.091 €	510.300 €	413.148 €	333.581 €	268.594 €	215.626 €	172.611 €	137.686 €	109.352 €	86.372 €	67.816 €	52.899 €
	OPT upgrade ICD				376.983 €	306.733 €	248.813 €	201.443 €	162.648 €	130.962 €	105.135 €	84.162 €	67.133 €	53.318 €	42.113 €	33.066 €	25.792 €
	OPT total cost				7.378.982 €	6.003.923 €	4.870.202 €	3.943.002 €	3.183.635 €	2.563.410 €	2.057.896 €	1.647.367 €	1.314.048 €	1.043.639 €	824.318 €	647.221 €	504.855 €
2015	OPT hospitalization					6.228.829 €	5.068.100 €	4.111.090 €	3.328.411 €	2.687.406 €	2.163.855 €	1.737.134 €	1.390.594 €	1.109.229 €	880.968 €	695.833 €	546.339 €
	OPT follow-up					773.169 €	629.091 €	510.300 €	413.148 €	333.581 €	268.594 €	215.626 €	172.611 €	137.686 €	109.352 €	86.372 €	67.816 €
	OPT upgrade ICD					376.983 €	306.733 €	248.813 €	201.443 €	162.648 €	130.962 €	105.135 €	84.162 €	67.133 €	53.318 €	42.113 €	33.066 €
	OPT total cost					7.378.982 €	6.003.923 €	4.870.202 €	3.943.002 €	3.183.635 €	2.563.410 €	2.057.896 €	1.647.367 €	1.314.048 €	1.043.639 €	824.318 €	647.221 €
2016	OPT hospitalization						6.228.829 €	5.068.100 €	4.111.090 €	3.328.411 €	2.687.406 €	2.163.855 €	1.737.134 €	1.390.594 €	1.109.229 €	880.968 €	695.833 €
	OPT follow-up						773.169 €	629.091 €	510.300 €	413.148 €	333.581 €	268.594 €	215.626 €	172.611 €	137.686 €	109.352 €	86.372 €
	OPT upgrade ICD						376.983 €	306.733 €	248.813 €	201.443 €	162.648 €	130.962 €	105.135 €	84.162 €	67.133 €	53.318 €	42.113 €
	OPT total cost						7.378.982 €	6.003.923 €	4.870.202 €	3.943.002 €	3.183.635 €	2.563.410 €	2.057.896 €	1.647.367 €	1.314.048 €	1.043.639 €	824.318 €
2017	OPT hospitalization							6.228.829 €	5.068.100 €	4.111.090 €	3.328.411 €	2.687.406 €	2.163.855 €	1.737.134 €	1.390.594 €	1.109.229 €	880.968 €
	OPT follow-up							773.169 €	629.091 €	510.300 €	413.148 €	333.581 €	268.594 €	215.626 €	172.611 €	137.686 €	109.352 €
	OPT upgrade ICD							376.983 €	306.733 €	248.813 €	201.443 €	162.648 €	130.962 €	105.135 €	84.162 €	67.133 €	53.318 €
	OPT total cost							7.378.982 €	6.003.923 €	4.870.202 €	3.943.002 €	3.183.635 €	2.563.410 €	2.057.896 €	1.647.367 €	1.314.048 €	1.043.639 €
2018	OPT hospitalization								6.228.829 €	5.068.100 €	4.111.090 €	3.328.411 €	2.687.406 €	2.163.855 €	1.737.134 €	1.390.594 €	1.109.229 €
	OPT follow-up								773.169 €	629.091 €	510.300 €	413.148 €	333.581 €	268.594 €	215.626 €	172.611 €	137.686 €
	OPT upgrade ICD								376.983 €	306.733 €	248.813 €	201.443 €	162.648 €	130.962 €	105.135 €	84.162 €	67.133 €
	OPT total cost								7.378.982 €	6.003.923 €	4.870.202 €	3.943.002 €	3.183.635 €	2.563.410 €	2.057.896 €	1.647.367 €	1.314.048 €
2019	OPT hospitalization									6.228.829 €	5.068.100 €	4.111.090 €	3.328.411 €	2.687.406 €	2.163.855 €	1.737.134 €	1.390.594 €
	OPT follow-up									773.169 €	629.091 €	510.300 €	413.148 €	333.581 €	268.594 €	215.626 €	172.611 €
	OPT upgrade ICD									376.983 €	306.733 €	248.813 €	201.443 €	162.648 €	130.962 €	105.135 €	84.162 €
	OPT total cost									7.378.982 €	6.003.923 €	4.870.202 €	3.943.002 €	3.183.635 €	2.563.410 €	2.057.896 €	1.647.367 €
2020	OPT hospitalization										6.228.829 €	5.068.100 €	4.111.090 €	3.328.411 €	2.687.406 €	2.163.855 €	1.737.134 €
	OPT follow-up										773.169 €	629.091 €	510.300 €	413.148 €	333.581 €	268.594 €	215.626 €
	OPT upgrade ICD										376.983 €	306.733 €	248.813 €	201.443 €	162.648 €	130.962 €	105.135 €
	OPT total cost										7.378.982 €	6.003.923 €	4.870.202 €	3.943.002 €	3.183.635 €	2.563.410 €	2.057.896 €
2021	OPT hospitalization											6.228.829 €	5.068.100 €	4.111.090 €	3.328.411 €	2.687.406 €	2.163.855 €
	OPT follow-up											773.169 €	629.091 €	510.300 €	413.148 €	333.581 €	268.594 €
	OPT upgrade ICD											376.983 €	306.733 €	248.813 €	201.443 €	162.648 €	130.962 €
	OPT total cost											7.378.982 €	6.003.923 €	4.870.202 €	3.943.002 €	3.183.635 €	2.563.410 €
2022	OPT hospitalization												6.228.829 €	5.068.100 €	4.111.090 €	3.328.411 €	2.687.406 €
	OPT follow-up												773.169 €	629.091 €	510.300 €	413.148 €	333.581 €
	OPT upgrade ICD												376.983 €	306.733 €	248.813 €	201.443 €	162.648 €
	OPT total cost												7.378.982 €	6.003.923 €	4.870.202 €	3.943.002 €	3.183.635 €
2023	OPT hospitalization													6.228.829 €	5.068.100 €	4.111.090 €	3.328.411 €
	OPT follow-up													773.169 €	629.091 €	510.300 €	413.148 €
	OPT upgrade ICD													376.983 €	306.733 €	248.813 €	201.443 €
	OPT total cost													7.378.982 €	6.003.923 €	4.870.202 €	3.943.002 €
2024	OPT hospitalization														6.228.829 €	5.068.100 €	4.111.090 €
	OPT follow-up														773.169 €	629.091 €	510.300 €
	OPT upgrade ICD														376.983 €	306.733 €	248.813 €
	OPT total cost														7.378.982 €	6.003.923 €	4.870.202 €
2025	OPT hospitalization															6.228.829 €	5.068.100 €
	OPT follow-up															773.169 €	629.091 €
	OPT upgrade ICD															376.983 €	306.733 €
	OPT total cost															7.378.982 €	6.003.923 €
2026	OPT hospitalization																6.228.829 €
	OPT follow-up																773.169 €
	OPT upgrade ICD																376.983 €
	OPT total cost																7.378.982 €
Total cost per year		6.272.134 €	11.375.469 €	15.515.141 €	18.866.692 €	21.572.782 €	23.751.681 €	25.500.893 €	26.901.155 €	28.018.096 €	28.905.188 €	29.605.859 €	30.155.996 €	30.585.123 €	30.917.781 €	31.173.500 €	31.368.248 €

Table D.1.: Budget impact OPT

2011	CRT-P implantation	7.987.987 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-P replacement	0 €	0 €	0 €	0 €	0 €	0 €	2.812.704 €	0 €	0 €	0 €	0 €	0 €	926.776 €	0 €	0 €	0 €
	CRT-P hospitalization	4.851.199 €	4.569.663 €	3.896.114 €	3.317.914 €	2.819.844 €	2.391.677 €	2.023.959 €	1.709.152 €	1.439.209 €	1.207.546 €	1.008.331 €	837.603 €	691.746 €	568.170 €	463.100 €	374.242 €
	CRT-P follow-up	966.708 €	830.356 €	708.769 €	604.254 €	514.103 €	436.502 €	369.773 €	312.575 €	263.468 €	221.273 €	184.945 €	153.774 €	127.114 €	104.500 €	85.252 €	68.955 €
	CRT-P upgrade CRT-D	103.040 €	88.524 €	75.576 €	64.444 €	54.841 €	46.573 €	39.462 €	33.365 €	28.130 €	23.630 €	19.755 €	16.429 €	13.584 €	11.170 €	9.115 €	7.374 €
	CRT-P total cost	13.908.933 €	5.488.542 €	4.680.459 €	3.986.613 €	3.388.788 €	2.874.753 €	5.245.897 €	2.055.093 €	1.730.807 €	1.452.449 €	1.213.032 €	1.007.808 €	1.759.220 €	683.840 €	557.467 €	450.570 €
2012	CRT-P implantation		7.987.987 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-P replacement		0 €	0 €	0 €	0 €	0 €	0 €	2.812.704 €	0 €	0 €	0 €	0 €	0 €	926.776 €	0 €	0 €
	CRT-P hospitalization		4.851.199 €	4.569.663 €	3.896.114 €	3.317.914 €	2.819.844 €	2.391.677 €	2.023.959 €	1.709.152 €	1.439.209 €	1.207.546 €	1.008.331 €	837.603 €	691.746 €	568.170 €	463.100 €
	CRT-P follow-up		966.708 €	830.356 €	708.769 €	604.254 €	514.103 €	436.502 €	369.773 €	312.575 €	263.468 €	221.273 €	184.945 €	153.774 €	127.114 €	104.500 €	85.252 €
	CRT-P upgrade CRT-D		103.040 €	88.524 €	75.576 €	64.444 €	54.841 €	46.573 €	39.462 €	33.365 €	28.130 €	23.630 €	19.755 €	16.429 €	13.584 €	11.170 €	9.115 €
	CRT-P total cost		13.908.933 €	5.488.542 €	4.680.459 €	3.986.613 €	3.388.788 €	2.874.753 €	5.245.897 €	2.055.093 €	1.730.807 €	1.452.449 €	1.213.032 €	1.007.808 €	1.759.220 €	683.840 €	557.467 €
2013	CRT-P implantation			7.987.987 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-P replacement			0 €	0 €	0 €	0 €	0 €	0 €	2.812.704 €	0 €	0 €	0 €	0 €	0 €	926.776 €	0 €
	CRT-P hospitalization			4.851.199 €	4.569.663 €	3.896.114 €	3.317.914 €	2.819.844 €	2.391.677 €	2.023.959 €	1.709.152 €	1.439.209 €	1.207.546 €	1.008.331 €	837.603 €	691.746 €	568.170 €
	CRT-P follow-up			966.708 €	830.356 €	708.769 €	604.254 €	514.103 €	436.502 €	369.773 €	312.575 €	263.468 €	221.273 €	184.945 €	153.774 €	127.114 €	104.500 €
	CRT-P upgrade CRT-D			103.040 €	88.524 €	75.576 €	64.444 €	54.841 €	46.573 €	39.462 €	33.365 €	28.130 €	23.630 €	19.755 €	16.429 €	13.584 €	11.170 €
	CRT-P total cost			13.908.933 €	5.488.542 €	4.680.459 €	3.986.613 €	3.388.788 €	2.874.753 €	5.245.897 €	2.055.093 €	1.730.807 €	1.452.449 €	1.213.032 €	1.007.808 €	1.759.220 €	683.840 €
2014	CRT-P implantation				7.987.987 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-P replacement				0 €	0 €	0 €	0 €	0 €	0 €	2.812.704 €	0 €	0 €	0 €	0 €	0 €	926.776 €
	CRT-P hospitalization				4.851.199 €	4.569.663 €	3.896.114 €	3.317.914 €	2.819.844 €	2.391.677 €	2.023.959 €	1.709.152 €	1.439.209 €	1.207.546 €	1.008.331 €	837.603 €	691.746 €
	CRT-P follow-up				966.708 €	830.356 €	708.769 €	604.254 €	514.103 €	436.502 €	369.773 €	312.575 €	263.468 €	221.273 €	184.945 €	153.774 €	127.114 €
	CRT-P upgrade CRT-D				103.040 €	88.524 €	75.576 €	64.444 €	54.841 €	46.573 €	39.462 €	33.365 €	28.130 €	23.630 €	19.755 €	16.429 €	13.584 €
	CRT-P total cost				13.908.933 €	5.488.542 €	4.680.459 €	3.986.613 €	3.388.788 €	2.874.753 €	5.245.897 €	2.055.093 €	1.730.807 €	1.452.449 €	1.213.032 €	1.007.808 €	1.759.220 €
2015	CRT-P implantation					7.987.987 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-P replacement					0 €	0 €	0 €	0 €	0 €	0 €	2.812.704 €	0 €	0 €	0 €	0 €	0 €
	CRT-P hospitalization					4.851.199 €	4.569.663 €	3.896.114 €	3.317.914 €	2.819.844 €	2.391.677 €	2.023.959 €	1.709.152 €	1.439.209 €	1.207.546 €	1.008.331 €	837.603 €
	CRT-P follow-up					966.708 €	830.356 €	708.769 €	604.254 €	514.103 €	436.502 €	369.773 €	312.575 €	263.468 €	221.273 €	184.945 €	153.774 €
	CRT-P upgrade CRT-D					103.040 €	88.524 €	75.576 €	64.444 €	54.841 €	46.573 €	39.462 €	33.365 €	28.130 €	23.630 €	19.755 €	16.429 €
	CRT-P total cost					13.908.933 €	5.488.542 €	4.680.459 €	3.986.613 €	3.388.788 €	2.874.753 €	5.245.897 €	2.055.093 €	1.730.807 €	1.452.449 €	1.213.032 €	1.007.808 €
2016	CRT-P implantation						7.987.987 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-P replacement						0 €	0 €	0 €	0 €	0 €	0 €	2.812.704 €	0 €	0 €	0 €	0 €
	CRT-P hospitalization						4.851.199 €	4.569.663 €	3.896.114 €	3.317.914 €	2.819.844 €	2.391.677 €	2.023.959 €	1.709.152 €	1.439.209 €	1.207.546 €	1.008.331 €
	CRT-P follow-up						966.708 €	830.356 €	708.769 €	604.254 €	514.103 €	436.502 €	369.773 €	312.575 €	263.468 €	221.273 €	184.945 €
	CRT-P upgrade CRT-D						103.040 €	88.524 €	75.576 €	64.444 €	54.841 €	46.573 €	39.462 €	33.365 €	28.130 €	23.630 €	19.755 €
	CRT-P total cost						13.908.933 €	5.488.542 €	4.680.459 €	3.986.613 €	3.388.788 €	2.874.753 €	5.245.897 €	2.055.093 €	1.730.807 €	1.452.449 €	1.213.032 €
2017	CRT-P implantation							7.987.987 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-P replacement							0 €	0 €	0 €	0 €	0 €	0 €	2.812.704 €	0 €	0 €	0 €
	CRT-P hospitalization							4.851.199 €	4.569.663 €	3.896.114 €	3.317.914 €	2.819.844 €	2.391.677 €	2.023.959 €	1.709.152 €	1.439.209 €	1.207.546 €
	CRT-P follow-up							966.708 €	830.356 €	708.769 €	604.254 €	514.103 €	436.502 €	369.773 €	312.575 €	263.468 €	221.273 €
	CRT-P upgrade CRT-D							103.040 €	88.524 €	75.576 €	64.444 €	54.841 €	46.573 €	39.462 €	33.365 €	28.130 €	23.630 €
	CRT-P total cost							13.908.933 €	5.488.542 €	4.680.459 €	3.986.613 €	3.388.788 €	2.874.753 €	5.245.897 €	2.055.093 €	1.730.807 €	1.452.449 €
2018	CRT-P implantation								7.987.987 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-P replacement								0 €	0 €	0 €	0 €	0 €	0 €	2.812.704 €	0 €	0 €
	CRT-P hospitalization								4.851.199 €	4.569.663 €	3.896.114 €	3.317.914 €	2.819.844 €	2.391.677 €	2.023.959 €	1.709.152 €	1.439.209 €
	CRT-P follow-up								966.708 €	830.356 €	708.769 €	604.254 €	514.103 €	436.502 €	369.773 €	312.575 €	263.468 €
	CRT-P upgrade CRT-D								103.040 €	88.524 €	75.576 €	64.444 €	54.841 €	46.573 €	39.462 €	33.365 €	28.130 €
	CRT-P total cost								13.908.933 €	5.488.542 €	4.680.459 €	3.986.613 €	3.388.788 €	2.874.753 €	5.245.897 €	2.055.093 €	1.730.807 €
2019	CRT-P implantation									7.987.987 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-P replacement									0 €	0 €	0 €	0 €	0 €	0 €	2.812.704 €	0 €
	CRT-P hospitalization									4.851.199 €	4.569.663 €	3.896.114 €	3.317.914 €	2.819.844 €	2.391.677 €	2.023.959 €	1.709.152 €
	CRT-P follow-up									966.708 €	830.356 €	708.769 €	604.254 €	514.103 €	436.502 €	369.773 €	312.575 €
	CRT-P upgrade CRT-D									103.040 €	88.524 €	75.576 €	64.444 €	54.841 €	46.573 €	39.462 €	33.365 €
	CRT-P total cost									13.908.933 €	5.488.542 €	4.680.459 €	3.986.613 €	3.388.788 €	2.874.753 €	5.245.897 €	2.055.093 €
2020	CRT-P implantation										7.987.987 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-P replacement										0 €	0 €	0 €	0 €	0 €	0 €	2.812.704 €
	CRT-P hospitalization										4.851.199 €	4.569.663 €	3.896.114 €	3.317.914 €	2.819.844 €	2.391.677 €	2.023.959 €
	CRT-P follow-up										966.708 €	830.356 €	708.769 €	604.254 €	514.103 €	436.502 €	369.773 €
	CRT-P upgrade CRT-D										103.040 €	88.524 €	75.576 €	64.444 €	54.841 €	46.573 €	39.462 €
	CRT-P total cost										13.908.933 €	5.488.542 €	4.680.459 €	3.986.613 €	3.388.788 €	2.874.753 €	5.245.897 €
2021	CRT-P implantation											7.987.987 €	0 €	0 €	0 €	0 €	0 €
	CRT-P replacement											0 €	0 €	0 €	0 €	0 €	0 €
	CRT-P hospitalization											4.851.199 €	4.569.663 €	3.896.114 €	3.317.914 €	2.819.844 €	2.391.677 €
	CRT-P follow-up											966.708 €	830.356 €	708.769 €	604.254 €	514.103 €	436.502 €
	CRT-P upgrade CRT-D											103.040 €	88.524 €	75.576 €	64.444 €	54.841 €	46.573 €
	CRT-P total cost											13.908.933 €	5.488.542 €	4.680.459 €	3.986.613 €	3.388.788 €	2.874.753 €
2022	CRT-P implantation												7.987.987 €	0 €	0 €	0 €	0 €
	CRT-P replacement												0 €	0 €	0 €	0 €	0 €
	CRT-P hospitalization												4.851.199 €	4.569.663 €	3.896.114 €	3.317.914 €	2.819.844 €
	CRT-P follow-up												966.708 €	830.356 €	708.769 €	604.254 €	514.103 €
	CRT-P upgrade CRT-D												103.040 €	88.524 €	75.576 €	64.444 €	54.841 €
	CRT-P total cost												13.908.933 €	5.488.542 €	4.680.459 €	3.986.613 €	3.388.788 €
2023	CRT-P implantation													7.987.987 €	0 €	0 €	0 €
	CRT-P replacement													0 €	0 €	0 €	0 €
	CRT-P hospitalization													4.851.199 €	4.569.663 €	3.896.114 €	3.317.914 €
	CRT-P follow-up													966.708 €	830.356 €	708.769 €	604.254 €
	CRT-P upgrade CRT-D													103.040 €	88.524 €	75.576 €	64.444 €
	CRT-P total cost													13.908.933 €	5.488.542 €	4.680.459 €	3.986.613 €
2024	CRT-P implantation														7.987.987 €	0 €	0 €
	CRT-P replacement														0 €	0 €	0 €
	CRT-P hospitalization														4.851.199 €	4.569.663 €	3.896.114 €
	CRT-P follow-up														966.708 €	830.356 €	708.769 €
	CRT-P upgrade CRT-D														103.040 €	88.524 €	75.576 €
	CRT-P total cost														13.908.933 €	5.488.542 €	4.680.459 €
2025	CRT-P implantation															7.987.987 €	0 €
	CRT-P replacement															0 €	0 €
	CRT-P hospitalization															4.851.199 €	4.569.663 €
	CRT-P follow-up															966.708 €	830.356 €
	CRT-P upgrade CRT-D															103.040 €	88.524 €
	CRT-P total cost															13.908.933 €	5.488.542 €

Yearly cohort of 850 patients		Average costs of the cohort in the follow-up year															
year	Cost categories	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
2011	CRT-D implantation	19.873.272 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-D replacement	0 €	0 €	0 €	0 €	0 €	9.422.973 €	0 €	0 €	0 €	0 €	4.494.798 €	0 €	0 €	0 €	0 €	1.882.417 €
	CRT-D hospitalization	4.862.788 €	4.690.601 €	4.098.134 €	3.574.824 €	3.110.795 €	2.700.425 €	2.337.967 €	2.019.070 €	1.738.014 €	1.490.115 €	1.270.963 €	1.077.984 €	908.643 €	761.430 €	632.936 €	521.441 €
	CRT-D follow-up	1.158.383 €	1.019.683 €	891.656 €	778.477 €	678.028 €	589.114 €	510.507 €	441.283 €	380.212 €	326.290 €	278.570 €	236.502 €	199.546 €	167.384 €	139.277 €	114.859 €
	CRT-D total cost	25.894.443 €	5.710.284 €	4.989.790 €	4.353.301 €	3.788.823 €	12.712.515 €	2.848.474 €	2.460.353 €	2.118.225 €	1.816.405 €	6.044.331 €	1.314.486 €	1.108.190 €	928.813 €	772.213 €	2.518.717 €
2012	CRT-D implantation		19.873.272 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-D replacement		0 €	0 €	0 €	0 €	0 €	9.422.973 €	0 €	0 €	0 €	0 €	4.494.798 €	0 €	0 €	0 €	0 €
	CRT-D hospitalization		4.862.788 €	4.690.601 €	4.098.134 €	3.574.824 €	3.110.795 €	2.700.425 €	2.337.967 €	2.019.070 €	1.738.014 €	1.490.115 €	1.270.963 €	1.077.984 €	908.643 €	761.430 €	632.936 €
	CRT-D follow-up		1.158.383 €	1.019.683 €	891.656 €	778.477 €	678.028 €	589.114 €	510.507 €	441.283 €	380.212 €	326.290 €	278.570 €	236.502 €	199.546 €	167.384 €	139.277 €
	CRT-D total cost		25.894.443 €	5.710.284 €	4.989.790 €	4.353.301 €	3.788.823 €	12.712.515 €	2.848.474 €	2.460.353 €	2.118.225 €	1.816.405 €	6.044.331 €	1.314.486 €	1.108.190 €	928.813 €	772.213 €
2013	CRT-D implantation			19.873.272 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-D replacement			0 €	0 €	0 €	0 €	0 €	9.422.973 €	0 €	0 €	0 €	0 €	4.494.798 €	0 €	0 €	0 €
	CRT-D hospitalization			4.862.788 €	4.690.601 €	4.098.134 €	3.574.824 €	3.110.795 €	2.700.425 €	2.337.967 €	2.019.070 €	1.738.014 €	1.490.115 €	1.270.963 €	1.077.984 €	908.643 €	761.430 €
	CRT-D follow-up			1.158.383 €	1.019.683 €	891.656 €	778.477 €	678.028 €	589.114 €	510.507 €	441.283 €	380.212 €	326.290 €	278.570 €	236.502 €	199.546 €	167.384 €
	CRT-D total cost			25.894.443 €	5.710.284 €	4.989.790 €	4.353.301 €	3.788.823 €	12.712.515 €	2.848.474 €	2.460.353 €	2.118.225 €	1.816.405 €	6.044.331 €	1.314.486 €	1.108.190 €	928.813 €
2014	CRT-D implantation				19.873.272 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-D replacement				0 €	0 €	0 €	0 €	0 €	9.422.973 €	0 €	0 €	0 €	0 €	4.494.798 €	0 €	0 €
	CRT-D hospitalization				4.862.788 €	4.690.601 €	4.098.134 €	3.574.824 €	3.110.795 €	2.700.425 €	2.337.967 €	2.019.070 €	1.738.014 €	1.490.115 €	1.270.963 €	1.077.984 €	908.643 €
	CRT-D follow-up				1.158.383 €	1.019.683 €	891.656 €	778.477 €	678.028 €	589.114 €	510.507 €	441.283 €	380.212 €	326.290 €	278.570 €	236.502 €	199.546 €
	CRT-D total cost				25.894.443 €	5.710.284 €	4.989.790 €	4.353.301 €	3.788.823 €	12.712.515 €	2.848.474 €	2.460.353 €	2.118.225 €	1.816.405 €	6.044.331 €	1.314.486 €	1.108.190 €
2015	CRT-D implantation					19.873.272 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-D replacement					0 €	0 €	0 €	0 €	0 €	9.422.973 €	0 €	0 €	0 €	0 €	4.494.798 €	0 €
	CRT-D hospitalization					4.862.788 €	4.690.601 €	4.098.134 €	3.574.824 €	3.110.795 €	2.700.425 €	2.337.967 €	2.019.070 €	1.738.014 €	1.490.115 €	1.270.963 €	1.077.984 €
	CRT-D follow-up					1.158.383 €	1.019.683 €	891.656 €	778.477 €	678.028 €	589.114 €	510.507 €	441.283 €	380.212 €	326.290 €	278.570 €	236.502 €
	CRT-D total cost					25.894.443 €	5.710.284 €	4.989.790 €	4.353.301 €	3.788.823 €	12.712.515 €	2.848.474 €	2.460.353 €	2.118.225 €	1.816.405 €	6.044.331 €	1.314.486 €
2016	CRT-D implantation						19.873.272 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-D replacement						0 €	0 €	0 €	0 €	0 €	9.422.973 €	0 €	0 €	0 €	0 €	4.494.798 €
	CRT-D hospitalization						4.862.788 €	4.690.601 €	4.098.134 €	3.574.824 €	3.110.795 €	2.700.425 €	2.337.967 €	2.019.070 €	1.738.014 €	1.490.115 €	1.270.963 €
	CRT-D follow-up						1.158.383 €	1.019.683 €	891.656 €	778.477 €	678.028 €	589.114 €	510.507 €	441.283 €	380.212 €	326.290 €	278.570 €
	CRT-D total cost						25.894.443 €	5.710.284 €	4.989.790 €	4.353.301 €	3.788.823 €	12.712.515 €	2.848.474 €	2.460.353 €	2.118.225 €	1.816.405 €	6.044.331 €
2017	CRT-D implantation							19.873.272 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-D replacement							0 €	0 €	0 €	0 €	0 €	9.422.973 €	0 €	0 €	0 €	0 €
	CRT-D hospitalization							4.862.788 €	4.690.601 €	4.098.134 €	3.574.824 €	3.110.795 €	2.700.425 €	2.337.967 €	2.019.070 €	1.738.014 €	1.490.115 €
	CRT-D follow-up							1.158.383 €	1.019.683 €	891.656 €	778.477 €	678.028 €	589.114 €	510.507 €	441.283 €	380.212 €	326.290 €
	CRT-D total cost							25.894.443 €	5.710.284 €	4.989.790 €	4.353.301 €	3.788.823 €	12.712.515 €	2.848.474 €	2.460.353 €	2.118.225 €	1.816.405 €
2018	CRT-D implantation								19.873.272 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-D replacement								0 €	0 €	0 €	0 €	0 €	9.422.973 €	0 €	0 €	0 €
	CRT-D hospitalization								4.862.788 €	4.690.601 €	4.098.134 €	3.574.824 €	3.110.795 €	2.700.425 €	2.337.967 €	2.019.070 €	1.738.014 €
	CRT-D follow-up								1.158.383 €	1.019.683 €	891.656 €	778.477 €	678.028 €	589.114 €	510.507 €	441.283 €	380.212 €
	CRT-D total cost								25.894.443 €	5.710.284 €	4.989.790 €	4.353.301 €	3.788.823 €	12.712.515 €	2.848.474 €	2.460.353 €	2.118.225 €
2019	CRT-D implantation									19.873.272 €	0 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-D replacement									0 €	0 €	0 €	0 €	0 €	9.422.973 €	0 €	0 €
	CRT-D hospitalization									4.862.788 €	4.690.601 €	4.098.134 €	3.574.824 €	3.110.795 €	2.700.425 €	2.337.967 €	2.019.070 €
	CRT-D follow-up									1.158.383 €	1.019.683 €	891.656 €	778.477 €	678.028 €	589.114 €	510.507 €	441.283 €
	CRT-D total cost									25.894.443 €	5.710.284 €	4.989.790 €	4.353.301 €	3.788.823 €	12.712.515 €	2.848.474 €	2.460.353 €
2020	CRT-D implantation										19.873.272 €	0 €	0 €	0 €	0 €	0 €	0 €
	CRT-D replacement										0 €	0 €	0 €	0 €	0 €	9.422.973 €	0 €
	CRT-D hospitalization										4.862.788 €	4.690.601 €	4.098.134 €	3.574.824 €	3.110.795 €	2.700.425 €	2.337.967 €
	CRT-D follow-up										1.158.383 €	1.019.683 €	891.656 €	778.477 €	678.028 €	589.114 €	510.507 €
	CRT-D total cost										25.894.443 €	5.710.284 €	4.989.790 €	4.353.301 €	3.788.823 €	12.712.515 €	2.848.474 €
2021	CRT-D implantation											19.873.272 €	0 €	0 €	0 €	0 €	0 €
	CRT-D replacement											0 €	0 €	0 €	0 €	0 €	9.422.973 €
	CRT-D hospitalization											4.862.788 €	4.690.601 €	4.098.134 €	3.574.824 €	3.110.795 €	2.700.425 €
	CRT-D follow-up											1.158.383 €	1.019.683 €	891.656 €	778.477 €	678.028 €	589.114 €
	CRT-D total cost											25.894.443 €	5.710.284 €	4.989.790 €	4.353.301 €	3.788.823 €	12.712.515 €
2022	CRT-D implantation												19.873.272 €	0 €	0 €	0 €	0 €
	CRT-D replacement												0 €	0 €	0 €	0 €	0 €
	CRT-D hospitalization												4.862.788 €	4.690.601 €	4.098.134 €	3.574.824 €	3.110.795 €
	CRT-D follow-up												1.158.383 €	1.019.683 €	891.656 €	778.477 €	678.028 €
	CRT-D total cost												25.894.443 €	5.710.284 €	4.989.790 €	4.353.301 €	3.788.823 €
2023	CRT-D implantation													19.873.272 €	0 €	0 €	0 €
	CRT-D replacement													0 €	0 €	0 €	0 €
	CRT-D hospitalization													4.862.788 €	4.690.601 €	4.098.134 €	3.574.824 €
	CRT-D follow-up													1.158.383 €	1.019.683 €	891.656 €	778.477 €
	CRT-D total cost													25.894.443 €	5.710.284 €	4.989.790 €	4.353.301 €
2024	CRT-D implantation														19.873.272 €	0 €	0 €
	CRT-D replacement														0 €	0 €	0 €
	CRT-D hospitalization														4.862.788 €	4.690.601 €	4.098.134 €
	CRT-D follow-up														1.158.383 €	1.019.683 €	891.656 €
	CRT-D total cost														25.894.443 €	5.710.284 €	4.989.790 €
2025	CRT-D implantation															19.873.272 €	0 €
	CRT-D replacement															0 €	0 €
	CRT-D hospitalization															4.862.788 €	4.690.601 €
	CRT-D follow-up															1.158.383 €	1.019.683 €
	CRT-D total cost															25.894.443 €	5.710.284 €
2026	CRT-D implantation																19.873.272 €
	CRT-D replacement																0 €
	CRT-D hospitalization																4.862.788 €
	CRT-D follow-up																1.158.383 €
	CRT-D total cost																25.894.443 €
Total cost per year		**25.894.443 €**	**31.604.726 €**	**36.594.516 €**	**40.947.817 €**	**44.736.640 €**	**57.449.155 €**	**60.297.629 €**	**62.757.982 €**	**64.876.207 €**	**66.692.612 €**	**72.736.943 €**	**74.051.429 €**	**75.159.619 €**	**76.088.432 €**	**76.860.645 €**	**79.379.362 €**
Incremental budget CRT-D vs CRT-P		**11.985.510 €**	**12.207.252 €**	**12.516.583 €**	**12.883.271 €**	**13.283.306 €**	**23.121.068 €**	**20.723.645 €**	**21.128.906 €**	**21.516.324 €**	**21.880.279 €**	**26.711.579 €**	**27.018.257 €**	**26.367.227 €**	**26.612.200 €**	**26.826.946 €**	**28.895.093 €**
Incremental budget CRT-D vs ORT		**19.622.308 €**	**20.229.257 €**	**21.079.376 €**	**22.081.124 €**	**23.163.858 €**	**33.697.474 €**	**34.796.736 €**	**35.856.927 €**	**36.858.111 €**	**37.787.423 €**	**43.131.084 €**	**43.895.432 €**	**44.574.496 €**	**45.170.651 €**	**45.687.145 €**	**48.011.114 €**

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