Rapid HTA report

Implantable cardiac resynchronization therapy and defibrillator (CRT-D) in patient with heart failure

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Authors, Clinical expert and External Reviewers declare that they do not receive benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

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Sommario

In Italia, le malattie cardiovascolari sono una delle principali cause di mortalità, morbilità e disabilità. Tra tutte le malattie cardiovascolari, un ruolo importante è rappresentato dallo scompenso cardiaco (HF). In Italia ci sono circa 600.000 persone affette da HF (dopo i 65 anni la prevalenza si avvicina al 10%) e si stima il raddoppio della frequenza di questa patologia ogni dieci anni. Dal punto di vista clinico la limitata riserva cardiaca dei pazienti affetti da HF è dipendente dalla contrazione atriale, dalla sincronizzazione della contrazione del ventricolo sinistro e da un'anormale interazione tra il ventricolo destro e sinistro. Gli obiettivi del trattamento in pazienti con HF sono alleviare i sintomi e i segni (ad esempio l'edema), evitare il ricovero ospedaliero e migliorare la sopravvivenza. I pazienti ancora sintomatici in terapia medica ottimale sono quelli candidati al trattamento con device per la terapia di resincronizzazione (CRT-P). Alcuni pazienti con problemi di aritmia ventricolare possono invece necessitare del trattamento di defibrillazione. Nel presente report abbiamo confrontato gli effetti, ovvero: efficacia, effetti collaterali e la costo-efficacia del defibrillatore tricamerale (CRT-D), che combina entrambe le predette terapie, rispetto alla terapia con il solo dispositivo di risicronizzazione (CRT-P) o defibrillatore (ICD) nei pazienti con insufficienza cardiaca (QRS> 120 msec e bassa frazione di eiezione - EF). La ricerca in letteratura ha prodotto 1116 titoli che includono 8 revisioni sistematiche e 34 studi primari. Nel nostro studio abbiamo privilegiato l'analisi delle revisioni sistematiche più recenti e che coinvolgono popolazioni molto grandi di pazienti, la cui qualità metodologica è stata giudicata elevata utilizzando lo strumento AMSTAR. I pazienti con maggiore probabilità di trarre beneficio dall'impianto del CRT-D sono quelli con insufficienza cardiaca lieve o moderata. Lo studio di Chen et al ha esaminato i principali studi comparativi del CRT-D rispetto all'ICD indagando gli aspetti sopra descritti attraverso un'analisi effettuata per sottogruppi in base alla classe NYHA (New York Heart Association), alla durata del follow-up e alla progettazione dello studio. Seguendo questo approccio, lo studio di Chen et al mostra una significativa superiorità del CRT-D sull'ICD nel ridurre i ricoveri per insufficienza cardiaca e nel miglioramento della classe funzionale in tutti i sottogruppi. Ulteriori evidenze recenti mostrano l'efficacia del CRT-D nel blocco di branca, ma non analizzano gli altri disturbi della conduzione. Al momento non esiste una chiara evidenza circa l'efficacia della CRT-D nei pazienti con fibrillazione atriale (AF) o per quelli con QRS quasi normali. Tra i possibili rischi associati all'impianto e all'uso del dispositivo, gli studi MADIT-CRT e RAFT mostrano una maggiore incidenza di complicanze

procedurali come pneumotorace, infezioni, ematoma della tasca e problemi connessi al catetere nel gruppo dei pazienti con CRT-D rispetto a quelli con ICD. Chen et al, nello studio citato, registrano un aumento significativo nella dislocazione dei cateteri e nella dissezione del seno coronarico. Sebbene queste complicazioni non siano state fatali, tuttavia hanno determinato un aumento della durata della degenza, diminuendo, quindi, la qualità della vita. Le nostre osservazioni preliminari non sono dissimili da quelle del comitato di valutazione del NICE (June 2014) contenute nel recente documento preliminare di orientamento "Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure" (review TA95 e TA120).

Sintesi

In Italia, le malattie cardiovascolari sono una delle principali cause di mortalità, morbilità e disabilità. Tra tutte le malattie cardiovascolari, un ruolo importante è rappresentato dallo scompenso cardiaco (HF). La prevalenza di tale patologia in Italia è di circa 600.000 persone (dopo i 65 anni la prevalenza si avvicina al 10%), con un'incidenza destinata a raddoppiarsi ogni dieci anni. Il sesso femminile, tradizionalmente sottorappresentato negli studi clinici cardiovascolari, rappresenta circa il 40-50% dei pazienti ospedalizzati per HF.

Dal punto di vista clinico la limitata riserva cardiaca dei pazienti affetti da HF è dipendente dalla contrazione atriale, dalla sincronizzazione della contrazione dei ventricoli, e da un'anormale interazione tra il ventricolo destro e sinistro. Gli obiettivi del trattamento in pazienti con HF sono di alleviare i sintomi e i segni (ad esempio dispnea, congestione), evitare il ricovero ospedaliero, e migliorarne la sopravvivenza. L'inibizione dell'attivazione neuro-ormonale (renin-angiotensin-aldosterone system [RAAS] e del sistema nervoso simpatico) mediante ACEI/ARB, beta-bloccanti e antagonisti dell'aldosterone, conferisce un beneficio sulla sopravvivenza a lungo termine. I pazienti ancora sintomatici in terapia medica ottimale e con evidenza elettrocardiografica di disturbi della conduzione intraventricolare (QRS>120 ms) possono essere candidati a terapia di resincronizzazione cardiaca (CRT-P). Tale terapia ha dimostrato, in diversi trials clinici e metanalisi, di migliorare la prognosi complessiva del paziente con HF (riduzione della mortalità, miglioramento della classe funzionale e della qualità di vita, miglioramento della tolleranza allo sforzo) attraverso anche un miglioramento funzionale a livello cardiaco con riduzione delle volumetrie ventricolari (rimodellamento inverso) ed incremento della frazione di eiezione (EF). La terapia elettrica con defibrillatore (ICD) non migliora la funzione cardiaca, ma ha invece lo scopo di prevenire la morte aritmica in questi pazienti.

Nel presente report abbiamo confrontato gli effetti, ovvero: efficacia, effetti collaterali e la costo-efficacia del defibrillatore tricamerale (resincronizzazione+defibrillatore [CRT-D]) rispetto alla terapia con solo dispositivo di terapia di resicronizzazione (CRT-P) o defibrillatore (ICD), nei pazienti con insufficienza cardiaca: QRS>120 msec e ridotta frazione di eiezione (EF<=35%).

La ricerca in letteratura ha prodotto 1116 titoli che includono 8 revisioni sistematiche e 34 studi primari. Nel nostro studio abbiamo privilegiato l'analisi delle revisioni sistematiche più recenti, che hanno coinvolto popolazioni molto grandi di pazienti, la cui qualità metodologica è stata giudicata elevata utilizzando lo strumento AMSTAR. Da questi studi si evince che, nonostante l'avanzamento della terapia farmacologica, la prognosi dei pazienti con insufficienza cardiaca non

è migliorata molto. L'evidenza, inotre, mostra che, in questi pazienti, l'ICD riduce la mortalità secondaria a morte improvvisa da fibrillazione ventricolare, senza tuttavia alcuna influenza sulla mortalità e/o riospedalizzazione per insufficienza cardiaca, non avendo alcun impatto sulla funzione ventricolare.

D'altro canto, il CRT-P, associato ad una terapia farmacologica ottimale, ha dimostrato di poter migliorare in modo significativo gli outcomes associati al miglioramento della funzione ventricolare, in quei pazienti con insufficienza cardiaca nei quali la contrazione cardiaca non è sincrona.

Pertanto, poiché i potenziali candidati a CRT sono tipicamente anche candidati ad ICD, a causa della depressa funzione ventricolare sinistra, ragionevolmente l'ipotesi di combinare le funzioni di CRT-P e ICD in un unico device (CRT-D) dovrebbe significativamente migliorare la prognosi nei pazienti scompensati (MADIT investigators 2006), considerato che, per quanto ridotto, può ancora persistere un rischio di morte improvvisa nei pazienti che ricevono la CRT-P.

Tuttavia, le attuali linee guida disponibili sono in gran parte silenti sul confronto, in termini di efficacia, e sull'indicazione ad utilizzare un semplice dispositivo CRT-P piuttosto che un dispositivo CRT più ICD (CRT-D).

Lo studio RAFT, nel lungo periodo di follow-up dei pazienti in cui è stato impiantato il CRT-D, ha mostrato una significativa riduzione di mortalità, morbilità e ospedalizzazione; anche se tali risultati venivano osservati solo nei pazienti con follow-up più lungo, introducendo un ulteriore bias. Al fine di superare queste limitazioni, in una recente metanalisi Chen ha esaminato i principali studi di confronto tra CRT-D versus ICD, attraverso un'analisi effettuata per sottogruppi in base alla classe NYHA, alla durata del follow-up e alla progettazione dello studio [Chen2013]. Si è così osservata una significativa superiorità del CRT-D sull'ICD nel ridurre i ricoveri per insufficienza cardiaca e nel miglioramento della classe funzionale in tutti i sottogruppi.

La recente metanalisi di Siphai mostra l'efficacia del CRT-D nei pazienti con blocco di branca, ma non analizza altri disturbi della conduzione [Siphai 2012]. Stavrakis segnala una maggiore efficacia della CRT-D nei pazienti con QRS>=150 [Stavrakis 2012]. Il vantaggio numerico conferito dal CRT-D vs CRT-P, in termini di minor numero di morti improvvise, era però ampiamente compensato dal numero di pazienti morti per insufficienza della capacità della pompa, i quali sono anche più numerosi, e nei quali il CRT-D in realtà ha mostrato un trend peggiore (non significativo) rispetto al CRT-P. Tuttavia, il numero esiguo di eventi è tale da non consentire di raggiungere una conclusione definitiva rispetto alla superiorità di un dispositivo sull'altro.

Per quanto riguarda i grandi trials clinici randomizzati, soltanto il COMPANION ha direttamente confrontato gli esiti clinici dei pazienti randomizzati al CRT-P vs CRT-D; e nessuna chiara

superiorità del CRT-D è emersa in maniera inequivocabile. I dati di COMPANION tuttavia, per quanto interessanti, non possono essere considerati definitivi, poiché: a) basati su di un gruppo relativamente piccolo di pazienti; b) la decisione di procedere con l'impianto del CRT-P si è basata esclusivamente su criteri ECG relativamente ampi (durata QRS>120 msec), che tendeva quindi ad includere anche pazienti che possono essere considerati meno sensibili alle CRT, diluendo così possibili benefici del solo CRT-P; c) la terapia medica ottimale si riferisce al 2000, quando lo studio è stato progettato, e quindi non può più essere considerato lo stato dell'arte.

Per quanto riguarda le complicanze, gli studi MADIT-CRT e RAFT hanno mostrato una maggiore incidenza di complicanze procedurali (pneumotorace, infezioni, ematoma della tasca, problemi di funzionamento del catetere) nel gruppo CRT-D rispetto all'ICD. Nella stessa metanalisi di Chen et al, è riportato un aumento significativo della dislocazione dei cateteri e della dissezione del seno coronarico. Anche se queste complicazioni non sono state fatali hanno tuttavia prolungato la durata della degenza, interferendo negativamente sulla qualità della vita. Dato che questi risultati sono stati estrapolati da gruppi di pazienti con età media inferiore a quella che si riscontra nella normale pratica clinica, la maggiore incidenza di complicanze procedurali deve essere ben considerata in pazienti di età avanzata prima di decidere in favore del CRT-D.

Pertanto, le prove a sostegno della preferenza di un CRT-D piuttosto che CRT-P sono scarse e la prescrizione di un tipo di dispositivo piuttosto che l'altro, è spesso dettata da motivazioni geografiche, economiche o di altri fattori, piuttosto che da una solida guida evidence-based. [Exner DV 2012].

Le nostre osservazioni preliminari non sono dissimili da quelle del comitato di valutazione del NICE contenute nel recente documento preliminare di orientamento [NICE 2014], che raccomanda l'impianto di defibrillatori, di resincronizzazione cardiaca (CRT) con defibrillatore (CRT-D) o con stimolazione (CRT-P) come opzioni di trattamento per le persone con HF, che hanno disfunzione ventricolare sinistra con una LVEF del 35% o meno [NICE 2014].

Dalla nostra analisi di contesto risulta che, ad oggi, in Italia sono commercializzati 73 modelli dai cinque produttori di CRT-D. Riguardo ai consumi, nelle regioni a più basso indice demografico (Val D'Aosta, Molise, Basilicata) si registra il più alto rapporto tra volume di consumo dei dispositivi in esame e numero di abitanti.

Abstract

In Italy, cardiovascular disease is a leading cause of mortality, morbidity, and disability. Among all cardiovascular diseases, a prominent role is played by heart failure (HF), with 600,000 people suffering from heart failure. It is estimated that the frequency of this condition will double with each decade of age. The limited cardiac reserve of HF patients is also critically dependent on atrial contraction, synchronized contraction of the left ventricle, and a normal interaction between the right and left ventricles. The goals of treatment in patients with established HF are to relieve symptoms and signs (e.g. oedema), prevent hospital admissions, and improve survival. Patients still symptomatic on optimal medical therapy should be considered for electrical device (cardiac resynchronization therapy – CRT-P). Some inviduals with a history or arythmia may also benefit from defibrillation to prevent suddent death.

We reviewed the evidence on effectiveness, harms and cost effectiveness of intra cardiac defibrillators with resynchronising devices (CRT-D) compared to each intervention alone (ICD, CRT-P) in people with hearth failure (QRS >120 msec and low EF). We indentified 1,116 titles and included 8 systematic reviews and 34 primary studies. We privileged evidence from recent large systematic reviews whose methodological quality was high according to the AMSTAR instrument.

Despite the development of drug therapy, prognosis of patients with HF has not improved much. Those more likely to benefit from CRT-D insertion are those with mild to moderate heart failure. The individual patient meta-analysis by Chen et al considered the major studies comparing CRT-D versus ICD and investigated these series through analysis conducted for subgroups according to NYHA class, duration of follow-up, and design of the study. The study by Chen et al shows a significant superiority of CRT-D on ICD in reducing hospitalizations for heart failure and improvement in functional class in all subgroups. Additional recent evidence shows efficacy of CRT-D in bundle branch block but not in the other conduction disturbances. At present there is no clear evidence about the effectiveness of CRT-D in patients with atrial fibrillation (AF) or for those with near normal QRS. The MADIT-CRT and RAFT studies show a higher incidence of procedural complications such as pneumothorax, device-related infections, pocket hematoma, catheter problems in the CRT-D group than in the ICD. Chen et al report the significant increase in the dislocation of catheters and dissection of the coranary sinus. Although these complications have not been fatal, they have increased the duration of hospitalization and decreased the quality of life. Our preliminary observations are not dissimilar from those made by the NICE appraisal committee in it's recent preliminary guidance document "Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure" (review TA95 e TA 120, June 2014).. Best evidence suggests that CRT-D is not dominant compared to

CRT-P. The most recent studies comparing ICD with CRT-D come to different conclusions, possibly because of the less serious type of patients included in the studies.

1. Technology and current treatments

1.1 Clinical problem

In Italy, cardiovascular disease is a leading cause of mortality, morbidity, and disability. In 2003 there were 588,897 deaths from all cardiovascular disease, of which 82,059 (34%) due to ischemic heart disease [http://www.istat.it/sanita/health, http://www.salute.gov.it/portale/salute/p1_5.jsp?lingua=italiano&id=43&area=Malattie_cardiovascolari].

Hypertension, hypercholesterolemia, diabetes, and obesity are the main factors that influence the risk of having cardiovascular disease [Perk 2012].

Among all cardiovascular diseases, a prominent role is played by heart failure (HF); this is a chronic, progressive condition in which the heart muscle is unable to pump enough blood to meet the body's needs for blood and oxygen. It is caused by structural or functional abnormalities of the heart [Braunwald 2013]. The syndrome of HF is a global public health problem, affecting an estimated 26 million people worldwide, with a prevalence of 5.7 million patients in the United States [Ambrosy 2015, Go 2013], and an additional 15 million patients in the European Countries [McMurray 2012].

In Italy there are about 600,000 people suffering from HF. It is estimated that the frequency of this condition will double with each decade of age (after 65 years prevalence approaches 10%). Patients with HF tend to have a poor prognosis, the 5-year mortality being approximately 50%-worse than that of many cancers [Askoxylakis 2010] and poor quality of life, because of a high degree of functional impairment and disability and of need of frequent hospitalizations. Indeed, in our country, HF is the leading cause of hospital admissions, and a major driver of health-related expenditure [Ambrosy 2014, Go 2013]. For all these various aspects, HF is considered a public health problem of enormous importance [Ambrosy 2014].

From a clinical point of view, we now recognize 2 distinct forms of heart failure: a) HF with reduced ejection fraction (HFrEF), which is characterized by an enlargement of left ventricle and a substantially depressed systolic contractile function; and, b) HF with preserved ejection fraction (HFpEF), in which instead left ventricular geometry and systolic function are largely preserved, whereas impaired diastolic relaxation of LV plays a major role [Braunwald 2013]. Interestingly, in spite of such apparently discrepant characteristics, both conditions share a similar (and gloomy)

prognosis; risk factors also tend to be similar, although differences can be found with respect to specific prevalence of each.

Cardiac and noncardiac comorbidities are extremely prevalent among HF patients [Braunwald 2013]. About 30-40% of HF cases develop after a myocardial infarction, frequently resulting in systolic dysfunction. A history of hypertension and atrial fibrillation could be found approximately in 70% and 40%, respectively, of patients hospitalized for HF, and the prevalence of these comorbidities is even higher in HFpEF, where they directly contribute to diastolic dysfunction and impaired ventricular filling. Similarly, noncardiac comorbidities including diabetes mellitus, anemia, chronic kidney disease and chronic obstructive pulmonary disease may be found in over one-third of HF patients, thus influencing the pathophysiological progression of HF and limiting initiation and/or titration of drug and diuretic therapy [Ambrosy 2014].

In contrast to HFrEF, HF with preserved EF (HFpEF) is poorly characterized as a clinical entity, although it seems to have a different epidemiological and aetiological profile from HFrEF [Lam 2011]. Patients with HFpEF tend to be older and more often female and obese compared to HFrEF. Furthermore, they are less likely to have Coronary Artery Disease (CAD) and more likely to have hypertension and atrial fibrillation (AF) [Brouwers 2013].

1.2 Epidemiological data

The epidemiology of HF has changed considerably over the last two decades, as a consequence of the progressive increase in life expectancy of the general population and of the reduction of early mortality from myocardial infarction. This is particularly important for its impact on social and direct costs on the health system. In fact, incidence and prevalence of HF increase dramatically with age, reaching, respectively, 15/1000 and approximately 10/100 inhabitants after age of 80 years, with a mean age of patients admitted with a primary diagnosis of HF typically ranging from 70 to 75 years [Ambrosy 2014].

Incidence of HF is estimated about 670,000 new cases/year [Go 2013]. About 1-2% of all hospitalizations are HF Hospitalizations (HFH), representing as already mentioned the leading cause of hospitalization for a disease condition both in the United States and Europe [Zannad 2009].

Variations in age exist across different Countries, with older patients being more represented in the major North American registries as opposed to patients enrolled in countries with developing economies [Atherton 2012]. This observation is likely explained by differences in the prevalence of underlying risk factors.

A peculiar case is represented by women. Female patients have traditionally been underrepresented in cardiovascular clinical trials [Franconi 2011, Hsich 2009]; however, available administrative data suggest that approximately 40-50% of patients hospitalized for HF are female [Ambrosy 2014]. Female patients with HF tend to be older at the time of initial diagnosis and are more likely to suffer from HF with preserved ejection fraction (HFpEF) [Galvao 2006]. After adjusting for differences in baseline characteristics, women have comparable outcomes to men.

The most common etiology of HF in Western countries is represented by CAD, whereas HF secondary to uncontrolled hypertension, valvular pathology and congenital heart disease are likely to be more common in the developing world [Braunwald 2013, Ambrosy 2014, Gheorghiade 2006].

Depending on which EF cut-off is chosen to dichotomize normality (i.e. 40% to 45%), and the population under consideration, at least half of patients with HF can be classified as having a reduced EF (i.e. HFrEF). HFrEF is the best understood type of HF in terms of pathophysiology and treatment [Braunwald 2013]. However, the true epidemiologic breakdown of HF patients by EF is unknown, since hospital-based registries conducted to date have not routinely measured EF during index admission.

1.3 Treatments and clinical pathways

Two key neurohormonal systems activated in HF are the renin–angiotensin–aldosterone system and sympathetic nervous system. While being initially compensatory of acute HF changes, over time they end up causing further myocardial injury, as these systemic responses have detrimental effects on blood vessels, kidneys, muscles, bone marrow, lungs and liver. Therefore, a pathophysiological 'vicious cycle' develops, accounting for many of the clinical features of the HF syndrome. Blocking these two key processes is the basis of modern effective treatment of HF [Zuchi 2010].

The limited cardiac reserve of HF patients is also critically dependent on atrial contraction, synchronized contraction of the left ventricle and a normal interaction between the right and left ventricles. Intercurrent events affecting any of these [e.g. development of AF, or of conduction abnormalities, such as left bundle branch block (LBBB)], or imposing an additional haemodynamic load on the failing heart (e.g. anaemia), can lead to acute decompensation and failure.

The goals of treatment in patients with established HF are to relieve symptoms and signs (e.g. oedema), prevent hospital admission and improve survival [Mcmurray 2012].

Reductions in mortality and hospital admission rates both reflect the ability of effective treatments to slow or prevent progressive worsening of HF. This is often accompanied by reverse LV remodelling and a reduction in circulating natriuretic peptide concentrations [Masson 2008].

Despite recent developments in evidence-based drug and device therapy for ambulatory HF patients with reduced EF, there have been few advances in the management of hospitalized HF patients, for whom treatment still being intravenous diuretics and/or vasodilators [Vaduganathan 2013].

Medical therapy for HF patients, the majority of whom presenting with normal perfusion and evidence of congestion, focuses on the following goals:

- Preload and afterload reduction for symptomatic relief using vasodilators (nitrates, hydralazine, nipride, nesiritide, ACEI/ARB) and diuretics.
- Inhibition of deleterious neurohormonal activation (renin-angiotensin-aldosterone system [RAAS], and sympathetic nervous system) using ACEI/ARB, beta-blockers and aldosterone antagonists, resulting in long-term survival benefit.

Preload reduction results in decreased pulmonary capillary hydrostatic pressure and reduction of fluid transudation into the pulmonary interstitium and alveoli. Preload and afterload reduction provide symptomatic relief. Inhibition of the RAAS and sympathetic nervous system produces vasodilation, thereby increasing cardiac output and decreasing myocardial oxygen demand. Besides reducing symptoms, inhibition of the RAAS and neurohormonal factors also results in significant reductions in morbidity and mortality rates, as they counteract major mechanisms of perpetuation and aggravation of the vicious cycle; over time, this will may lead to regression of geometrical alterations of left ventricle (i.e. "reverse remodelling" and improvement of ejection fraction [Mcmurray 2012]. Diuretics are effective in preload reduction by increasing urinary sodium excretion and decreasing fluid retention, with improvement in cardiac function, symptoms, and exercise tolerance [Mcmurray 2012].

Once congestion is minimized, a combination of 3 types of drugs (a diuretic, an ACEI or an ARB, and a beta-blocker) is recommended in the routine management of most patients with HF [Mcmurray 2012]. This combination can accomplish all of the above goals. ACEIs/ARBs and beta-blockers are generally used together. Beta-blockers are started once euvolemic status has been achieved and gradually up titrated.

If there is evidence of organ hypoperfusion, use of inotropic therapies and/or mechanical circulatory support (i.e. intra-aortic balloon pump, extracorporeal membrane oxygenator [ECMO], left ventricular assist device [LVAD]) and continuous hemodynamic monitoring are indicated. If arrhythmia is present and if uncontrolled ventricular response is thought to contribute to the clinical scenario of acute HF, either pharmacologic rate control or emergent cardioversion with restoration of sinus rhythm is recommended [Mcmurray 2012].

Patients still symptomatic on optimal medical therapy should be considered for electrical device (cardiac resynchronization therapy) or LVAD. In particular, as evidenced by the Euro cardiac

resynchronization therapy survey [Committee TCSS 2009], 41% of HF patients with LVEF ≤35% also had a QRS duration ≥120 ms, reflecting possible dissinchrony of cardiac contraction. Of these, 7% had RBBB, 34% had LBBB or other intraventricular conduction delay (IVCD) and 17% had QRS ≥150 ms. As evidenced by numerous large, well-controlled clinical trials, patients with clinical evidence of cardiac dyssynchrony who are refractory to optimal medical therapy, may benefit from cardiac resynchronization therapy (CRT), which substantially alters the natural course of congestive HF (CHF) [Brignole 2013]. The favorable physiological impact of CRT is seen in its positive effects on ventricular remodeling, with a reduction in left ventricular volumes and an increase in ejection fraction. This in turn results in long-term clinical benefits, with improved quality of life and functional capacity and a concomitant decline in hospitalization for HF and overall mortality [Brignole 2013].

For patients with HFpEF there are currently no available evidence-based therapies, although medical comorbidities should be treated accordingly [Senni 2014].

1.4 Description of the technology

Over the past three decades, electronic cardiac devices (ECDs) have been used to electrically stimulate the heart. ECDs include:

- Pacemaker (not discussed in this report);
- Implantable cardioverter-defibrillator (ICD) to provide early defibrillation and cardioversion of life-threatening arrhythmias;
- Cardiac resynchronization therapy (CRT or CRT-P);
- Cardiac resynchronization therapy and defibrillator (CRT-D or CRT ICD or CRT+ICD) combines functions of CRT-P and ICD devices to both improve the heart's pumping efficiency and defibrillate the heart internally in an acute arrhythmic event**.**

Implantable cardioverter-defibrillators (ICD)

ICD is indicated in patients with high risk of cardiac arrhythmias, in which the device is typically under stand-by condition, and it acts to restore normal heart rhythm when life-threatening arrhythmias occur. ICD can automatically detect both ventricular (VT/VF) and atrial tachyarhythmias (AT/AF), delivering therapies using a shock (defibrillation/cardioversion) or rapid ventricular pacing to stop the arrhythmias.

During the shock the defibrillator delivers the energy required to reset the heart muscle restoring a normal cardiac rhythm. ICD also reacts to bradyarrhythmias using pacing therapies (if the heartbeat is less than a predetermined value, the device stimulates with an appropriate rate). In addition the device records any electrical event that may have happened and can be

interrogated, thus being able to provide diagnostic information and monitoring, useful for the evaluation of the system and the clinical treatment of the patient.

ICDs can be divided mainly in 3 categories:

- single chamber ICDs
- dual chamber ICDs
- CRT-ICDs

Single-chamber ICDs have only a right ventricular lead, dual-chamber ICDs have a right atrial and right ventricular lead, and CRT-ICDs have an additional lead placed epicardially or via the coronary sinus to stimulate the LV [Kadish 2005]. ICDs are programmed through an external computer (programmer) located in an ambulatory or hospital setting to set the device according to the specific patient's characteristics.

Cardiac resynchronization therapy (CRT)

CRT provides strategic electrical stimulation to right atrium, right ventricle and left ventricle to coordinate ventricular contractions and improve cardiac output in patients with ventricular asynchrony. This is commonly associated with HF. The primary objective of CRT is the restoration of a normal ventricular activation pattern. Second, CRT allows the optimization of the atrioventricular interval in patients with sinus rhythm [Strickberger 2005]. A cardiac resynchronization pacemaker without ICD capability (CRT-P) is used in patients with ventricular dysfunction who are not candidates for an automatic cardioverter-defibrillator-type device.

Cardiac resynchronization therapy and defibrillator (CRT-D)

As CRT-D combines ICD and CRT-P; the main characteristics and functional operation are comparable to ICD and CRT-P described above. To date several CRT-Ds are available in the market, each producer providing several models and many versions. In Italian market each producer offers several models, mainly differing in battery life span, MRI compatibility, wireless telemetry, diagnostic system, programs and modality of intervention (such as antitachycardia pacing - ATP) in VF (ventricular fibrillation) zone, inappropriate shock avoidance system, remote monitoring and leads connector (DF-1 or DF-4)[1]. These features are meant to improve efficacy of treatment and quality of life of the patient, as described below and detailed for each model in Appendix 1:

- CRT-D MRI-conditional allows to perform MRIs on patients under set condition.

[1] These two standards allow an interchangeable use of different models of leads and CRT-D useful in re-implant avoiding leads replacement.

- Some CRT-Ds are provided with antitachycardia pacing (ATP) in FV zone consisting of a therapy for rapid VT (ventricular tachyarhythmias) detected in the VF zone;
- Inappropriate ICD shock diagnosis is a diagnostic system to avoid patient pain and can help to safeguard battery life;
- Quadripolar left ventricular (LV) lead avoids phrenic nerve stimulation (PNS) and pacing around myocardial areas of scar, possibly improving response to CRT;
- Diagnostics for HF: the system can predict worsening HF using intrathoracic impedance and fluid accumulation and/or elaborating cardiac parameters;
- In automatic Optimization of Cardiac Resynchronization Therapy (AV and VV intervals optimization) the algorithm automatically optimizes atrioventricular and interventricular intervals.
- Battery life is an important characteristic because longer life span means prolonging the time before battery replacement or re-implant, reducing risks for patient and costs [Bilal Alam 2013]. The battery status can be detected by telemetry or by programmer. Because different parameters are adopted by producers to evaluate device life span, this characteristic is not reported in Appendix.

Finally, models can differ also by year of commercialization due to the very dynamic CRT-D's market. This is reflected by the approximately one year turnover of models. The rapid technical development of CRT and CRT-D devices in the last decade has introduced difficulties in their assessment, as comparative analysis must be made comparing like with like. Some of the populations to which this document refers have received submodels of apparently the same device or different devices with different functionalities.

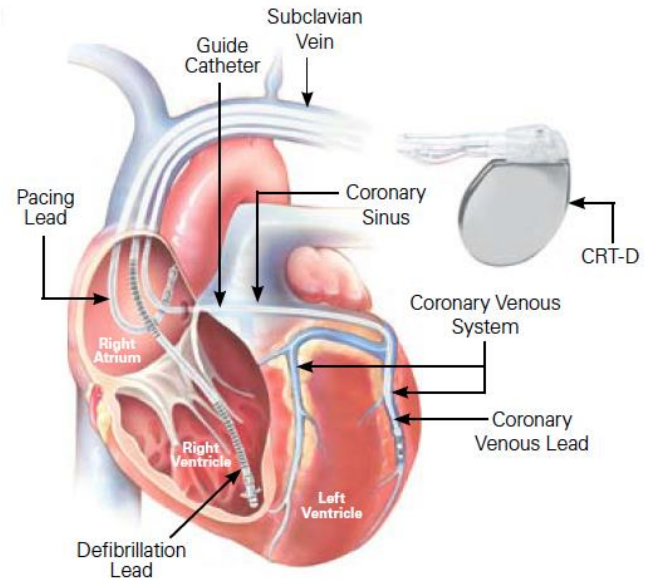


Fig 1.1: CRT-D implant

CRT-D is programmed through an external computer (programmer) located in an ambulatory or hospital setting to set the device according to the specific patient's characteristics. The programmer is used, also, to download and view clinical parametres during patients' follow up.

2. Report's objectives: policy and research questions

This rapid HTA report has been developed to answer the following questions:

Policy question: what is the optimal use of the CRT-D?

Research question:

1. What is the real use of CRT-D and its comparators in Italy?

2. What are the effects, in terms of effectiveness, safety and cost-effectiveness, of using the CRT-D compared either to CRT-P and ICD in patients with chronic heart failure?

3. CONTEXT OVERVIEW

3.1 CRT-D in the Italian market and regulatory status

In Italy CRT-Ds were registered on the General Repertory of medical devices (RDM) (as of 3rd January 2014) using the National Classification of Medical Devices (CND) code associated to this kind of devices: "J01050301 - DEFIBRILLATORI TRICAMERALI CON SENSORE" and, when available, the Global Medical Device Nomenclature (GMDN) code. Using the search results on RDM, integrating data with searches on the internet and with the contribution of manufacturers (i.e. manufacturers' websites) we made a picture of CRT-Ds in the Italian market shown in the following Tables 3.1 – 3.5.

All manufactures (Biotronik SE & Co. KG, Boston Scientific, Medtronic Inc, Sorin Group, St. Jude Medical) were invited individually in Agenas for a face to face meeting. We propose to manufactures a semi structurated interview based on the questionnaire reported in Appendix 1. All information reported in Tables 3.1 – 3.5 were authorized and approved by manufactures.

Table 3.1: CRT-Ds commercialized in Italy by Biotronik SE & Co. KG

N°	Manufacturer	Model	Product code	Version	RDM	CE mark	FDA approval
1	BIOTRONIK SE & CO. KG	Iforia 3 HF-T	383554	DF-1	754867/R	yes	-
2			383556	DF-4	756767/R	yes	pending
3		Iforia 5 HF-T	390111	DF-1	907474/R	yes	-
4			390113	DF-4	907477/R	yes	pending
5		Ilesto 5 HF-T	390110	DF-1	757534/R	yes	-
6			390112	DF-4	757557/R	yes	pending
7		Ilesto 7 HF-T	390055	DF-1	755248/R	yes	yes*
8			390061	DF-4	755267/R	yes	pending
9		Idova 7 HF-T	383560	DF-1	958239/R	yes	-
10			383561	DF-4	958238/R	yes	pending
11		Lumax 640 HF-T	381471	DF-1	466278/R	yes	yes*
12		Lumax 740 HF-T	381462	DF-1	466277/R	yes	yes*

*FDA approval without MRI conditional (ProMRI)

Table 3.2: CRT-Ds commercialized in Italy by Boston Scientific

N°	Manufacturer	Model	Product code	Version	RDM	GMDN	CE mark	FDA approval
13	Boston Scientific	AUTOGEN CRT-D	G172	DF-4	10097317/R	37265	yes	no
14			G173	DF-1	1009886/R	37265	yes	No
15			G175	DF-1	1009905/R	37265	yes	No
16		AUTOGEN X4 CRT-D	G177	DF-1	1009961/R	37265	yes	No
17			G179	DF-4	1009993/R	37265	yes	No
18		INOGEN CRT-D	G140	DF-4	1011351/R	37265	yes	No
19			G141	DF-1	1011361/R	37265	yes	No
20		INOGEN X4 CRT-D	G146	DF-1	1011368/R	37265	yes	Yes
21			G148	DF-4	1011387/R	37265	yes	Yes
22		Incepta CRT-D	P162	DF-4	361472/R	37265	yes	yes (N160)
23			P163	DF-1	361472/R	37265	yes	yes (N161)
24			P165	DF-1	361472/R	37265	yes	yes (N164)
25		Energen CRT-D	P142	DF-4	365834/R	37265	yes	yes (N140)
26			P143	DF-1	365834/R	37265	yes	yes (N141)
27		Punctua CRT-D	P052	DF-4	365853/R	37265	yes	yes (N050)
28		Punctua NE CRT-D	P053	DF-1	365887/R	37265	yes	yes (N051)

Table 3.3: CRT-Ds commercialized in Italy by Medtronic Inc

N°	Manufacturer	Model	Product code	Version	RDM	CE mark	FDA approval
29	Medtronic Inc	Consulta CRTD	D234TRK	DF-1	18103/R	yes	17/3/2008
30			D214TRM	DF-4	359778/R	yes	9/1/2012
31		Concerto II	D294TRK	DF-1	212134/R	yes	23/10/2008
32		Protecta XT CRTD	D354TRG	DF-1	306633/R	yes	25/3/2011
33			D354TRM	DF-4	342960/R	yes	9/11/2011
34		Protecta CRTD	D364TRG	DF-1	306634/R	yes	25/3/2011
35			D364TRM	DF-4	342963/R	yes	9/11/2011
36		Viva XT	DTBA2D1	DF-1	607678/R	yes	29/1/2013
37			DTBA2D4	DF-4	607680/R	yes	29/1/2013
38		VIVA™ QUAD XT	DTBA2QQ	IS-4/DF-4	712868 /R	yes	No
39			DTBA2Q1	IS-4/DF-1	1007932 /R	yes	No
40		Viva S	DTBB2D4	DF-4	636327/R	yes	29/1/2013
41			DTBB2D1	DF-1	636288/R	yes	29/1/2013
42			DTBB2QQ	IS-4/DF-4	712869/R	yes	No
43		Maximo II CRT-D	D284TRK	DF-1	18116/R	yes	17/3/2008
44			D264TRM	DF-4	359780/R	yes	9/1/2012
45		Cardia CRT-D	D384TRG	DF-1	391449/R	yes	no
46		Brava	DTBC2D4	DF-4	636338/R	yes	29/1/2013
47			DTBC2D1	DF-1	636335/R	yes	29/1/2013
48		Brava Quad	DTBC2QQ	IS-4/DF-4	712870 /R	yes	no
49			DTBC2Q1	IS-4/DF-1	1007933 /R	yes	no

Table 3.4: CRT-Ds commercialized in Italy by Sorin Group

N°	Manufacturer	Model	Product code	Version	RDM	GMDN	CE mark	FDA approval
50	Sorin Group	PARADYM RF CRT-D 9750	ICV1183	DF-1	718351	47940	yes	yes
51		PARADYM RF CRT-D SONR 9770	ICV1182	DF-1	718354	47940	yes	pending
52		PARADYM CRT-D 8750	ICV1054	DF-1	718375	47940	yes	yes
53		PARADYM 2 CRT-D 8752	TDF001C	DF-1	933354	47940	yes	no
54		INTENSIA SONR CRT-D 184	TDF019C	DF-4	1035790	47940	yes	no
55		PARADYM 2 CRT-D SONR 8772	TDF004C	DF-1	1126615	47940	yes	no
56		PARADYM SONR TRIV 8970	ICV1231	DF-1	1162287/R	47940	yes	no

Table 3.5: CRT-Ds commercialized in Italy by St Jude Medical

N°	Manufacturer	Model	Product code	Version	RDM	GMDN	CE mark	FDA approval
57	St. Jude Medical	Promote +	CD3211-36	DF-1	354238/R	37265	yes	yes
58			CD3211-36Q	DF-4	354254/R	37265	yes	yes
59		Promote Quadra	CD3239-40	DF-1	322934/R	35852	yes	no
60			CD3239-40Q	DF-4	322922/R	35852	yes	
61		Unify Quadra	CD3251-40	DF-1	414422/R	35852	yes	no
62			CD3251-40Q	DF-4	414425/R	35852	yes	
63		Unify Assura	CD3361-40	DF-1	868438/R	35852	yes	no
64			CD3361-40Q	DF-4	868443/R	35852	yes	
65			CD3361-40C	DF-1	836828/R	35852	yes	
66			CD3361-40QC	DF-4	836927/R	35852	yes	
67		Quadra Assura	CD3367-40	DF-1	868387/R	35852	yes	no
68			CD3367-40Q	DF-4	868415/R	35852	yes	
69			CD3367-40C	DF-1	836788/R	35852	yes	
70			CD3367-40QC	DF-4	836807/R	35852	yes	
71		Quadra Assura MP	CD3371-40	DF-1	843768/R	35852	yes	no
72			CD3371-40Q	DF-4	843771/R	35852	yes	no
73			CD3371-40C	DF-1	1122379/R	47270	yes	no
74			CD3371-40QC	DF-4	1122380/R	47270	yes	no

3.2 Use of the technology in Italy

Multiple sources of data on cardiac devices exist.

In Italy, for example, the pacemaker (PM) and implantable cardioverter-defibrillator (ICD) Registry of the Italian Association of Arhythmology and Cardiac Pacing (AIAC) [Proclemer et al. 2013] monitors the main information about demographics, clinical characteristics, main indications for PM/ICD therapy and device types from the Italian collaborating centers. AIAC requires hospitals to submit prospectively data on cardiac device implantation activity.

Due to voluntary participation in the registry, the number of centers is variable over the years and the national coverage is not homogeneous. In addition, since 2012, AIAC has been implementing new procedures for collecting data: the collaborating centers submit their information directly via the web. Finally, since the registry scope is that of monitoring PM and ICD implants, data regarding CRT-P implants are only partial, and the registry does not record clinical variables needed to characterize patients with heart failure (e.g., ECG duration; presence of Left-Bundle branch block).

In Europe, for example, additional sources of data exist as EUCOMED report medical devices' market sharing, however direct access to EUCOMED database is not allowed without the approval of the participating companies. Due to our time constrains respect to the EUCOMED procedure of authorization and the uncertainty in the possibility of data publication we decided to don't ask any information.

Given the above, we decided not to analyze the information contained in AIAC and EUCOMED database.

We decided to use only the information contained in the New Health Information System (NSIS) as the official source of the Ministry of Health that contains the data validated and standardized in all the national territory. Among the wide information contained in NSIS we selected hospital discharges "SDO" and "flusso consumi" database helpful for our analysis.

3.2.1 Data and Variables of hospital discharges

The source of data for this study was the 2012 national hospital discharges administrative database (SDO 2012). Cardiac device implants were identified from ICD-9-CM (International Classification of Diseases - 9th Edition-Clinical modification) codes reported in table 3.6. We searched records discharges that presented at least one of those codes corresponding to principal and other procedures.

Table 3.6: ICD9-CM procedure codes linked with cardiac devices implantation.

Code	Description
00.50	Implantation of cardiac resynchronization pacemaker without mention of defibrillation, total system (CRT-P)
00.51	Implantation of cardiac resynchronization defibrillator, total system (CRT-D)
00.52	Implantation or replacement of transvenous lead into left ventricular coronary venous system
00.53	Implantation or replacement of cardiac resynchronization pacemaker, pulse generator only (CRT-P)
00.54	Implantation or replacement of cardiac resynchronization defibrillator, pulse generator only (CRT-D)
37.94	Implantation or replacement of automatic cardioverter-defibrillator, total system (AICD)
37.95	Implantation of automatic cardioverter-defibrillator lead(s) only
37.96	Implantation of automatic cardioverter-defibrillator pulse generator only
37.97	Replacement of automatic cardioverter-defibrillator lead(s) only
37.98	Replacement of automatic cardioverter-defibrillator pulse generator only
37.72	Initial insertion of transvenous leads into atrium and ventricle
37.73	Initial insertion of transvenous lead into atrium
37.74	Insertion or replacement of epicardial lead [electrode] into epicardium

Initial exploration showed that 52,863 Italian hospital discharges out of a total 10,259,779 discharges, matched with at least one of the above procedures.

We focused on discharges due to implantation of automatic cardioverter/defibrillator (AICD), or cardiac resynchronization therapy pacemaker (CRT-P) or defibrillator (CRT-D). Table 3.7 lists all specific procedures codes combinations that allow the classification of the patient's discharges into groups associated with the use of the cardiac devices we were interested in. If any combination was identified, the discharge was placed into the "Other" group and not considered in our investigation.

Table 3.7: Definition of ICD9-CM procedure code combination for implantation of AICD or CRT-P or CRT-D

Cardiac Devices	Definition based on recorded cardiac device procedure codes
CRT-D	00.51
CRT-D Upgrade	00.54 and (37.74 or 37.97)
CRT-P	00.50
CRT-P Upgrade	00.53 and (37.73 or 37.72 or 00.52)
ICD	37.94 or (37.95 and 37.96) or (37.97 and 37.98)
ICD Upgrade	(00.54 and 37.73 and 00.52) or (00.54 and 00.52)

Hospital discharges were analysed to estimate the number of implantations accordingly to the codes' combinations.

Table 3.8 shows the estimate number of cases for each procedure carried out during 2012.
Patients who had 1 or more cardiac device procedures and patients with CRT-D or CRT-P or ICD upgrade could not be placed with certainty in one of investigated groups. In light of these considerations we decided to group and analyse the data reported in table 3.8.

Tab 3.8: Volumes discharges of cardiac devices implantation – SDO 2012

Procedure	Discharges number	
	Absolute value	%
New CRT-D	4,461	25.7
CRT-D upgrade	28	0.2
New CRT-P	1,227	7.1
CRT-P upgrade	178	1.0
New ICD	10,803	62.2
ICD upgrade	442	2.5
Multiple procedure (max 3)	228	1.3
Sub total	17,367	100.0
Other	35,496	
Total	52,863	

Source: Age.na.s. analysis based on SDO2012

Data for 35,496 procedures were identified and discarded. In this group the 74.8% were coded as ICD-9-CM procedure codes corresponding to implantation of pacemaker (37.72 and 37.80 and 37.83) which are outside our topic of interest.

3.2.2 Statistical analysis

Descriptive analyses were done on national and regional estimates on the numbers of cardiac device implantations by patient. Hospital characteristics were estimated and tabulated.
Crude and standardized regional rates of cardiac devices implantations (adjusted by gender and age) were calculated. We used the direct method with ISTAT 2012 Italian population as a standard. Crude and standardised rates were constructed on the assumption that each single procedure has been carried out on a single patient who was resident in the Region where he/she underwent the procedure. The database used did not show the patient's code identification, so it was necessary to assume residence to achieve standardized rates. Data management and analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC).

3.2.3 Results

Table 3.9 shows the national estimates of new CRT-D, new CRT-P and new ICD systems implanted in 2012 in Italy. The most frequent procedure was ICD (62.2%) followed by total CRT-D (25.7%) and CRT-P (7.7%).

The "Other" row presents the number of patients who had more cardiac device procedures but could not be placed with certainty in the first 3 groups.

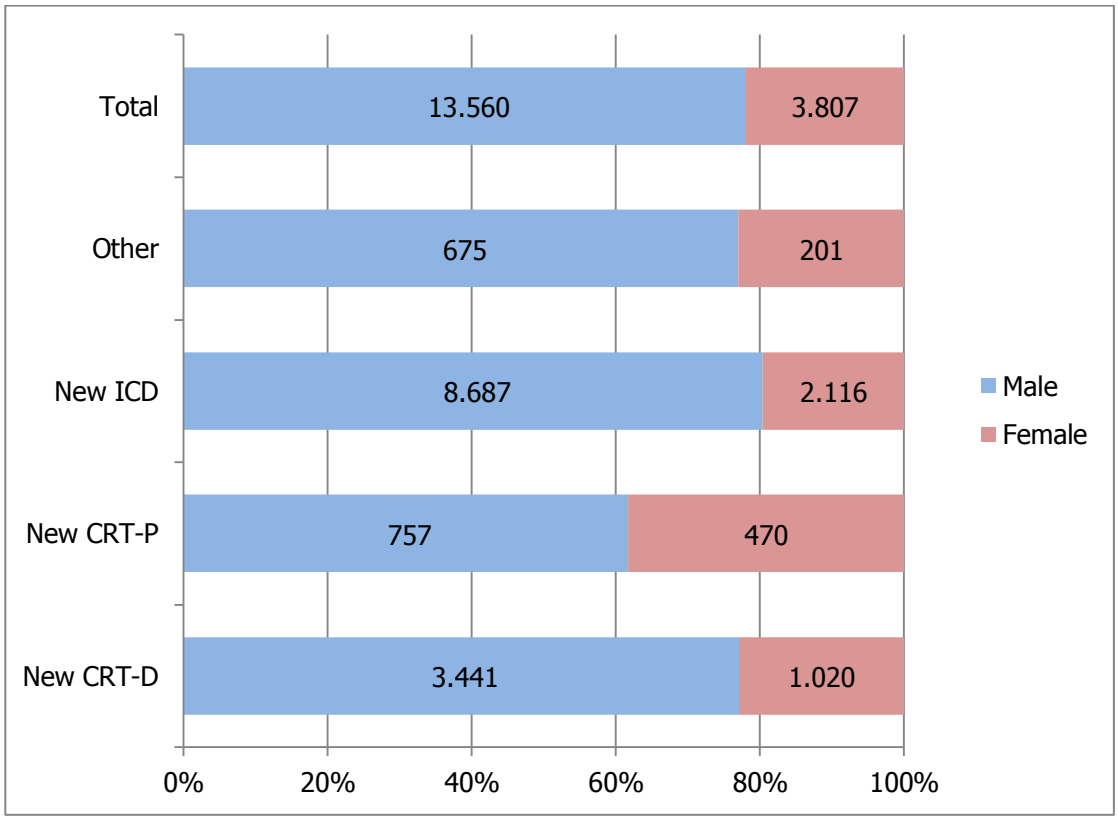
Table 3.9: Estimate volumes discharge for cardiac devices implantation relevant to our investigation – SDO 2012

Procedure	Discharges number	
	Absolute value	%
New CRT-D	4,461	25.69
New CRT-P	1,227	7.07
New ICD	10,803	62.20
Other	876	5.04
Total	17,367	100.00

Source: Age.na.s. analysis based on SDO2012

The data in the table reports on the 17,367 cases of single and simple CRT and ICD implantations. The data on discharges of cardiac procedures broken down by gender (Fig 3.1), show that approximately 80% of procedures were performed on males for most cardiac device implantations, except for CRT-P where the percentage of men undergoing these procedures was around 60%.

Fig 3.1: Hospital discharges per type of cardiac devices implantation and gender– SDO 2012 (absolute and percentage values)



Source: Age.na.s. analysis based on SDO 2012

Patients aged 65 or over accounted for 71.51% of CRT-D patients, around 83% of ICD patients, and over 89% of CRT-P patients (see table 3.10).

Table 3.10: Hospital discharge per type of cardiac devices implantation and age class – SDO 2012 (percentage values)

Age class (years)	New CRT-D	New CRT-P	New ICD	Other	Total
0-24	0.07	0.16	1.05	0.46	0.07
25-64	28.42	10.43	36.07	22.60	28.42
65-74	38.80	21.03	32.86	34.25	38.80
75-84	31.07	50.77	27.08	38.13	31.07
85+	1.64	17.60	2.94	4.57	1.64
Total (%)	100.00	100.00	100.00	100.00	100.00
Total (absolute values)	4,461	1,227	10,803	876	17,367

Source: Age.na.s. analysis based on SDO 2012

Looking at single cardiac implant estimates (CRT-D, CRT-P e ICD), Table 3.11 shows the distribution of cases by region in residents of each region.

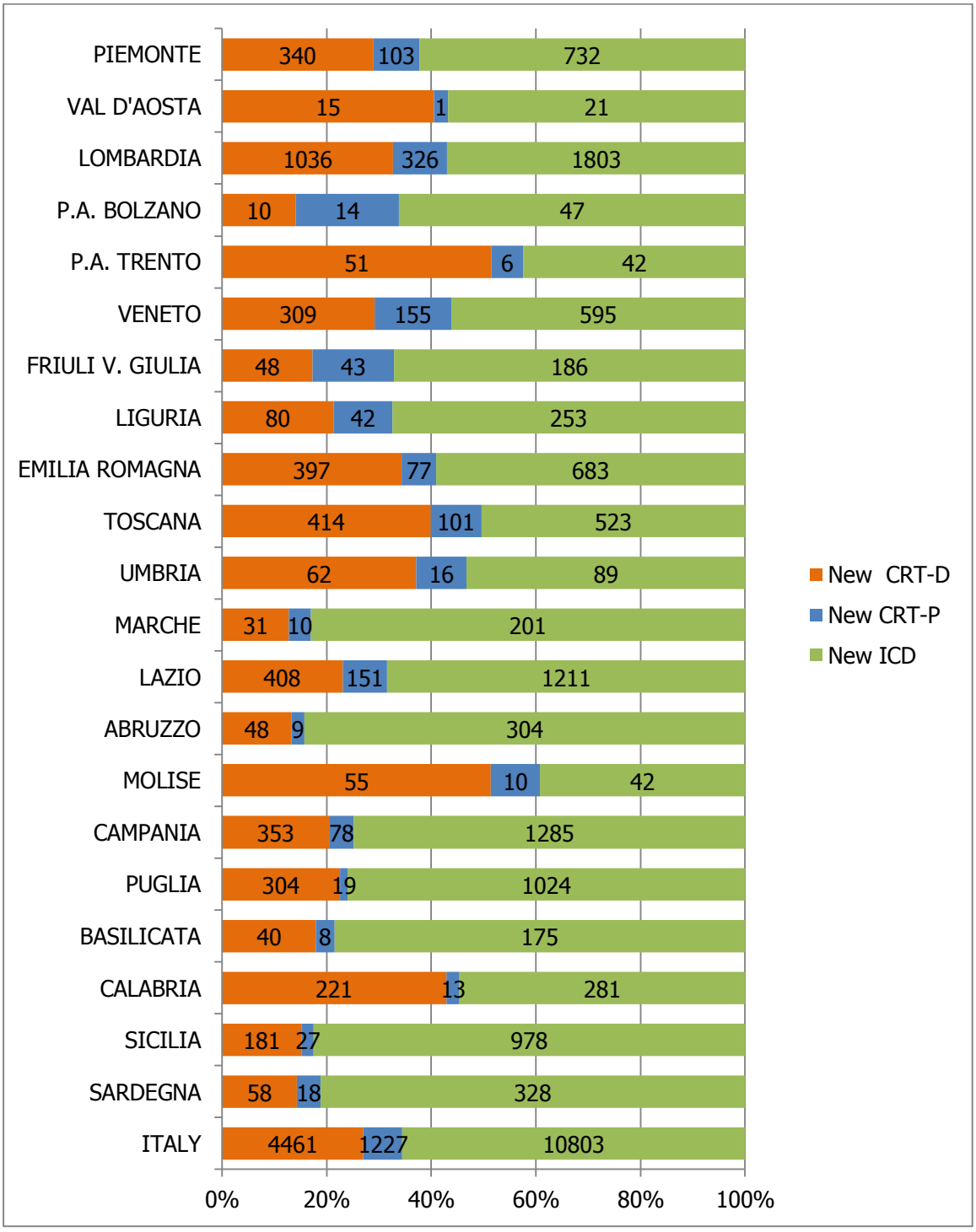
For all procedures of implantable cardiac device, most hospitalizations were carried out in the region of residence of the patients.

Table 3.11: Distribution of total discharges volumes in residents of each region by region and type of device - SDO 2012

Region	New CRT-D		New CRT-P		New ICD	
	Absolute values	% residents	Absolute values	% residents	Absolute values	% residents
PIEMONTE	340	92.35	103	95.15	732	95.22
VAL D'AOSTA	15	100.00	1	100.00	21	95.24
LOMBARDIA	1,036	87.45	326	92.64	1,803	88.24
P.A. BOLZANO	10	100.00	14	78.57	47	95.74
P.A. TRENTO	51	92.16	6	66.67	42	88.10
VENETO	309	96.12	155	97.42	595	96.97
FRIULI V. GIULIA	48	93.75	43	97.67	186	91.94
LIGURIA	80	95.00	42	97.62	253	92.09
EMILIA ROMAGNA	397	71.28	77	80.52	683	86.97
TOSCANA	414	89.61	101	92.08	523	88.15
UMBRIA	62	85.48	16	93.75	89	93.26
MARCHE	31	96.77	10	100.00	201	93.03
LAZIO	408	93.87	151	96.69	1,211	93.31
ABRUZZO	48	81.25	9	100.00	304	94.74
MOLISE	55	60.00	10	100.00	42	73.81
CAMPANIA	353	98.30	78	96.15	1,285	96.65
PUGLIA	304	91.12	19	89.47	1,024	96.29
BASILICATA	40	75.00	8	100.00	175	90.29
CALABRIA	221	98.64	13	92.31	281	98.93
SICILIA	181	96.69	27	100.00	978	98.77
SARDEGNA	58	98.28	18	94.44	328	98.48
ITALIA	4,461	89.80	1,227	93.81	10,803	93.47

In all regions, there was a higher use of ICD (most of the regions exceeded 60%) except for the Molise and PA Trento (about 40%), followed by CRT-D (most of the regions exceeds 20%) and CRT-P (see Fig. 3.2).

Fig 3.2: Hospital discharges distribution per type of cardiac devices implantation and region – SDO 2012 (absolute and percentage values)



Source: Age.na.s. analysis based on SDO 2012

Table 3.12 reports crude rates of use by procedure broken down by Region. Table 3.13 shows the corresponding standardized rates (adjusted by gender and age)

Table 3.12: Crude rate of use by procedure broken down by Region per 10,000 resident inhabitants – SDO 2012

Region	CRT-D		CRT-P		ICD	
	Absolute values	Crude rate	Absolute values	Crude rate	Absolute values	Crude rate
PIEMONTE	314	0.95	98	0.29	697	1.60
VAL D'AOSTA	15	2.55	1	3.72	20	2.13
LOMBARDIA	906	1.22	302	0.41	1,591	1.64
TRENTINO A. A.	57	0.76	15	0.39	82	0.91
VENETO	297	0.80	151	0.41	577	1.19
FRIULI V. GIULIA	45	0.49	42	1.97	171	1.78
LIGURIA	76	0.63	41	0.49	233	1.64
EMILIA ROMAGNA	283	0.75	62	0.18	594	1.37
TOSCANA	371	1.33	93	0.32	461	1.26
UMBRIA	53	0.81	15	0.23	83	1.31
MARCHE	30	0.47	10	0.15	187	1.21
LAZIO	383	0.91	146	0.30	1,130	2.05
ABRUZZO	39	0.41	9	0.41	288	2.20
MOLISE	33	2.23	10	0.72	31	1.24
CAMPANIA	347	0.85	75	0.18	1,242	2.15
PUGLIA	277	0.93	17	0.06	986	2.43
BASILICATA	30	0.69	8	0.36	158	3.63
CALABRIA	218	1.51	12	0.16	278	1.63
SICILIA	175	0.40	27	0.07	966	2.23
SARDEGNA	57	0.40	17	0.13	323	1.97
ITALIA	4,006	0.88	1,151	0.28	10,098	1.76

Source: Age.na.s. analysis based on SDO 2012; Italian population as reported by ISTAT 2012

The rate of use of new CRT-P has greater variation between regions than the other two procedures. Standardized regional rates showed the highest variability among Regions for CRT-P implantation (Variation Coefficient - VC 157,54%) and an important variability also for new CRT-D and new ICD (respectively 60.78 % and 36.53%) (table 3.13).

In Val d'Aosta and Molise, new CRT-D has the highest rates of use (2.56 and 2.17 per 10,000 inhabitants) followed by Calabria and Toscana.

The great variability of new CRT-P use was attributable to the two outlier values of the Val D'Aosta and Friuli Venezia Giulia (3.72 and 2.02 for inhabitants 10,000). In fact, all other Regions show values relatively homogeneous and less than one.

Focusing on new ICD, Basilicata, Puglia and Campania had the highest standardized rates of use (Table 3.13).

Table 3.13: Standardized rate and standard mean deviation of use by procedure broken down by Region per 10,000 resident inhabitants – SDO 2012

Region	CRT-D		CRT-P		ICD	
	Standardized rate (°)	Mean deviation	Standardized rate (°)	Mean deviation	Standardized rate (°)	Mean deviation
PIEMONTE	0.89	-0.06	0.26	-0.28	1.48	-0.29
VAL D'AOSTA	2.56*	1.61	3.72*	3.17	2.09	0.33
LOMBARDIA	1.23	0.28	0.42	-0.12	1.63	-0.14
TRENTINO A. A.	0.79	-0.16	0.41	-0.13	0.95	-0.82
VENETO	0.81	-0.13	0.42	-0.12	1.19	-0.58
FRIULI V. GIULIA	0.46	-0.49	2.02*	1.48	1.70	-0.07
LIGURIA	0.56	-0.38	0.40	-0.14	1.44	-0.33
EMILIA ROMAGNA	0.71	-0.23	0.17	-0.37	1.30	-0.47
TOSCANA	1.25	0.31	0.29	-0.25	1.17	-0.60
UMBRIA	0.78	-0.17	0.21	-0.34	1.26	-0.51
MARCHE	0.45	-0.50	0.14	-0.40	1.15	-0.62
LAZIO	0.93	-0.01	0.31	-0.23	2.09	0.32
ABRUZZO	0.39	-0.55	0.40	-0.14	2.12	0.35
MOLISE	2.17*	1.22	0.67	0.13	1.18	-0.59
CAMPANIA	0.93	-0.02	0.21	-0.33	2.50	0.73
PUGLIA	0.96	0.01	0.06	-0.48	2.58	0.81
BASILICATA	0.70	-0.25	0.35	-0.19	3.58*	1.81
CALABRIA	1.54	0.59	0.16	-0.39	1.68	-0.09
SICILIA	0.42	-0.52	0.08	-0.46	2.33	0.56
SARDEGNA	0.41	-0.54	0.14	-0.40	1.95	0.19
Means	0.95		0.54		1.77	
Standard Deviation	0.58		0.85		0.65	
VC	60.78		157.54		36.53	

Source: Age.na.s. analysis based on SDO 2012

°Standard Population: Italian population as reported by ISTAT 2012.

*statistically significant 95%: means deviation divided by standard deviation more than 1.96 as an absolute value.

3.3 Consumption of CRT-D, CRT-P and ICD in Italy

We analyzed the national database "Flusso consumi" run by Ministry of Health with the aim of identifying the real consumption of devices assessed in this report (in terms of number of devices purchased) in Italian public health structures, for the years 2012 and 2013.

The database is fed by Italian Regions that gather data from public health care providers in their territory. The database was created in 2011 with a piloting phase in 2012 and its maintenance became mandatory in 2013. During the pilot phase the database was powered by about 87% of health care providers, while in the first half of 2013 from 92% [http://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&p=dalministero&id=1418].

We extracted data related to:

- the consumption of active implantable devices (J0105 CND) marketed within health national system: ICD (J01050101), CRT-D (J01050301) and CRT-P (J01050201);
- the contract price of each CRT-D device as listed in the tables 3.1-3.5 reported in paragraph 3.1.

In particular we searched the reports CNS003 and CRT009 respectively.

Concerning the 2012 the real national consumption was of 4,999 for CRT-D, 3,126 for CRT-P and 3,030 for ICD devices. The detailed data, distributed for each Region, are reported in Table 3.14.

Table 3.14: 2012 devices consumptions

Regions	CRT-D	CRT-P	ICD
ABRUZZO	116	121	26
BASILICATA	82	73	6
CALABRIA	95	50	38
CAMPANIA	466	535	200
EMILIA-ROMAGNA	449	173	418
FRIULI VENEZIA GIULIA	97	99	37
LAZIO	6	1	1
LIGURIA	150	48	115
LOMBARDIA	1,104	530	894
MARCHE	131	72	110
MOLISE	23	39	17
PA BOLZANO	29	12	89
PA TRENTO	41	22	28
PIEMONTE	239	114	251
PUGLIA	189	213	61
SARDEGNA	No data	No data	No data
SICILIA	350	409	215

TOSCANA	823	337	207
UMBRIA	48	33	13
VALLE D'AOSTA	27	10	10
VENETO	534	235	294
TOTAL	**4,999**	**3,126**	**3,030**

Source: Agenas analysis based on national database "Flusso consumi", year 2012.

NB For 2012 only Lazio reported one centre's data

In 2013 the real national consumption increased for all three devices reaching 5,735 for CRT-D, 4,206 for CRT-P and 3,981 for ICD devices. The detailed data, distributed for each Region, are reported in Table 3.15.

Table 3.15: 2013 device consumption**s**

Regions	CRT-D	CRT-P	ICD
ABRUZZO	160	104	17
BASILICATA	54	79	15
CALABRIA	131	92	62
CAMPANIA	462	499	166
EMILIA-ROMAGNA	380	168	562
FRIULI VENEZIA GIULIA	120	120	40
LAZIO	410	429	603
LIGURIA	122	57	91
LOMBARDIA	1,229	549	961
MARCHE	139	88	129
MOLISE	14	33	4
PA BOLZANO	20	5	66
PA TRENTO	52	11	6
PIEMONTE	385	289	345
PUGLIA	318	451	108
SARDEGNA	No data	No data	No data
SICILIA	297	472	216
TOSCANA	860	427	247
UMBRIA	23	32	13
VALLE D'AOSTA	19	3	13
VENETO	540	298	317
TOTAL	**5,735**	**4,206**	**3,981**

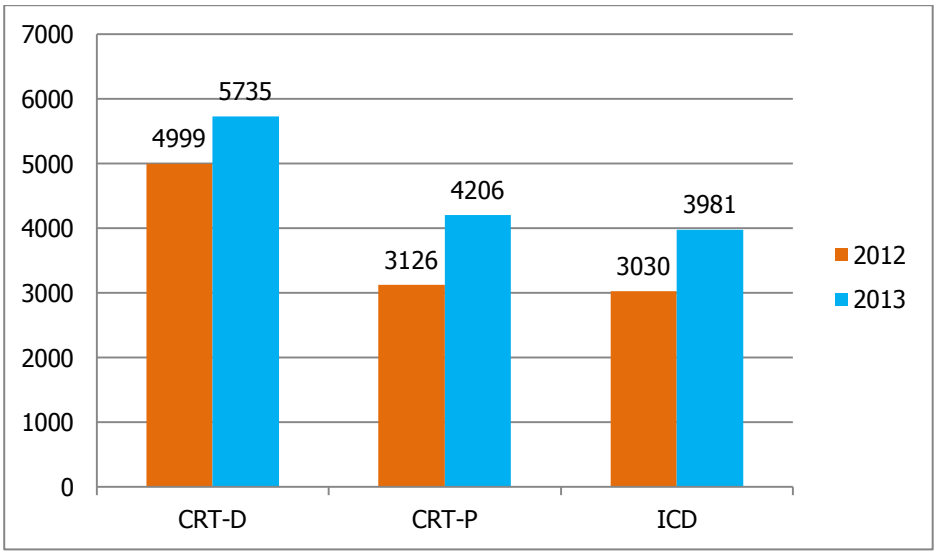
Source: Agenas analysis based on national database "Flusso consumi", year 2013.

Figure 3.3 shows graphically the increasing trend of consumption in 2012 and 2013 for all devices considered. Specifically, device consumption in 2013 compared to 2012 increased by 14.72% for CRT-D, by 34.55% for CRT-P and by 31.39% for ICD devices.

This trend could be only slightly influenced by partial data available for 2012 (piloting phase). It is important to note that, in Lazio Region, the increase of the total consumption for all devices is quite peculiar. As already reported, in 2012 during the piloting phase, only one public health provider gave its

own data. Indeed the high increase has been partially affected from a greater flow of data due to more providers submitting their own data to the Region.

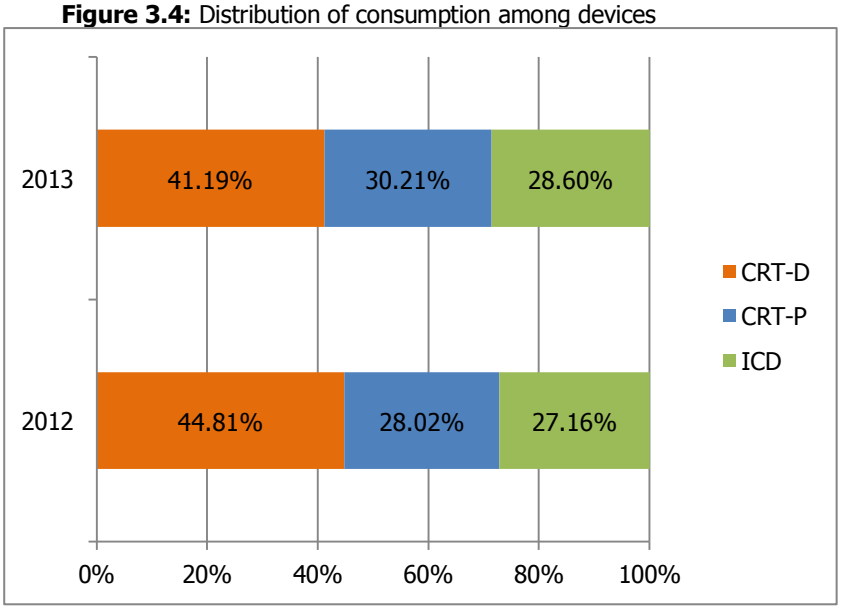
Figure 3.3: Trend of consumption in 2012 and 2013



Source: Agenas analysis based on national database "Flusso consumi", years 2012 and 2013.

Figure 3.4 shows that CRT-D consumption represents about the half of consumptions of the three devices considered.

Figure 3.4: Distribution of consumption among devices



Source: Agenas analysis based on national database "Flusso consumi", years 2012 and 2013.

We gathered the price of all CRT-D devices marketed in Italy and we pulled out the minimum and maximum price for 2012 and 2013.

No relevant differences in price ranges between the years considered were identified, but the minimum price showed a slight increase of about 300 Euros (ranging from 7,000 to 7,290 Euros) and the maximum price a similar small reduction, decreasing from 17,250 to 17,000 Euros (Tab 3.16).

Table 3.16: Prices range of CRT-D

Year	Price Range (€)
2012	7,000.00 - 17,250.00
2013	7,290.00 - 17,000.00

3.4 Conclusion

This analysis is based on administrative data (SDO). To allow decision makers to have a wide-ranging view on which to base their final decision, it is useful to match this examination with the analysis of other sources of information.

ICD is the most implanted device especially in men aged 65 and over, with an increasing yearly trend. There are relatively small numbers of extra resident implants by region and when rates are standardized the incidence of intervention is similar among regions. Demographically small regions (Val D'aosta, Molise and Basilicata) have a significantly higher number of implants. The regions with the most organised health services (Lombardia, Veneto, Toscana, Emilia, Umbria) show similar pattern of use.

Comparing data from SDO with those from "Flusso comsumi" we observed that, in 2012, in Italy ICDs were the most used device (65% of all implants), with 3,030 units bought (30% of units bought), and a 10,803 implanted. The ratio of 3:1 is the opposite for CRT-P with 1,227 implanted devices and 3,126 bought. For CRT-D, 4,999 were bought and 4,461 were implanted. It is important to bear in mind that as the date of purchase is unknown, it is possible that a proportion of these devices were implanted in the early months of 2013. In addition some of the Regions, like Lazio, did not report purchases to the database in 2012 (8 devices in total were reported) but 1,680 were implanted.

From "Flusso consumi" data, multiplying contract price (minimum and maximum respectively) and CRT-D amount bought, it results an estimate of total CRT-D device costs for 2013 ranging from 41,808,150 to 97,495,000 Euros.

Readers must bear in mind that the purchase data may be incomplete, thereby underestimating the total.

4. Effectiveness and safety

4.1 Methods

We searched the following databases: EMBASE, MEDLINE, Cochrane Library (including the DARE and HTA databases) and clinicaltrials.gov using combinations of the following keywords:

- **For the technology:** implantable cardioverter-defibrillators (ICDs), automatic internal defibrillators, implantable defibrillators, biventricular pacing systems, CRT, CRT-P and CRT-D.

- **For the intervention:** resynchronization therapy, defibrillation

Searches were performed with no time restriction but only full-text in English and Italian articles were considered.
Only studies on humans were considered.

Searches were conducted on 24-28 February 2014. (See Appendix 2)

In addition to the searches we contacted and held meetings with five producers Boston Scientific, Biotronic, Medtronic Inc, Sorin Group, St Jude Medical.
At all meetings we asked which models each producer currently marketed in Italy, details of the use and functions of each model, approximate costs of each model, business volume by region (if available). We also asked each producer to identify studies which could fit our inclusion criteria. At each meeting, minutes of the discussion were kept and countersigned by all participants. The discussion was confidential but the synopsis tables of devices and their use are not and are reported in Appendix 1:

- Tab.1, CRT-D produced and commercialized in Italy by Biotronik
- Tab.2, CRT-D produced and commercialized in Italy by Boston Scientific
- Tab.3, CRT-D produced and commercialized in Italy by Medtronic Inc
- Tab.4, CRT-D produced and commercialized in Italy by Sorin Group
- Tab.5, CRT-D produced and commercialized in Italy by St Jude Medical

4.2 Results of literature review

Our searches identified 1116 potentially interesting titles and after a first screening and de-duplication, 191 records were identified as potentially relevant. After reading the abstract 42 were assessed as potentially contributing requiring knowledge and 149 were excluded (See Figure 4.1 for the flow of studies in the review, table 4.1 for summary of reasons of exclusion and Appendix 3 for list of excluded studies with reasons for exclusion by study).

Figure 4.1: Flow-chart of the studies.

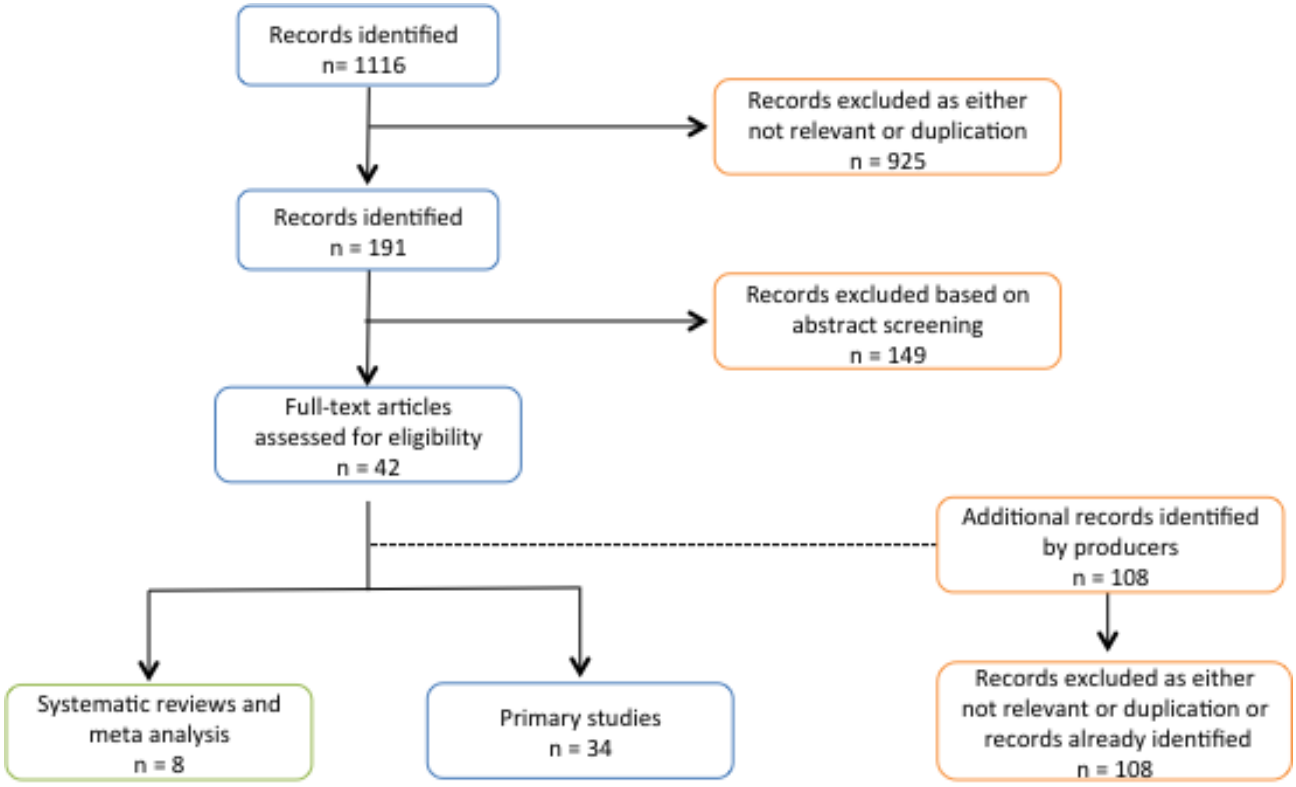


Table 4.1: Summary of the excluded studies with reason for exclusion.

Reason of exclusion	Number of studies excluded
Prognostic study	49
Non comparative study	38
Comparators do not fit inclusion criteria	22
Retrospective study	18
No data reported	7
Secondary pubblication	6
Economic evaluation	4

Missing abstract	2
Imaging study	2
Upgrading study	1
Earlier version of previous study	1
Total excluded	149

Primary studies included

We identified 34 primary comparative studies that fitted our inclusion criteria. See Appendix 4 for the list.

Data from systematic reviews

We identified 8 systematic reviews that fitted our inclusion criteria, see Appendix 5 for the list and Appendix 6 for the Synopsis of included systematic reviews and meta-analysis.

The systematic reviews were assessed for quality using the AMSTAR checklist [http://amstar.ca/Amstar_Checklist.php]

We searched for ongoing trials on clinicaltrials.gov [http://clinicaltrials.gov/ct2/home]. We identified two comparative studies: NCT01790841 and NCT02087189. They were excluded for not complying with our inclusion criteria.

We found that the evidence searches of the 8 reviews spanned the years 2005 – 2012, although the reviews had been published 1-2 years later. The reviews addressed a variety of different questions with different designs (e.g. aggregate data reviews, network meta-analysis and individual patients data analyses). The total number of participants included was 49,497, but events were obviously far fewer.

4.3 Study Results

The oldest review by Abdullah (Abdullah 2005) and colleagues (with 18 trials, 2 cohort studies and 10,853 participants with LVSD) showed an effect on all cause mortality in recipients of CRD and ICD separately and in combination, however ICD recipients were aged 57-67 and belonged to the three lowest NYHA classes. The second oldest review (Lam 2007 with searches up to mid 2006) failed to find clear evidence of dominance of the combined device despite its network design in 8,307 patients with LVD aged 52-67. However it is dominant when compared to optimum pharmacological therapy.

The review by Wells included 12 trials identified by the end of 2010 carried out on 7,538 patients aged 62 to 67 with mild to moderate HF with a QRS interval of more than 120 msecs. The review tested the effect of adding CRT or ICD alone or in combination to optimal pharmacological therapy and found the addition of CRT superior to optimal pharmacological therapy alone and CRT-D dominant compared to CRT alone in terms of deaths avoided. This even in patients assessed NYHA I and II classes with a QRS of 120 msecs but not in the higher classes of NYHA.

Next in the chronological order of searches (September 2010) is the review by Jiang and colleagues (Jiang 2012) who compared the effects of CRT and CRT-D with the combined device.
The evidence base is relatively small with a total of 3,404 participants with LVSD from 7 randomised and non randomised studies. Although the review concluded the combined device was dominant on all-cause mortality but the authors rightly caution about robustness of the relatively small dataset and the relative shortness of the average follow-up (12 months).

The Bertoldi et al review was designed to assess the effect of CRT alone compared with the combination CRT and ICD on overall mortality in 8,284 patients aged 62 -70 with LV disfunction and HF. The data are from 12 studies. The authors report dominance of the combined intervention carried over in classes NYHA III e IV.
Furthemore the review by Chen (Chen et al 2012) who reviewed four trials with a total of 1,655 participants looking at the effects of CRT-D with ICD compared to ICD on its own evaluatingthe quality of life of those who took part. Scores for QoL were significantly higher in the higher NYHA classes, indicating maximum benefit, but no significant effect was reported in NYHA classes I and II.
The individual patient data meta-analysis by Cleland and colleagues does not have a search date, as the date were provided by the funder of the study (Medtronic Inc) from Medtronic studies published in the period 2002-2010 comparing defibrillator with pacemaker. The aim was prognostic: to identify reliable predictors of response in the 3,872 participants with a median age of 66. The QRS duration was identified as a powerful predictor of response in terms of all cause mortality and morbidity..

The logical thread of most of the reviews is the same as progressively more data become available from more trials, the uncertainty and seemingly contradictory findings are more likely to be resolved.

This brief description of the included studies shows the apparent abundant evidence at our disposal and the very complicated nature of the topic. Other than last and most recent and powerful systematic review and meta-analysis, in the line up is that by Chen et al (Chen et al 2013). This includes data from 5,674 participants in 8 randomised controlled trials. The rationale for carrying out yet another review is that despite the development of drug therapy, prognosis of patients with HF has not improved much. Those more likely to benefit from CRT-D insertion are those with mild to moderate HF. Evidence shows that ICDs reduce mortality in these failure patients due to the reduction of sudden death by ventricular fibrillation, but this however does not reduce mortality or rehospitalization due to episodes of pump failure, as it has no impact on ventricular function. Instead, CRT-P associated with optimal drug therapy has been shown to significantly improve outcomes linked to improve ventricular function in HF patients in whom cardiac contraction is not synchronous (see below). Thus, there are logical reasons for the hypothesis that the association CRT + ICD, by concomitantly acting on both improvemt of cardiac function and on prevention of arrhythmic death would significantly improve the prognosis of HF patients (MADIT investigators 2006). Although earlier studies designed to test this hypothesis have failed due to the confounding effects of drug therapy, population and length of follow up of patients, more recently the RAFT study showed a significant reduction of HF hospitalization, mortality, and morbidity in long-term follow-up for CRT+ICD. However, because these results could be observed only in patients with the longest prognosis, this already introduces an addictional bias. To overcome these limitations, the study of Chen considered the eight major studies (with 50 or more participants) comparing CRT-D versus ICD and investigated these series through analysis conducted for subgroups according to NYHA class, duration of follow-up, and design of the study [Chen 2013]. Following this approach, the study by Chen et al shows a significant superiority of CRT-D on ICD in reducing hospitalizations for HF and improvement in functional class in all subgroups. The same subgroup analysis shows a benefit on survival in all mentioned subgroups, and a more evident effect in the longer follow up. However, subgroups of patients with bundle branch block, near-normal QRS, and atrial fibrillation were not analyzed in this study for lack of data.

The recent study by Siphai shows efficacacy of CRT-D in bundle branch block but not in the other conduction disturbances [Siphai 2012]. Stavrakis reports greater effectiveness of CRT-D in patients with QRS>= 150 [Stavrakis 2012]. At the moment there is no clear evidence about the effectiveness of CRT-D in patients with AF. The MADIT-CRT and RAFT studies show a higher incidence of procedural complications such as pneumothorax, infection-related devices, pocket hematoma, catheter problems in the CRT-D group than in the ICD. Chen et al, in the

aforementioned study, noted the significant increase in the dislocation of catheters and dissection of the coranary sinus. Although these complications have not been fatal, they have however increased the duration of hospitalization and then decreased the quality of life (see also Harms chapter). As these results were extrapolated to patient groups with lower average age than that which occurs in normal clinical practice, the higher incidence of procedural complications should be well considered in patients of advanced age before deciding in favour of CRT-D.

Having established that CRT is a very effective therapy in the majority (but not all) patients with cardiac asynchrony, an important question remains: which is the most effective form of CRT in such patients? Is CRT-P alone as effective as combined CRT+ICD (i.e. CRT-D)? Unfortunately, only a few, small, trials have addressed this issue, with the possible exception of the COMPANION trial [Bristow 2004], which randomized 1520 HF patients with NYHA class III and IV to optimal medical therapy (OPT - diuretics, angiotensin-converting–enzyme inhibitors, beta-blockers, and spironolactone) alone, or in combination with CRT-P or CRT-D. Patients were included with HF due to either ischemic or nonischemic cardiomyopathies and needed to have a QRS interval of at least 120 msec. As compared with optimal pharmacologic therapy alone, CRT-P decreased the risk of the primary end point (hazard ratio, 0.81; P=0.014), to the same extent as did CRT-D (hazard ratio, 0.80; P=0.01). The risk of the combined end point of death or hospitalization for HF was reduced by 34 percent in the CRT-P group (P<0.002) and by 40 percent in the CRT-D group (P<0.001 for the comparison with the pharmacologic-therapy group). CRT-P reduced the risk of the secondary end point of death from any cause by 24 percent (P=0.059) and CRT-D reduced the risk by 36 percent (P=0.003).

4.4 Safety

Safety considered as losses of capture, cardiac device infections and frequency of adverse events between CRT-D and CRT-P recipients is a crucial topic. The MADIT-CRT and RAFT studies [Noyes 2013, Birnie 2013] show a higher incidence of procedural complications such as pneumothorax, device-related infections, pocket hematoma, and catheteric problems in the CRT-D group than in the ICD. Chen et al note the significant increase in the dislocation of catheters and dissection of the coranary sinus. The European CRT registry reported a 9% rate of peri-procedural complications in CRT-D vs 12% in CRT-P recipients (ns) [Dickstein 2013]. In contrast, Schuchert et al [Schuchert 2013] observed a three-fold higher rate of lead-related complications in CRT-D than in CRT-P recipients (almost entirely due to loss of electrical capture). In this study, variable technical skills among operators would not explain this observation, as both systems were implanted by the same physicians at each centre. Furthermore, the sensing function of ICD leads must be flawless, which may explain the earlier and more frequent detection of adverse events

than in CRT-P recipients. Despite the similarity of the atrial and LV stimulation leads in both study groups, authors observed a higher rate of lead-related complications in the CRT-D than in the CRT-P group. The overall incidence of device-related infections is increasing [Cabell 2004]. Klug and Romeyer-Bouchrad in their respective studies found that implantation of dual- and triple-chamber devices was associated with a two-fold higher risk of infection than implantation of single chamber devices [Klug 2007] [Romeyer-Bouchard 2010]. Johansen in a direct comparison between CRT-D and CRT-P, observed that CRT-P was associated with a nearly 5.5-fold higher risk of infection [Johansen 2011]. In contrast, Schuchert et al observed no difference in the incidence of infections between the two patient groups, suggesting that the more complex CRT-D systems are not associated with a greater risk of infections.

5. Economic analysis

5.1 Methods

The economic analysis comprised mainly a systematic review of economic evidence and a context analysis in terms of activities volume and contract prices.

Economic evaluations comparing directly the cardiac resynchronization therapy (CRT) individually either with the CRT-D (CRT plus ICD) or implantable cardioverter defibrillator (ICD) alone were included in our systematic review. We considered economic studies - cost-effectiveness, cost-utility, cost-benefit and cost analyses - published in the last 10 years, in English or Italian languages.

We searched the following main electronic databases: Medline, EMBASE, Cochrane Library, EcoLIT and Health Economic Evaluations Databases (HEED). Searches were conducted from 11st to 13rd March 2014 to identify all economic studies published from January 2004 to date. Search strategies are reported in details in Appendix 7. The results of the search strategy are listed in the Table 5.1.

Table 5.1: Databases searched and results

Database	Research date	Results
MedLine via OVID	11 march 2014	23
Embase	12 march 2014	289
CL EED	13 march 2014	27

Two reviewers screened titles and abstracts of records identified, resulting from the electronic databases' search, for potential eligibility independently. The full text of relevant papers were then retrieved and two reviewers formally assessed them, independently, with respect to their potential relevance according to the inclusion criteria. If it was unclear from an abstract or title whether a study was relevant, the full paper of the study was obtained for further information. Disagreements were resolved by discussion and when agreement was not reached, a third reviewer was consulted.

Data extraction was planned to be performed, independently and in duplicate, by two reviewers (MC and MRP). We intended to extract economic data related to CRT-D device and its comparators (CRT-P and ICD) with an ad hoc form. The form template is reported in Appendix 8. The methodological quality of economic studies was appraised using the CHEERS statement [Husereau D, 2013]. The context analysis was performed collecting data on volume of used devices and related contract prices from the national database of Italian Ministry of Health. Context data were referred to 2012 and 2013 years (see paragraph 3.3).

5.2 Results

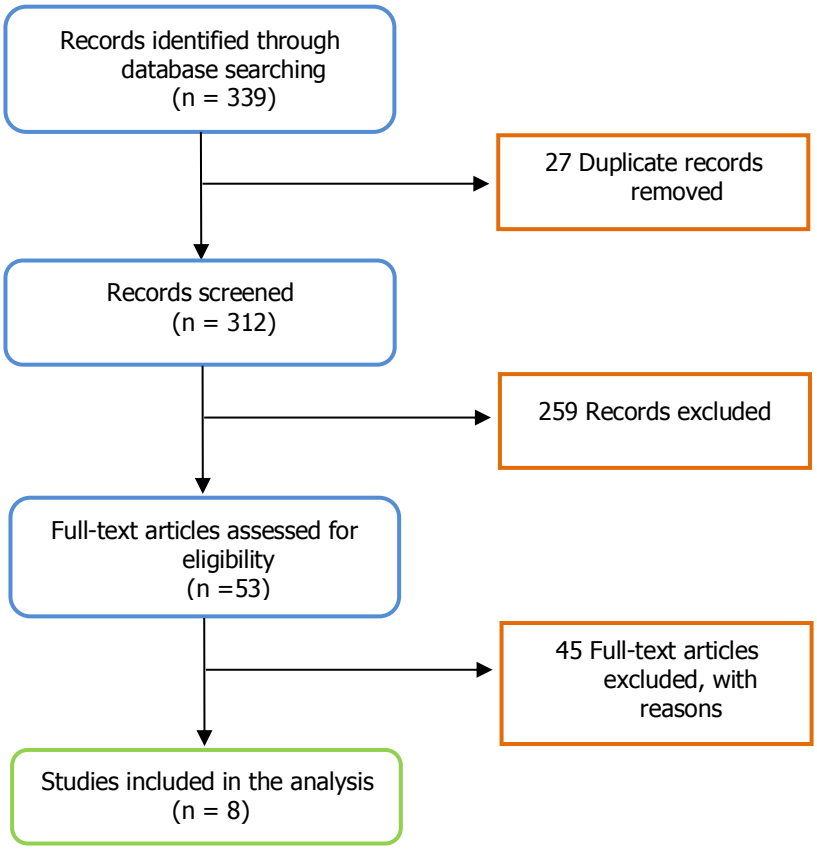
5.2.1 Systematic review

Through electronic searches we identified 339 titles/abstracts and selected 11 as relevant to our systematic review.

Twenty-seven records out of 339 were duplicates. Based on the relevance of titles and abstracts, 53 articles underwent full-text screening by two authors (MC and MRP); the disagreement was solved by discussion. After reading the full text of the studies, 45 studies were excluded because they did not meet inclusion criteria. The bibliographic references of excluded studies were listed, alongside reasons for their exclusion, in Appendix 9. Regarding 7 studies only abstract from conference/congress could be retrieved; first authors of the abstract were contacted by mail with the request to receive the full paper for the inclusion in our systematic review.

Eight articles met our eligibility criteria (Fig 5.1). The bibliographic references of the studies included in this systematic review were reported at Appendix 10.

Figure 5.1: Flow-chart of economic evidence



5.2.2 Economic studies analysis

Data were extracted from the included economic studies and reported in tables. Table 5.2 showed the main study features of each economic evaluation. Five of the included economic analyses were based on decision model, two used trial data [MADIT-CRT and CART-HF] and one developed a model for cost analysis.

Five studies performed a cost-effectiveness and a cost-utility analysis, except the study by Fox et al [Fox 2007] which included only cost-utility analysis, and two studies performed a cost analysis. Among the five model based studies, three considered lifetime horizon and the last two carried out an economic evaluation over seven and twenty years.

Regarding the analysis' perspective, 4 of 8 studies were carried out from national health system perspective, 3 from third party payer and last one from the hospital.

Three studies compared the cost-effectiveness of CRT-D with ICD; 4 studies compared CRT-P vs CRT-D while one performed both comparisons: CRT-P vs CRT-D and CRT-D vs ICD.

Three of the included studies were funded by devices' manufacturer; while one study did not receive specific grant from any funding agency in the public, commercial or not for profit sectors and two did not declare this information; the last two received a public funding, one from UK HTA Programme and one from Brazilian National institute of Science and Technology for HTA (IATS).

Table 5.2: Economic analyses included in the Systematic review

Study	Objective	Study type	Analysis type	Country and price year	Perspective	Time horizon	Comparison	Funding
Noyes et al, 2013	To evaluate 4-year cost-effectiveness of CRT-ICD compared to ICD alone using MADIT-CRT data	Trial based (MADIT CRT)	CEA and CUA	USA, 2008	Third party payer	4 years	CRT-D vs ICD	Boston Scientific
Neyt et al, 2011	To assess the cost-effectiveness of cardiac resynchronization therapy (CRT) both with CRT-P and with CRT-D in patients with NYHA functional class III/IV	Decision model	CEA and CUA	Belgium, NR	Third party payer	Lifetime	CRT-P+OPT vs OPT CRT-D+OPT vs OPT CRT-D+OPT vs CRT-P+OPT	None
Yao et al, 2007	To evaluate the long term ICER of CRT-P and MT compared to MT alone; in addition we evaluated the cost-effectiveness of CRT-ICD + MT vs MT and the relative cost-effectiveness of CRT-P and CRT-D	Decision model	CEA and CUA	UK, NR	UK NHS	Lifetime	CRT-P+MT vs MT CRT-D+MT vs MT CRT-D+MT vs CRT-P+MT	Medtronic Inc.
Fox et al, 2007	To assess the clinical effectiveness and cost-effectiveness of CRT for people with HF and evidence of dyssynchrony by comparing CRT-P and CRT-D devices each with OPT and with each other	Decision model	CUA	UK, 2005	UK NHS	Lifetime	CRT-P vs OPT CRT-D vs OPT CRT-D vs CRT-P	HTA Programme on behalf of NICE
Feldman et al,2005	To estimate the cost effectiveness of CRT-P and CRT-D for patients living with HF modeling the COMPANION trial data	Decision model (Trial based COMPANION)	CEA and CUA	USA, 2004	Third party payer (Medicare and Medicaid services)	7 years	CRT-D vs CRT-P vs OPT	NR
Bentkover et al, 2007	To evaluate the economic outcomes associated with ICD+CRT therapy versus ICD treatment alone, by applying representative costs for the provinces of Quebec and Ontario to medial resource and patient diary data collected from the CART-HF study.	Trial based (CART-HF)	CA	Canada (Quebec and Ontario)	NHS	3-6 months	CRT-D vs ICD	Guidant Inc Canada

Bertoldi et al, 2013	To perform a cost-effectiveness study of CRT in HF patients in Brazil, using a Markov process decision-analytic model to address the incremental cost-effectiveness ratio of adding CRT to the standard of care in HF patients.	Decision-analytic model (Markov model)	CEA and CUA	Brazil, 2010	NHS Brazilian	20 years	CRT-P vs OMT CRT-D vs OMT CRT-D vs ICD CRT-D vs CRT-P	National Institute of Science and Technology for Health Technology Assessment (IATS) Brazil
Boriani et al, 2013	To determine the long-term costs of extending device longevity in four patients populations requiring a single-chamber implantable cardioverter-defibrillator (ICD) or requiring cardiac resynchronization therapy with defibrillation (CRT-D) device over a 15-year time window.	Model	CA	Europe, 2012	Hospital	15 years	ICD vs CRT-D	NR

Legend
CA: cost-analysis
CEA: cost-effectiveness analysis
CUA: cost-utility analysis
CRT-D: cardiac resynchronization therapy with implantable cardioverter defibrillator
CRT-P: cardiac resynchronization therapy
HF: heart failure
ICD: implantable cardioverter defibrillator
MT: medical therapy
NR: not reported
NHS: national health system
NYHA: New York heart association
OPT: optimal pharmacological therapy

5.2.3 Study description

Noyes et al 2013 estimated incremental cost effectiveness ratio (ICER) measuring effectiveness results and the total costs of CRT-D compared to ICD alone within the US subgroup of the MADIT-CRT trial. Patients of either sex and at least 21 years of age, enrolled in the RCT, were in NYHA class I or II and they had a left ventricular ejection fraction of 30% or less, and prolonged intra-ventricular conduction with a QRS duration of 130 milliseconds or more. Sub group analyses were performed for patients with and without left bundle branch block (LBBB) since the benefits of CRT-D therapy were observed to be most relevant in patients with LBBB conduction disturbance. MADIT CRT trial primary clinical endpoint was a non-fatal HF event or death from any cause, whichever came first; hence to evaluate either the survival and the survival free of HF events 2 versions of life-years (LY) and QALY were measured: overall (unrestricted) LY and QALY and HF free LY and QALY. Utility weights were estimated using the EQ-5D questionnaire[2]. Healthcare resources utilization data were collected including hospitalization for implantation procedure, number of hospitalization during follow up, emergency room and physician visits, outpatients surgeries and diagnostic tests and procedures. The related costs were estimated on the basis of in-trial data and administrative databases; consistently to third payer perspective only direct costs were estimated. Costs for device plus implantation accounted for 70% or more of the total costs. Benefits and costs were discounted at a 3% rate. Estimates of results were reported in the Table 5.3 Economic results [Noyes et al, 2013].

Table 5.3: Economic results [Noyes et al, 2013]

	CRT-D	ICD	Economic results	Authors' conclusions	Quality appraisal
All patients				This study provides evidence that the cost of improving life expectancy with CRT in high-risk cardiac patients with LBBB is reasonable by the societal standards and is worth being covered by public health insurance plans, but with no real evidence of value in non-LBBB patients. Within the LBBB subgroup, cost-effectiveness was especially strong in females and in the age group 65–74 years—well under $25,000/QALY in each subgroup studied except the oldest age group, 75+ years of age, which is well above the currently utilized threshold of $50,000/QALY	13 Yes 2 No 7 Partially 5 NA
Cost ($)	62,600	57,050	ICER:		
UnLY	3.61	3.54	$80,910/unLY		
UnQALY	3.16	3.07	$58,330/unQALY		
HF-free-LY	3.29	3.02	$21,100/HF-freeLY		
HF-free-QALY	2.89	2.65	$22,920/ HF-free-QALY		
LBBB patients					
Cost ($)	60,090	56,730	ICER:		
UnLY	3.66	3.51	$23,330/unLY		
UnQALY	3.25	3.05	$16,640/unQALY		
HF-free-LY	3.41	2.94	$7,180/HF-freeLY		
HF-free-QALY	3.04	2.58	$7,320/ HF-free-QALY		
Non-LBBB patients					
Cost ($)	68,100	57,600	CRT-D DOMINATED		
UnLY	3.50	3.62			
UnQALY	2.97	3.13			
HF-free-LY	3.02	3.22			
HF-free-QALY	2.57	2.82			

Legend
UnLY: unrestricted life years gained
UnQALY: unrestricted quality adjusted life years gained

[2] EQ-5D is a prescored health utility assessment system defined over 5 domains of health: mobility, self-care, usual activity, pain and emotional health.

HF-free-LY: heart failure free life years gained
HF-free-QALY: heart failure free quality adjusted life years gained
LBBB: left bundle branch block
CRT-D: cardiac resynchronization therapy with implantable cardioverter defibrillator
ICD: implantable cardioverter defibrillator
ICER: incremental cost-effectiveness ratio
NA: not applicable

ICER over 4 years in all patients was $58.330/unrestricted QALY and $22,920/HF free QALY; within the LBBB subgroup the ICER was even more positive by measuring $16,640 per unrestricted QALY and $7,320 per HF free QALY. As regards sex and age groups, analysed within LBBB group, ICERs were less than $25,000 for each gender and for age groups <75 years. CRT-D was dominated by ICD for non-LBBB patients, hence ICERs were not calculated for this group.

The probability of CRT-D to be cost-effective compared with ICD alone varying the willingness to pay (WTP) threshold (CEAC) showed that the chance that CRT-D is cost-effective is about 40% at a WTP of $50.000/QALY and it increases to almost 80% for a WTP of $100,000.

LBBB subgroup analysis highlighted that differences in health outcomes between the two devices increased significantly in each year for HF free LY/QALYs and for unrestricted outcome (except the first year). Over a longer time horizon the ongoing reduction in HF events will probably be related with more reduction in mortality determining a likely more favourable ICER.

Missing or incomplete data represent the major limit of this economic evaluation; besides the observed variation in the way CRT-ICD and ICD were implanted, reimbursed and monitored among the study centres limit the transferability of the above described economic results to other contexts.

Neyt et al (2011) developed a Markov simulation model over a lifetime horizon to assess the cost effectiveness of cardiac resynchronization therapy either with CRT-P and CRT-D. A cohort of 1,000 CRT eligible patients with moderate to severe HF (NYHA class III-IV), ejection fraction ≤35% and a wide QRS complex was considered. In the base case scenario the cohort corresponded to the patients of COMPANION trial. According to the model patients could receive OPT (optimal pharmacological therapy), CRT-P and CRT-D treatment being at risk of hospitalization due to HF and all-cause mortality in each monthly cycle. Patients receiving CRT-P/D were also at risk of procedure related mortality. In addition patients surviving OPT could upgrade to ICD while patients undergone CRT-P therapy could upgrade to CRT-D. Rates of transition among the different health states were derived from literature. The treatment effects measured through all-cause mortality and hospitalization rates were drawn from COMPANION trial[3] and integrated by study assumptions. Specifically monthly probability of death was assumed to be time dependent, hence the absolute monthly increase in mortality of the normal age and gender adjusted Belgian population was added; hospitalization rates were assumed to be constant over the full lifetime

horizon. The procedure related mortality was drawn from a systematic review of RCT by Fox et al integrated by study assumption; as regards the upgrade and crossover probabilities estimates from the model of Bond et al and Fox et al were used as input of the model. LYs and QALYs gained were calculated to express the lifelong effectiveness results. Utility values were based on literature sources.

The analysis included direct healthcare costs according to the perspective adopted (third payer). Cost items comprised first implantation of devices, replacement, hospitalization, follow up medication (monthly cost), follow up visits and tests and costs of crossover and updated implantation. Costs data were taken from Belgian data (e.g. Belgian technical cell, Belgian centre for pharmacotherapeutic information, etc.), experts opinion and, in some cases, inferred. To capture parameter uncertainty, input variables were modelled as probabilistic values in relation to the characteristics of each variable.

Both benefits and costs were discounted at a rate of 3% and 1.5% respectively on the basis of national pharmacoeconomic guidelines. Economic results stemming from the economic evaluation were reported in the Table 5.4 Economic results [Neyt et al, 2011].

Table 5.4: Economic results [Neyt et al, 2011]

	CRT-D vs OPT	CRT-D vs OPT	CRT-D vs CRT-P	Authors' conclusions	Quality appraisal
Incremental C (€) Incremental LYG Incremental QALY	14,745 1.15 1.31	45,624 1.85 1.86	30,879 0.70 0.55	Based on efficiency arguments, CRT-P can be recommended for NYHA class III/IV patients if there is a WTP more than €11,000/QALY. Current evidence is insufficient to show the superiority of CRT-D over CRT-P. With a threefold-higher device cost, CRT-D's cost-effectiveness is questionable. Further clinical research should focus on the added value of CRT-D over CRT-P.	16 Yes 2 No 6 Partially 3 NA
ICER:	12,834/LYG 11,219/QALY	26,638/LYG 25,639/QALY	44,080/LYG 56,615/QALY		

Legend
C: costs
LYG: life years gained
QALY: quality adjusted life years gained
ICER: incremental cost-effectiveness ratio
CRT-D: cardiac resynchronization therapy with implantable cardioverter defibrillator
OPT: optimal pharmacological therapy
CRT-P: cardiac resynchronization therapy
WTP: willingness to pay
NA: not applicable

Based on the indirect comparison, CRT-D treatment provided an incremental life expectancy of 0.70 LYG compared to CRT-P with a cost of €30,879 and, taking into account the quality of life, the incremental benefit was 0.55 QALY. An ICER of 57,000/QALY was estimated in the base case

[3] COMPANION trial compared the CRT-P as well as CRT-D versus OPT allowing an indirect comparison between CRT-P and CRT-D to be made.

scenario, suggesting that the incremental benefit associated to CRT-D seems to be too marginal to make this treatment more cost-effective than CRT-P. The cost-effectiveness acceptability curves showed that at a WTP for a QALY >€11,000 CRT-P seems to be the best treatment option; the WTP should be more than €56,000/QALY for CRT-D to have the probability of 50% to be cost effective respect to CRT-P. Scenario analyses highlighted that the difference in cost-effectiveness between CRT-D and CRT-P is mainly due to higher device price whereas the incremental benefit was marginal.

The main limitations of this economic analysis, according to the authors, are the short terms follow up of trials necessitating extrapolation assumptions; external validity of trial results that hinder their generalizability and the lack of using generic utility instruments to measure quality of life.

Yao et al (2007) developed Markov model to evaluate the long term incremental cost-effectiveness of both CRT-P and CRT-D plus medical therapy (MT) compared to MT alone; in addition the relative cost-effectiveness of CRT-P and CRT-ICD was evaluated. The study focused on patients affected with heart disease who were in NYHA class III/IV, despite receiving standard medical therapy, with left ejection fraction <35%, a left ventricular end-diastolic dimension of ≥30mm and a QRS interval of >120ms on the electrocardiogram. The model was comprised of a short term model representing costs/benefits of device implantation and a long term (lifelong term) model capturing costs/effects of device after successful implantation. During each phase patients could move between NYHA classes on the basis of different CRT treatment; experiencing sudden death and unplanned hospitalization (with or without further procedure) depending on NYHA class, treatment (CRT±ICD and MT) and time. The majority of effectiveness data and rates, expressed as transition probabilities were taken from CARE-HF trial, whereas the reduction of sudden death due to ICD was based on CARE-HF and COMPANION trials' results. Lifelong effectiveness outcomes were estimated in terms of life years gained and QALY. Utility scores associated to each NYHA class were estimated from quality of life values from CARE-HF trial assessed using EQ-5D questionnaire. Costs analysis was undertaken form UK NHS perspective including cost of devices, of implantation procedure, of hospitalization (both during implantation and unplanned), of medical care and drug costs. Cost data were drawn from CARE–HF trial and integrated by assumptions. Costs and benefits were discounted at a rate of 3.5%. Table 5.5 shows the economic results for the base case[4].

[4] In the base case patients started at a fixed age of 65 years, the length of follow up was the lifetime and the battery life was assumed to be 6 years for CRT-P and 7 for CRT-D (manufacturer information).

Table 5.5: Economic results [Yao et al, 2007]

	MT	(CRT-P) + MT	(CRT-D) + MT	Authors' conclusions	Quality appraisal
Cost (€)	39,060	53,996	87,350	Long term treatment with CRT-P+MT appears cost-effective compared with MT alone. CRT-D+MT was also cost-effective, although to a lesser extent, compared with CRT-P+MT at a willingness to pay of €44,100 (£30,000) per QALY, in the treatment of patients with moderate to severe HF characterized by dyssynchrony, except in those who have a poor life expectancy.	16 Yes 1 No 8 Partially 2 NA
LYs	6.10	8.23	9.16		
QALYs	4.08	6.06	6.75		
ICER/LYs (€): CRT-P+MT vs MT CRT-D+MT vs MT CRT-D+MT vs CRT-P+MT		7,011 35,864 15,780			
ICER/QALYs (€): CRT-P+MT vs MT CRT-D+MT vs MT CRT-D+MT vs CRT-P+MT		7,538 47,909 18,017			

Legend
LYs: life years gained
QALYs: quality adjusted life years gained
ICER: incremental cost-effectiveness ratio
MT: medical therapy
CRT-P: cardiac resynchronization therapy
CRT-D: cardiac resynchronization therapy with implantable cardioverter defibrillator
WTP: willingness to pay
NA: not applicable

The ICER of (CRT-D)+MT compared to (CRT-P)+MT was €47,909/QALY and €35,864/LY gained. On the basis of a WTP of €44,100 (£30,000/QALY) (CRT-D)+MT had only 40% to be cost-effective compared to (CRT-P)+MT. The base case showed that long term treatment with CRT-D is not cost-effective compared to CRT-P at a WTP threshold of €44,100. However sensitivity analysis showed that age of patients affects significantly the ICER; in younger patients (aged 55 and 60 years) the ICER decreases under the threshold and CRT-D becomes cost-effective due to longer potential period when patient is at risk of sudden death. The cost-effectiveness results were sensitive to the length of follow up since it represents the patient's exposure to the risk of sudden death as well as to device battery life. In fact increasing CRT-D battery life from 6 to 8 years the incremental cost for QALY fall to €43,506 under the WTP threshold. The analysis has some limitations as stated by the authors, specifically it is based on simulation rather than direct observation and the lack of evidence comparing CRT-D directly with CRT-P.

Fox et al (2007) assessed the clinical effectiveness and cost-effectiveness of CRT for people with HF and evidence of dyssynchrony by comparing CRT-P and CRT-D devices each with OPT and with each other. Besides a Markov model was developed to assess the lifetime cost-effectiveness of each device with the others. A hypothetical cohort of 1,000 people of different starting ages (30-90 years) with HF due to left ventricular systolic dysfunction and QRS duration >120ms and eligible to CRT were modelled for their lifetime. Patients could receive either a CRT-P or CRT-D device or to remain on OPT alone. A cycle length of 4 weeks was used and 3 sub models were

developed for each of the three devices options (CRT-P, CRT-D and ICD) in addition to OPT. Patients with CRT could experience perioperative complications, adverse events (lead displacement or infection); hospitalization (due to HF); arrhythmic event; device replacement; no events. Depending on the events that occurred patients could die (all causes mortality is considered as well), be stable, undergo a heart transplantation, upgrade either to CRT-D or ICD (CRT-P patients), regress to OPT. People on OPT could experience hospitalization (due to HF), arrhythmic event or no events; accordingly they can potentially die, undergo an heart transplantation, upgrade only to an ICD device, be stable. The transition probabilities among the health states were drawn from literature (SR performed by the same author and included in the report and other clinical trials) or, when no data were available, from experts' opinions. Lifetime effectiveness results in terms of QALYs were derived from the model.

Direct medical costs were collected including implantation of devices, managing device-related problems (lead displacement/failure, lead infection and battery replacement/failure), non-elective hospitalization and outpatient follow up visits. Cost data were drawn from UK NHS database integrated by model assumptions. Costs and benefits were measured in pounds and discounted at a rate of 3.5%. Cost-utility analysis results are shown in Table 5.6: Economic results [Fox et al, 2007].

Table 5.6: Economic results [Fox et al, 2007]

	CRT-P	CRT-D	Authors' conclusions	Quality appraisal
Cost (£)	20,997	32,687	When measured using a lifetime time horizon and compared with OPT, the CRT devices (CRT-P ICER £16,735, CRT-D £23,650) are estimated to be cost-effective at a WTP of £30,000/QALY, CRT-P is cost-effective at a WTP threshold of £20,000/QALY. When the cost-effectiveness of all three treatment strategies are compared with each other, the estimated net benefit from CRT-D is less than with the other two strategies, until the WTP threshold exceeds £40,160/QALY.	18 Yes 1 No 3 Partially 3 NA
QALYs	3.08	4.09		
ICER/QALYs (£)	40,160			

Legend
QALYs: quality adjusted life years gained
ICER: incremental cost-effectiveness ratio
CRT-P: cardiac resynchronization therapy
CRT-D: cardiac resynchronization therapy with implantable cardioverter defibrillator
WTP: willingness to pay
NA: not applicable

In the base case for a mixed age cohort CRT-D device provided an incremental 0.29 QALY compared with CRT-P. Varying the start age incremental QALYs increased with lowering the age. Compared with OPT the Markov model base case analysis (over a lifetime) estimated that CRT-P conferred an additional 0.70 QALYs for an additional ICER of £11,635/QALY gained for a mixed age cohort. CRT-D versus CRT-P conferred an

additional 0.29 QALYs for an additional £11,689 per person, giving an ICER of £40,160/QALY for a mixed age cohort.

Feldman et al (2005) (Table 5.7) created a model to better understand the relationship of the clinical benefits and health care costs related to CRT, in patients with NYHA functional class III-IV. They replicated, with the model, the treatment observed in the COMPANION trial to adjust the different enrollment and duration of follow-up, aimed to assign costs to resource utilization as documented in the trial and to extend the period of observation.

Survival, costs and quality of life were projected based on parameters derived from trial data. The base case follow-up period was seven years. To calculate incremental cost per life-year gained and cost per quality-adjusted life year (QALY) gained for CRT-D and CRT-P relative to OPT the model included cost of treatment, survival and preference-weighted survival. The study did not directly compare CRT-D with CRT-P.

They resulted that cumulative costs for the average patient were higher in the CRT-D and CRT-P that for the OPT; regarding the survival, modeled, 40% of patients in the CRT-D and 33% of patients in the CRT-P were alive, compared with 23% of patients in the OPT arm; after applying preference weights QALYs were 3.15 for CRT-D, 3.01 for CRT-P and 2.30 for OPT. Cost-effectiveness analysis show that CRT is economically viable and can be achieved at a reasonable cost.

Table 5.7: Synthesis of Economic results [Feldman et al, 2005]

	CRT-D	CRT-P	OPT	Authors' conclusions	Quality appraisal
Cumulative cost	$ 82,200	$ 59,900	$ 46,000	The cost-effectiveness analysis indicates that the clinical benefits of CRT are economically viable and can be achieved at a reasonable cost.	15 Yes 7 No 5 Partially
Cumulative average years survival	4.51	4.19	3.64		
Cumulative quality-adjusted survival	3.42	3.26	2.48		
Incremental cost per LY (CRT-D vs OPT and CRT-P vs OPT)	$46,700	$28,100	-		
Incremental cost per QALY (CRT-D vs OPT and CRT-P vs OPT)	$43,000	$19,600	-		

Legend
LY: life year gained
QALY: quality adjusted life year gained
ICER: incremental cost-effectiveness ratio
CRT-P: cardiac resynchronization therapy
CRT-D: cardiac resynchronization therapy with implantable cardioverter defibrillator
OPT: optimal pharmacological therapy

Bentkover et al analyzed the economic outcome associated with ICD+CRT therapy vs only ICD treatment, applying representative costs for the provinces of Quebec and Ontario, in patients in class NYHA II-IV with EF <35% and QRS >120 msec. The medial resource and patient diary data were collected from the CART-HF randomized controlled trial, collected during 6 months of follow-up.

They collected patient data from case report forms to record hospitalizations, pharmacological therapies, physician visits, as well as all resources utilized in the diagnosis and treatment of adverse events during the follow-up. Patient diary data were used to evaluate the productivity losses associated with medical treatment. The economic analysis contained five cost subcategories: pharmacological therapy, hospitalization, physician visits (as direct costs), productivity losses, considered indirect costs (identified from

a survey of Canadian wages in each province and from individual patient information), and adverse event. They conducted a sensitivity analysis to determine the break-even prices. Economic analyses for both the provinces of Ontario and Quebec found that the post-procedural costs associated with CRT-D were less than those for patients receiving ICD treatment alone. The treatment of HF patients with CRT-D and ICD may offer post-procedural cost savings compared to treatment with ICD alone. The results are reported in the Tables 5.8, 5.9 and 5.10.

Table 5.8: Economic model per-patient costs of Ontario

Cost per patient	CRT-D	ICD
Pharmacological therapy	C$636	C$866
Physician visits	C$54	C$25
Hospitalizations	C$4,631	C$6,511
Adverse events	C$143	C$143
Productivity losses	C$0	C$3
Total cos/patient	C$5,463	C$7,548

Table 5.9: Economic model per-patient costs of Quebec

Cost per patient	CRT-D	ICD
Pharmacological therapy	C$492	C$685
Physician visits	C$41	C$19
Hospitalizations	C$5,140	C$7,381
Adverse events	C$118	C$124
Productivity losses	C$0	C$3
Total cos/patient	C$5,791	C$8,211

Table 5.10: Synthesis of Economic results [Bentkover et al, 2007]

Comparison	Authors' conclusion	Quality Appraisal
CRT-D vs ICD	Economic analyses for both the provinces of Ontario and Quebec, found that the post-procedural costs associated with biventricular pacing were less than those for patients receiving ICD treatment alone.	8 No 17 Yes 2 Partially

Legend
CRT-D: cardiac resynchronization therapy with implantable cardioverter defibrillator
ICD: implantable cardioverter defibrillator

Bertoldi et al, 2013 performed a cost-effectiveness analysis of CRT in HF patients in Brazil, using a Markov process decision-analytic model, to address the incremental cost-effectiveness ratio of adding CRT to the standard of care in HF patients in class NYHA III-IV with EF < 35% and QRS >120 msec.

They built a model with two components: the first was a simple decision tree representing the costs and consequences of initial device implantation, in a short time, while the second was a state-transition Markov model representing the long term follow up of the hypothetical cohort until the 20 time horizon year. The model assessed 4 different scenarios in which the optimal medical therapy (OMT) was considered as base case: CRT-P vs OMT, ICD vs OMT, CRT-D vs ICD, CRT-D vs CRT-P. They used to collect data of effectiveness of ICD a meta-analysis [Nanthakumar et al]; for the CRT they conducted a systematic review of published clinical trial [twelve studies]. Regarding the effectiveness they considered also complications of device implantation and maintenance. About the utilities and costs they considered the estimate of one study [Gohler et al] that used the EuroQol 5D. They considered the following annual costs of OMT: physician visits, diagnostic tests, hospital admissions and government supplied medication from a Brazilian cohort. Medication cost were based on the Brazilian Ministry of Health database while the costs of consultations, diagnostic tests, procedures, hospital admission, device implantation and complications were obtained from the public healthcare systems codebooks.

The incremental cost-effectiveness ratio of CRT-P over conventional therapy was Int$29,441 per LY gained, and Int$ 15,723 per QALY gained. For the combination device, CRT-D, ICER were Int$ 43,054/LY and Int$36,940 /QALY over ICD alone, and Int$ 62,437/LY and Int$ 84,345/QALY over CRT-P. The one-sensitive analysis showed that the model was most sensitive to the cost of the devices, their impact of HF mortality, and the battery longevity, with longer battery longevities causing a reduction in the ICER of CRT-D over CRT-P or ICD. The authors considered, for the willingness-to-pay, the threshold suggested by the World Health Organization like Int$31,689; concequentely CRT-D device becomes cost-effective with costs below Int$48,160 and cost saving with costs below Int$33,351.

Table 5.11: Results per life-year gained

Treatment	Cost (Int$)	Incremental cost (Int$)	LYs	Incremental LYs	ICER (per LY gained) (Int$)
OMT	9615	-	5.92	-	-
CRT-P vs OMT	34,615	25,000	6.77	0.85	29,411
ICD vs OMT	60,897	51,282	6.90	0.98	52,328
CRT-D vs ICD	82,692	21,794	7.54	0.64	34,054
CRT-D vs CRT-P	82,692	48,076	7.54	0.77	62,437

Legend
LYs: life years gained
ICER: incremental cost-effectiveness ratio
OMT: optimal medical therapy
CRT-P: cardiac resynchronization therapy
ICD: implantable cardioverter defibrillator
CRT-D: cardiac resynchronization therapy with implantable cardioverter defibrillator
Int$:international dollar

Table 5.12: Results per quality-adjusted life-year gained

Treatment	Cost (Int$)	Incremental cost (Int$)	QALYs	Incremental QALYs	ICER (per QALY gained) (Int$)
OMT	9615	-	4.4	-	-
CRT-P vs OMT	34,615	25,000	5.99	1.59	15,723
ICD vs OMT	60,897	51,282	5.97	1.57	32,663
CRT-D vs ICD	82,692	21,794	6.56	0.59	36,940
CRT-D vs CRT-P	82,692	48,076	6.56	0.57	84,345

Legend
QALYs: quality adjusted life years gained
ICER: incremental cost-effectiveness ratio
OMT: optimal medical therapy
CRT-P: cardiac resynchronization therapy
ICD: implantable cardioverter defibrillator
CRT-D: cardiac resynchronization therapy with implantable cardioverter defibrillator

Table 5.13: Synthesis of Economic results [Bertoldi et al, 2013]

Comparison	Authors' conclusion	Quality Appraisal
CRT-P vs OMT ICD vs OMT CRT-D vs ICD CRT-D vs CRT-P	For patients scheduled to receive CRT-P devices, upgrading to CRT-D is costly, with a resulting ICER well above the suggested WTP threshold; for patients scheduled to receive ICD, the upgrade to CRT-D has an ICER that is only slightly above the improvement of battery longevity could make it an attractive strategy for patients that fulfill indication criteria for both devices.	6 No 19 Yes 2 Partially

Legend
OMT: optimal medical therapy
CRT-P: cardiac resynchronization therapy
ICD: implantable cardioverter defibrillator
CRT-D: cardiac resynchronization therapy with implantable cardioverter defibrillator

Boriani et al, 2013 performed a model-based cost analysis, in 4 different populations with different prognosis, to determine the cost-impact of extending device longevity in different clinical scenarios requiring treatment with ICD or CRT-D devices, because they stated that the cost of device therapy is not only attributable to the cost of the initial implantation but also to the cost of device replacements and associated complications. In their cost-analysis they considered the cost of devices, procedures, follow-up, post-implant management complications, in four different populations, during the different horizon time as well as the device longevity. The modeling study showed that device longevity has an important impact, adopting a long time horizon of 15 years, of device therapy. They concluded that the extending of longevity has an important impact in reducing long-term costs of device therapy reporting a substantial daily savings in favour of devices with extended longevity, in the range of 29-34%, depending on the clinical scenario. If the ICDs and CRT-Ds are considered equal for effectiveness, the device longevity should be considered an important factor of choice because determines a marked reduction in the daily costs.

Table 5.14: Synthesis of Economic results [Boriani et al, 2013]

Comparison	Authors' conclusion	Quality Appraisal
ICD vs CRT-D	Extending device longevity has an important impact in reducing long-term costs of device therapy, with substantial daily savings in favour of devices with extended longevity, in the range of 29-34%, depending on the clinical scenario.	10 No 16 Yes 1 Partially

Legend
ICD: implantable cardioverter defibrillator
CRT-D: cardiac resynchronization therapy with implantable cardioverter defibrillator

5.2.4 Methodological quality appraisal

The methodological quality of included economic studies was appraised through the CHEERS (Consolidated Health Economic Evaluation reporting Standards) checklist developed by ISPOR [Husereau et al, 2013]. The checklist aims at providing detailed guidance on the appropriate reporting of health economic evaluations. It comprises 24 recommendations divided into six main categories: title/abstract [2]; introduction [1]; methods [16]; results [5]; discussion [1] and other [2] [Husereau et al, 2013]. A simplified tool based on CHEERS was developed to assess the quality of the 12 cost-analyses described above. Recommendations judged to be pertinent only to cost-effectiveness, cost-utility or cost-benefit analyses were not applied (e.g. economic model based recommendations). The results of methodological quality appraisal were reported in the tables "Synthesis of Economic results" for each study (Tables 5.3-5.7, 5.10, 5.13-5.14).

As regards cost-effectiveness and cost-utility analyses included, overall quality reaches high level with most of the items (from 20 to 24 on 27) fully or partially satisfied; on the other hand overall quality of the 2 cost-analysis studies is quite high: 17/27 and 19/27 items, respectively, fully or partially satisfied.

5.3 Conclusion

Among the studies comparing CRT-D with ICD one is a cost-effectiveness analysis [Noyes et al, 2013] while other two studies are cost-analysis [Bentkover et al 2007, Boriani et al 2013].

Noyes concluded that CRT-D is reasonably more cost-effective compared to ICD, especially in patients with LBBB and aged < 75 years old (NYHA I-II). In non LBBB patients CRT-D was dominated by ICD.

Bentkover et al 2007, concluded that the post-procedural costs associated with CRT-D were less than those associated with ICD alone in patients in class NYHA II-IV with EF <35% and QRS >120 msec.

Boriani et al 2013, concluded that extending longevity of device has an important impact in reducing long-term costs of device therapy in 4 different populations with different prognosis.

All studies comparing CRT-D vs CRT-P concluded that, with a defined WTP in the base-case, CRT-D is not cost-effective. In particular, Neyt et al 2011, stated that the current evidence is insufficient to show the superiority in terms of cost-effectiveness of CRT-D over CRT-P in patients with moderate to severe HF (NYHA III-IV) with EF < 35% and wide QRS complex, and they recommended further clinical research to be performed. Yao et al 2007 concluded that the base-case shows that long-term treatment with CRT-D is not

cost-effective compared to CRT-P in similar patients at a willingness-to-pay threshold of € 44,100/QALY gained. Fox et al, 2007 declared that the estimated net benefit from CRT-D is less than with CRT-P until the WTP threshold exceeds £ 40,160/QALY gained, in patients with left ventricular systolic dysfunction and QRS >120 msec. Feldman et al 2005, did not carry out a direct cost-effectiveness comparisons in NYHA III-IV patients. The last study [Bertoldi et al, 2013], that compared the CRT-D vs ICD and CRT-D vs CRT-P, concluded that, with WTP equal to Int$31,689 suggested by WHO, the CRT-D is not cost-effective in both the comparisons. The population was class NYHA III-IV with EF < 35% and QRS >120 msec.

Available evidence suggests that CRT-D is not dominant compared to CRT-P, while the most recent studies comparing ICD with CRT-D come to different conclusions, possibly because of the less serious type of patient included in the Noyes study.

6. Discussion

A comprehensive analysis of the literature indicates superiority of CRT-D on CRT-P and ICD alone. This superiority is observed more significantly in series with greater follow-up (> 1 year). This is probably due to a higher incidence of conduction defects that occur in the more complex CRT-D lead set up primarily in the early periods after implantation. Therefore, this initial handicap is absorbed in the continuation of follow-up with an advantage in terms of reduced mortality and hospitalization rate. The longer follow-up is represented by series of patients with a better NYHA class at the time of implantation of the CRT-D.

According with the current state of the art CRT-D implantation is justified in patients who have adequate criteria for both CRT and ICD and presenting a prognosis> 1 year (NYHA class <IV, age < 80 years, no severe comorbidities, etc.). The same limited impact of CRT-D over CRT-P seems also evident when restricitng the analysis to more severly ill patients. In a retrospective subanalysis of COMPANION, for NYHA class IV patients, the median duration of follow-up for the primary end point was 7.2 months for OPT, 14.2 months for CRT, and 14.1 month for CRT-D. The primary end point of time to death or hospitalization for any cause was significantly and similarly prolonged by both CRT (HR, 0.64; P=0.02) or by CRT-D (HR, 0.62; P=0.01) compared with optimal medical therapy (OPT). Time to mortality or HF hospitalization was significantly improved by both CRT (HR, 0.57; P=0.01) and CRT-D (HR, 0.49; P=0.001) compared with OPT. Analysis of time to HF death or HF hospitalization demonstrated a significant benefit of CRT-D (CRT-D versus OPT: HR, 0.58; P=0.03), whereas there was a strong trend for a benefit of CRT versus OPT which missed significance (CRT versus OPT: HR, 0.64; P=0.07). Importantly, CRT did not differ from CRT-D for any of those endpoints.

Of particular relevance are the COMPANION subanalysis data with respect to the possibility of preventing cardiac arrhythmic death by the simoultaneous use of CRT-D [Carson et al 2005]. While there was an obvious advantage of using CRT-D compared to OPT alone, this advantage was largely lost when comparing CRT-D vs CRT-P, although there was an indication of benefit. However, the numerical advantage conferred by CRT-D vs CRT-P in terms of fewer sudden deaths, was largely offset by the number of patients who died of pump failure, who were more numerous, and in whom CRT-D actually showed a trend toward worse (not significant) results compared to CRT-P. In conclusion, in the COMPANION subanalysis, the absolute number of events was small, hence those results do not allow to reach a firm conclusion with respect to the superiority of one device over the other.

Our preliminary observations and findings are not dissimilar from those made by the NICE appraisal committee in their recent preliminary guidance document (NICE 2014). NICE recommends Implantable cardioverter defibrillators, cardiac resynchronisation therapy (CRT) with defibrillator (CRT-D) or CRT with pacing (CRT-P) as treatment options for people with HF who have left ventricular dysfunction with an LVEF of 35% or less (NICE 2014).

7. Conclusions

Given the limitations of COMPANION and earlier trials, and the paucity of data that have been specifically obtained thereafter, as of today the best summary of available evidence is still what was aptly conveyed by Bristow et al 10 years ago: "In selected patients, cardiac-resynchronization therapy with a pacemaker or a pacemaker–defibrillator can improve the clinical course of chronic HF due to a dilated cardiomyopathy. CRT-P is associated with a reduction in hospitalizations and symptoms and improved exercise tolerance and quality of life, and the addition of a defibrillator to cardiac-resynchronization therapy further reduces mortality. The decision of which of these two therapeutic options is appropriate for a particular setting is best determined on an individual basis by patients and their physicians" [Bristow 2004]. In short, the role of CRT in the management of HF depends largely on appropriate patient selection, the best criteria for which, however, are still a subject of debate, especially in those with minimal QRS abnormalities and atrial fibrillation for whom there is at present little evidence of benefit.

Recently, the European Society of Cardiology (ESC) published a focused update of device guidelines for patients with HF based on findings from more recent clinical trials [Brignole 2013]. For patients with NYHA Class III/IV HF, these updated guidelines specify that LV dilatation is no longer a requirement, Class IV patients should be ambulatory, and patients should have a reasonable expectation of survival for at least >6 months with good functional status.

For cardiac resynchronization therapy defibrillator (CRT-D) implantation, patients should have a reasonable expectation of survival for 1 year.

The document also underlines the importance of left bundle branch block (LBBB) morphology on ECG, reserving Class IA to patients with LV EF<35%, LBBB and QRS duration ≥150 ms (1).

With additional findings from MADIT-CRT and REVERSE, both of which demonstrated reduced HF morbidity, a new recommendation was made for patients with NYHA functional Class II HF for whom there is a Class IA indication. In the case of LV EF<35% and QRS width ≥150 ms, CRT, specified as preferentially CRT-D [Brignole 2013].

It is also evident that in certain regions the relative proportion of ICD implants vs CRT (-D and –P) largely exceeds national average, even after adjustments. Again, this is unlikely to be a reflection of different epidemiology or clinical characteristics. This finding is of even greater concern, given the solid evidence that ICDs can only prevent possible episodes of life-threating arrhythmias, but they do not beneficially influence the underlying alterations of cardiac function, as CRT does. Thus, it would be important to grant CRT to those patients in whom cardiac asynchrony is demonstrated.

We have no immediate clues as to what could be possible reasons for this low rate of CRT implants in certain regions (see par.3.3). However, it is possible that this may be a reflection of greater technical complexity of CRT implant (which may discourage some implant labs), and perhaps also importantly by possible lack of specific HF clinics which are instrumental in properly screening and identifying HF patients with cardiac asynchrony.

In conclusion, the issue of which device to implant in selected HF patients has many facets. In fact, while there are clear indications emerging from numerous trials endorsed by international guidelines, it must be appreciated that the patient population in the "real world" does not precisely match those of randomized trials; this is not just because of older age and/or greater burden of comorbidities frequently found outside trials, but because, by their very nature, most trials ended up enrolling patients in whom there was one clear, compelling indication for implant, and only one. In real world, however, many HF patients tend to have more than one possible indication for device therapy, as detailed below.

A) patients with depressed left ventricular function (i.e., ejection fraction below 30-35%) are at substantial risk of arrhythmic death, and therefore according to guidelines they are potential candidates to ICD implant; underlying etiology of cardiac disease (i.e., ischemic vs non-ischemic) is largely irrelevant in this scheme. However, this approach does not improve overall cardiac function, nor it influences progression of disease and death by pump failure. Furthermore, this recommendation makes no reference to the presence (or not) of LV asynchrony.

B) At the same time, there is consensus that CRT is an extremely powerful means to improve cardiac function and geometry in the majority (but not all) of HF patients who show LV asynchrony. Attempts to reduces or eliminate non-responders (e.g., by detailed echo or MRI assessment) have largely proven unsatisfactory.Thus, as of today CRT should be reserved for HF patients with: a) depressed ejection fraction; b) sinus rhythm; c) ECG width >120 msec, and d) left bundle branch block. These criteria leave about 40% of all patients out, in addition to non-responders (estimated at 25% of implants). Another major downside of CRT per se is its limited efficacy in reducing arrhythmic death.

With these considerations in mind, because potential CRT recipients typically are candidates for an ICD because of their severely depressed LV ejection fraction, clinicians have inferred that most CRT recipients should actually receive a CRT-D device, as it would seem logical to combine both CRT and ICD into one device (i.e., CRT-D), in hopes to have a two-pronge

approach to improving long-term outcome of HF patients. Regrettably, while intuitively sound, this approach has received little solid support by both randomized trials and guideline recommendations. Guidelines are largely silent on whether a CRT-P or a device CRT-D should be used. Indeed, evidence supporting this practice is scanty (McAlister FA, Ezekowitz J, Hooton N, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. JAMA 2007;297:2502–2514.), and the prescription of a CRT-D vs CRT-P device, as reviewed by Exner et al is often directed by geographic, economic, or other factors rather than by evidence-based guidance. (Exner DV, Auricchio A, Singh JP. Contemporary and future trends in cardiac resynchronization therapy to enhance response. Heart Rhythm. 2012;9(8 Suppl):S27–35). As for large randomized clinical trials, as already discussed only COMPANION has directly compared clinical outcomes of patients randomized to CRT-P vs CRT-D; and no clear superiority of CRT-D could be firmly established. Nevertheless, since there is a relatively small risk of sudden death in patients receiving CRT-P, (Boveda S, Marijon E, Jacob S, et al. Incidence and prognostic significance of sustained ventricular tachycardias in HF patients implanted with biventricular pacemakers without a back-up defibrillator: results from the prospective, multicentre, Mona Lisa cohort study. Eur Heart J 2009;30:1237–1244.), cardiologists quite often implant a CRT-D device in HF patients.

However, it must be kept in mind that CRT-D can only display its potential usefulness in patients presenting all criteria for CRT, that as discussed represent little more than half of HF population with depressed LV function. Furthermore, this decision must be weighed against the imperative that the favorable impact of CRT-D on reducing sudden death be balanced with the potential downsides of this therapy (e.g., shorter battery life span, higher risk for lead-related complications, and costs).

Cost-effectiveness and cost utility evidence, available so far, suggests that CRT-D is not dominant compared to CRT-P in patients with NYHA functional class III-IV, EF<35% and QRS complex (>120 msec). On the other hand a most recent study comparing ICD with CRT-D comes to different conclusions in patients with LBBB and aged < 75 years, possibly because of less serious type of patients (NYHA I-II).

Cost analyses comparing CRT-D vs ICD alone concluded that the post-procedural costs of CRT-D were less than those for ICD alone and, in long term, cost savings could increase with the extending of battery longevity of CRT-D.

In 2012 in Italy ICDs were the most used device (65% of all implants), with 3,030 units bought (30% of units bought), and a 10,803 implanted. The ratio of 3:1 is the opposite for CTR-P with

1,227 implanted devices and 3,126 bought. For CRT-D, 4,999 were bought and 4,461 were implanted. It is important to bear in mind that as the date of purchase is unknown, it is possible that a proportion of these devices were implanted in the early months of 2013. In addition some of the regions like Lazio did not report purchases to the database in 2012 (8 devices in total were reported) but 1,680 were implanted.

Readers must bear in mind that the purchase data may be incomplete, thereby underestimating the total.

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9. Competing interests declaration

The Authors declare that they will not receive either benefits or harms from the publication of this report.

None of the Authors have or have held shares, consultancies or personal relationships with any of the manufacturers of the devices assessed in this report.

Bibliography

Ambrosy AP, Fonarow GC, Butler J et al. The Global Health and Economic Burden of Hospitalizations for Heart Failure. JACC. 2014;63(12):1123ñ1133.

Askoxylakis V, Thieke C, Pleger ST, et al. Long-term survival of cancer patients compared to heart failure and stroke: a systematic review. BMC Cancer 2010;10:105.

Atherton JJ, Hayward CS, Wan Ahmad WA et al. Patient characteristics from a regional multicenter database of acute decompensated heart failure in Asia Pacific (ADHERE International-Asia Pacific). J Card Fail 2012;18:82ñ8

Bilal Alam M, Bilal Munir M, Rattan R et al. Battery longevity in cardiac resynchronization therapy implantable cardioverter defibrillators. Europace 2014 Feb;16(2):246-51.

Braunwald, E. Heart Failure. JACC 2013: 1(1), 1-20.

Brignole M, Auricchio A, Baron-Esquivias G et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013;34(29):2281ñ2329. doi:10.1093/eurheartj/eht150.

Brouwers FP, de Boer RA, van der Harst P et al. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. European Heart Journal, 2013;34(19):1424.

Cabell C, Heidenreich P, Chu V et al. Increasing rates of cardiac device infections among Medicare beneficiaries: 1990–1999. Am Heart J 2004;147:582–6).

Committee TCSS. European cardiac resynchronization therapy survey: rationale and design. Eur J Heart Fail. 2009;11(3):326-330.

Dickstein K, Bogale N, Priori S et al. The European cardiac resynchronization therapy survey. Eur Heart J 2009;30:2450–60.

Franconi F, Carru C, Malorni W, Vella S, Mercuro G The effect of gender on cardiovascular pharmacology. Curr Pharm Des 17:1095-107. 2011, IF 4.774.

Galvao M, Kalman J, DeMarco T et al. Gender differences in inhospital management and outcomes in patients with decompensated heart failure: analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Card Fail 2006;12:100 – 7.

Gheorghiade, M., Sopko, G., De Luca, L., Velazquez, E. J., Parker, J. D., Binkley, P. F., et al. Navigating the crossroads of coronary artery disease and heart failure. Circulation 2006;114(11):1202-1213.

Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. 2013;127(1):e6-e245.

Goldenberg I, Moss AJ, Hall WJ et al. Multicenter Automatic Defibrillator Implantation Trial (MADIT) II Investigators. Causes and consequences of heart failure after prophylactic implantation

of a defibrillator in the multicenter automatic defibrillator implantation trial II. Circulation. 2006 Jun 20;113(24):2810-7. Epub 2006 Jun 12.

Hsich EM, Pina IL. Heart failure in women: a need for prospective data. J Am Coll Cardiol 2009;54:491-8.

Johansen JB, Jørgensen OD, Møller M et al. Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. Eur Heart J 2011;32:991–8.).

Klug D, Balde M, Pavin D et al. PEOPLE Study Group. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. Circulation 2007; 116:1349–55

Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail 2011;13:18-28.

Masson S, Latini R, Anand IS et al. Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial). J Am Coll Cardiol 2008;52:997ñ1003

McMurray JJV, Adamopoulos S, Anker SD et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012.

National Institute for Health and Care Excellence. Final appraisal determination – implantable cardioverter defibrillators and cardiac resynchronization therapy for arrhythmias and heart failure (review of TA95 and TA120). June 2014.

Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33(13):1635-1701.

Proclemer A, Zecchin M, Lunati M, et al. The pacemaker and implantable cardioverter-defibrillator registry of the Italian Association of Arrhythmology and Cardiac Pacing - Annual Report 2012. G Ital Cardiol (Rome). 2013 Nov;14(11):784-96.

Romeyer-Bouchard C, Da Costa A, Dauphinot V et al. Prevalence and risk factors related to infections of cardiac resynchronization therapy devices. Eur Heart J 2010;31:203–10).

Schuchert A, Muto C, Maounis T et al. Lead complications, device infections, and clinical outcomes in the first year after implantation of cardiac resynchronization therapy defibrillator and cardiac resynchronization therapy-pacemaker. Europace (2013) 15, 71–76

Senni M, Paulus WJ, Gavazzi A, Fraser AG et al. New strategies for heart failure with preserved ejection fraction: the importance of targeted therapies for heart failure phenotypes. European Heart Journal doi:10.1093/eurheartj/ehu204. In press 2014

Shah AM, Mann DL. In search of new therapeutic targets and strategies for heart failure: recent advances in basic science. Lancet 2011;378:704-712

Siphai I, Chou JC, Hyden M et al. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Am Heart J 2012; 163: 260-7

Stavrakis S, Lazzara R, Thadani U. The benefit of cardiac resynchronization therapy and QRS duration: a meta-analysis. J Cardiovasc Electrophysiol 2012;23:163-8. PMID: 21815961

Vaduganathan M, Greene SJ, Ambrosy AP et al. The disconnect between phase II and phase III trials of drugs for heart failure. Nat Rev Cardiol 2013;10:85-97

Zannad F, Agrinier N, Alla F. Heart failure burden and therapy. Europace 2009;11 Suppl 5:1-9

Zuchi C, Tritto I, Ambrosio G. Angina pectoris in women: focus on microvascular disease. Cardiovasc Ther. 2010 Aug;28(4):187-201.

List of web site consulted

http://www.istat.it/sanita/health (access: March 2014)

http://www.salute.gov.it/portale/salute/p1_5.jsp?lingua=italiano&id=43&area=Malattie_cardiovascolari (access: March 2014)

https://nsis.sanita.it/ANS6/DISPO-CONRDM/AdapterHTTP (access: from March to June 2014)

http://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&p=dalministero&id=1141 (access: May 2014)

http://www.biotronik.com/ (access: April 2014)

http://www.bostonscientific.com (access: April 2014)

http://www.medtronic.com (access: April 2014)

http://www.sorin.com (access: April 2014)

http://www.sjm.com (access: April 2014)

List of acronyms and abbreviations

AT/AF , atrial tachyarhythmias / atrial fibrillation

CAD: Coronary Artery Disease

CRT = Cardiac Resynchronization Therapy

CRT-D: Cardiac resynchronization therapy and defibrillator

CRT-P: Cardiac resynchronization therapy and pacemaker

CND: Classificazione Nazionale Dispositivi medici – national classification of medical devices.

GMDN: global medical device nomenclature.

EF: ejection fraction

HF: heart failure

HFH: heart failure hospitalization

HFrEF: heart failure with reduced ejection fraction

HFpEF: heart failure with preserved ejection fraction

ICD: implantable cardioverter-defibrillators

LV: left ventricular

NOS: Newcastle-Ottawa Scale.

RAAS: renin-angiotensin-aldosterone system

RDM: general repertory of medical devices.

SSN: Servizio Sanitario Nazionale – the Italian national health service.

VT: ventricular tachycarhythmias

VF: ventricular fibrillation

Appendix 1 – CRT-D technical details

Verbale incontro tecnico con il Produttore:_____

data, _____

Presenti all'incontro: _____

Ordine del giorno e punti di discussione:

1) Analisi del quadro sinottico allegato al presente verbale riguardante la verifica dei modelli del dispositivo CRT-D prodotti dalla ditta e attualmente commercializzati in Italia, e le relative caratteristiche tecniche principali.
   Approfondimento delle caratteristiche tecniche dei vari dispositivi.

2) Verifica di eventuali differenze per la procedura di impianto ed espianto dei dispositivi.

3) Indicazione di studi comparativi (RCT e osservazionali prospettici) in corso o conclusi.

4) Disponibilità a fornire i costi per tipologia di modello e composizione del prezzo.

5) Disponibilità a fornire i dati dei volumi italiani di vendita (possibilmente per Regione).

6) Varie ed eventuali.

Tab 1 CRT-D produced and actually commercialized in the Italian market Biotronik SE & Co

Model	Indication	Functions	Remote Monitoring (follow up)	MRI conditional	ATP in FV zone	Diagnostics for heart failure	Inappropriate ICD shock diagnosis	Quadripolar	Automatic Optimization of Cardiac Resynchronization Therapy (AV and VV intervals optimization)
Iforia 3 HF-T	Prevention of sudden cardiac death. Bradycardiac treatment of arrhythmias and heart failure therapy with biventricular pacing	RF SafeSync telemetry, arrhythmias detection, SelectSense Advanced, Discrimination algorithm of supraventricular arrhythmias: SMART Detection, DFT manager, ATP (VD, VS, BiV), ATP one shot, ATP optimization, electrocautery mode, backup mode, interference mode, PostShock stimulation, MultiSelect LV Pacing, LV Sensing, LV T-Wave protection, VV Delay, RVsense Triggering, managing atrial arrhythmias, Automatic Threshold Measurement right and left, HeartFailure Monitor, Monitoring atrial fibrillation, SmartScale (thickness and volume reduction)	yes	no	yes	yes	yes	no	no
Iforia 5 HF-T		RF SafeSync telemetry, arrhythmias detection, SelectSense Advanced, Discrimination algorithm of supraventricular arrhythmias: SMART Detection, DFT manager, ATP (VD, VS, BiV), ATP one shot, ATP optimization, electrocautery mode , backup mode, interference mode, PostShock stimulation, MultiSelect LV Pacing, LV Sensing, LV T-Wave protection, VV Delay, RVsense Triggering, managing atrial arrhythmias, Automatic Control Ventricular Capture right and left, HeartFailure Monitor, Monitoring atrial fibrillation, SmartScale (thickness and volume reduction)	yes	yes	yes	yes	yes	no	no
Ilesto 5 HF-T		RF SafeSync telemetry, arrhythmias detection, SelectSense Advanced, Discrimination algorithm of supraventricular arrhythmias: SMART Detection, DFT manager, ATP (VD, VS, BiV), ATP one shot, ATP optimization, electrocautery mode, backup mode, interference mode, PostShock stimulation, MultiSelect LV Pacing, LV Sensing, LV T-Wave protection, VV Delay, RVsense Triggering, managing atrial arrhythmias, Automatic Control Ventricular Capture right and left, HeartFailure Monitor with thoracic impedance, Monitoring atrial fibrillation, SmartScale (thickness and volume reduction), ShockReduct (Inappropriate shock reduction), Remote scheduling for Home Monitoring	yes	yes	yes	yes	yes	no	no
Ilesto 7 HF-T		RF SafeSync telemetry, arrhythmias detection, SelectSense Advanced, Discrimination algorithm of supraventricular arrhythmias: SMART Detection, DFT manager, ATP (VD, VS, BiV), ATP one shot, ATP optimization, electrocautery mode, backup mode, interference mode, PostShock stimulation, MultiSelect LV Pacing, LV Sensing, LV T-Wave protection, VV Delay, RVsense Triggering, managing atrial arrhythmias, Automatic Control Ventricular Capture right and left, HeartFailure Monitor with thoracic impedance, Advanced monitoring of atrial fibrillation , SmartScale (thickness and volume reduction), ShockReduct (Inappropriate shock reduction), Extended longevity, Atrial NIPS, Remote scheduling for Home Monitoring	yes	yes	yes	yes	yes	no	no
Idova 7 HF-T		RF SafeSync telemetry, arrhythmias detection, SelectSense Advanced, Discrimination algorithm of supraventricular arrhythmias: SMART Detection, DFT manager, ATP (VD, VS, BiV), ATP one shot, ATP optimization, electrocautery mode, backup mode, interference mode, PostShock stimulation, MultiSelect LV Pacing, LV Sensing, LV T-Wave protection, VV Delay, RVsense Triggering, managing atrial arrhythmias, Automatic Control Ventricular Capture right and left, HeartFailure Monitor, , Advanced monitoring of atrial fibrillation , SmartScale (thickness and volume reduction), ShockReduct (Inappropriate shock reduction), Maximum energy stored 45 J at first shock, Extended longevity, Atrial NIPS, Remote scheduling for Home Monitoring	yes	yes	yes	yes	yes	no	no
Lumax 640 HF-T		RF SafeSync telemetry, arrhythmias detection, SelectSense Advanced, Discrimination algorithm of supraventricular arrhythmias: SMART Detection, DFT manager, ATP (VD, VS, BiV), ATP one shot, ATP optimization, electrocautery mode, backup mode, interference mode, PostShock stimulation, MultiSelect LV Pacing, LV Sensing, LV T-Wave protection, VV Delay, RVsense Triggering, managing atrial arrhythmias, Automatic Control Ventricular Capture right and left, HeartFailure Monitor	yes	yes	yes	yes	yes	no	no
Lumax 740 HF-T		RF SafeSync telemetry, arrhythmias detection, SelectSense Advanced, Discrimination algorithm of supraventricular arrhythmias: SMART Detection, DFT manager, ATP (VD, VS, BiV), ATP one shot, ATP optimization, electrocautery mode, backup mode, interference mode, PostShock stimulation, MultiSelect LV Pacing, LV Sensing, LV T-Wave protection, VV Delay, RVsense Triggering, managing atrial arrhythmias, Automatic Control Ventricular Capture right and left, HeartFailure Monitor with thoracic impedance, Advanced monitoring of atrial fibrillation	yes	yes	yes	yes	yes	no	no

Tab 2 CRT-D produced and actually commercialized in the Italian market by Boston Scientific

Model	Indication	Functions	Remote Monitoring (follow up)	MRI conditional	Antitachycardia Pacing (ATP) in FV zone	Diagnostics for heart failure	Inappropriate ICD shock diagnosis	Quadripolar	Automatic Optimization of Cardiac Resynchronization Therapy (AV and VV intervals optimization)
AUTOGEN CRT-D	These Boston Scientific Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) are indicated for patients with heart failure who receive stable otimal pharmacological therapy (OPT) for heart failure and who meet any one of the following classifications: 1. moderate to severe heart failure (NYHA Class III-IV) with EF ≤35% and QRS duration ≥ 120 ms 2. Left bundle branch block (LBBB) with QRS duration ≥ 130 ms, EF ≤30%, and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure. Boston Scientific CRT-Ds are also intended to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrythmias.	double sensors (minute ventilation + accelerometer) with availability of blended sensors; autothresholds RA, RV, LV; storage of the onset of arrhythmia with EGM; 5 LV sensing configurations, 6 LV pacing configurations;2 different families of discriminators (OBDE+ Rhythm ID), with fine tuning of Rhythm ID, Apnea Scan.	yes	no	yes	yes	yes	no	yes
		double sensors (minute ventilation + accelerometer) with availability of blended sensors; autothresholds RA, RV, LV; storage of the onset of arrhythmia with EGM; 5 LV sensing configurations, 6 LV pacing configurations; 2 different families of discriminators (OBDE+ Rhythm ID), with fine tuning of Rhythm ID, Apnea Scan.	yes	no	yes	yes	yes	no	yes
		double sensors (minute ventilation + accelerometer) with availability of blended sensors; autothresholds RA, RV, LV; storage of the onset of arrhythmia with EGM; 5 LV sensing configurations, 6 LV pacing configurations; 2 different families of discriminators (OBDE+ Rhythm ID), with fine tuning of Rhythm ID; LV-1 connector, Apnea Scan.	yes	no	yes	yes	yes	no	yes
AUTOGEN X4 CRT-D		double sensors (minute ventilation + accelerometer) with availability of blended sensors; autothresholds RA, RV; storage of the onset of arrhythmia with EGM; 8 LV sensing configurations, 17 LV pacing configurations; 2 different families of discriminators (OBDE+ Rhythm ID), with fine tuning of Rhythm ID, Apnea Scan.	yes	no	yes	yes	yes	yes	yes
		double sensors (minute ventilation + accelerometer) with availability of blended sensors; autothresholds RA, RV; storage of the onset of arrhythmia with EGM; 8 LV sensing configurations, 17 LV pacing configurations; 2 different families of discriminators (OBDE+ Rhythm ID), with fine tuning of Rhythm ID, Apnea Scan.	yes	no	yes	yes	yes	yes	yes
INOGEN CRT-D		storage of the onset of arrhythmia with EGM; 5 LV sensing configurations, 6 LV pacing configurations; 2 different families of discriminators (OBDE+ Rhythm ID);	yes	no	yes	yes	yes	no	yes
		storage of the onset of arrhythmia with EGM; 5 LV sensing configurations, 6 LV pacing configurations; 2 different families of discriminators (OBDE+ Rhythm ID);	yes	no	yes	yes	yes	no	yes
INOGEN X4 CRT-D		storage of the onset of arrhythmia with EGM; 8 LV sensing configurations, 17 LV pacing configurations;2 different families of discriminators (OBDE+ Rhythm ID);	yes	no	yes	yes	yes	yes	yes
		storage of the onset of arrhythmia with EGM;8 LV sensing configurations, 17 LV pacing configurations;2 different families of discriminators (OBDE+ Rhythm ID);	yes	no	yes	yes	yes	yes	yes
Incepta CRT-D		storage of the onset of arrhythmia with EGM;5 LV sensing configurations, 6 LV pacing configurations; 2 different families of discriminators (OBDE+ Rhythm ID), with fine tuning of Rhythm ID, Apnea Scan.	yes	no	yes	yes	yes	no	yes
		storage of the onset of arrhythmia with EGM;5 LV sensing configurations, 6 LV pacing configurations; 2 different families of discriminators (OBDE+ Rhythm ID), with fine tuning of Rhythm ID, Apnea Scan.	yes	no	yes	yes	yes	no	yes
		storage of the onset of arrhythmia with EGM; 5 LV sensing configurations, 6 LV pacing configurations; 2 different families of discriminators (OBDE+ Rhythm ID), with fine tuning of Rhythm ID; LV-1 connector, Apnea Scan.	yes	no	yes	yes	yes	no	yes
Energen CRT-D		storage of the onset of arrhythmia with EGM; 5 LV sensing configurations, 6 LV pacing configurations;2 different families of discriminators (OBDE+ Rhythm ID);	yes	no	yes	yes	yes	no	yes
		storage of the onset of arrhythmia with EGM; 5 LV sensing configurations, 6 LV pacing configurations; 2 different families of discriminators (OBDE+ Rhythm ID);	yes	no	yes	yes	yes	no	yes
Punctua CRT-D		storage of the onset of arrhythmia with EGM; 5 LV sensing configurations, 6 LV pacing configurations; 1 family of discriminators (OBDE);	yes	no	no	yes	yes	no	no
Punctua NE CRT-D		storage of the onset of arrhythmia with EGM; 5 LV sensing configurations, 6 LV pacing configurations; 1 family of discriminators (OBDE);	no	no	no	yes	yes	no	no

Tab 3 CRT-D produced and actually commercialized in the Italian market by Medtronic Inc

Model	Indication		Functions	Remote Monitoring (follow up)	MRI conditional	ATP in FV zone	Diagnostics for heart failure	Inappropriate ICD shock diagnosis	Quadripolar	Automatic Optimization of Cardiac Resynchronization Therapy (AV and VV intervals optimization)
Consulta CRTD	with atrial therapies	The system is indicated for use in patients who are at high risk of sudden death due to ventricular tachyarrhythmias and who have heart failure with ventricular dyssynchrony. The device is intended to provide atrial and/or ventricular antitachycardia pacing, cardioversion, and defibrillation for automated treatment of atrial and/or life-threatening ventricular tachyarrhythmias.	Digital implantable cardioverter defibrillator with cardiac resynchronization therapy (DDE-DDDR), RV Lead Integrity Alert, Wavelet, PR Logic®, and ATP programmable in RV/LV/BIV and ATP During Charging™ Feature, Active Can and SVC coil programmable, Complete Capture Management® Diagnostic (ACM, RVCM, LVCM), OptiVol® Fluid Status Monitoring,Conexus® Wireless Telemetry	yes	no	yes	yes	yes	no	no
Concerto II			Digital implantable cardioverter defibrillator with cardiac resynchronization therapy (DDE-DDDR), RV Lead Integrity Alert, Wavelet, PR Logic®, and ATP programmable in RV/LV/BIV and ATP During Charging™ Feature, Active Can and SVC coil programmable, Capture Management® Diagnostic (LVCM),OptiVol® Fluid Status Monitoring, Conexus® Wireless Telemetry	yes	no	yes	yes	yes	no	no
Protecta XT CRTD			Digital implantable cardioverter defibrillator with cardiac resynchronization therapy (DDE-DDDR) SmartShock™ Technology (RV Lead Noise Discrimination, RV Lead Integrity Alert, TWave Discrimination, Confirmation+, Wavelet, PR Logic®), and ATP programmable in RV/LV/BIV and ATP During Charging™ Feature, Active Can and SVC coil programmable, Complete Capture Management® Diagnostic (ACM, RVCM, LVCM),OptiVol® 2.0 Fluid Status Monitoring, Conexus® Wireless Telemetry	yes	no	yes	yes	yes	no	no
Protecta CRTD			Digital implantable cardioverter defibrillator with cardiac resynchronization therapy (DDE-DDDR) SmartShock™ Technology (RV Lead Noise Discrimination, RV Lead Integrity Alert, TWave Discrimination, Confirmation+, Wavelet, PR Logic®), and ATP programmable in RV/LV/BIV and ATP During Charging™ Feature, Active Can and SVC coil programmable, Complete Capture Management® Diagnostic (ACM, RVCM, LVCM), Conexus® Wireless Telemetry	yes	no	yes	no	yes	no	no
Viva XT			Digital implantable cardioverter defibrillator with cardiac resynchronization therapy (DDE-DDDR),PhysioCurve™ Design, AdaptivCRT™ Algorithm, CardioSync™ Optimization, SmartShock™ Technology (RV Lead Noise Discrimination, RV Lead Integrity Alert, TWave Discrimination, Confirmation+, Wavelet, PR Logic®), and ATP programmable in RV/LV/BIV and ATP During Charging™ Feature, Active Can and SVC coil programmable, Complete Capture Management® Diagnostic (ACM, RVCM, LVCM), OptiVol® 2.0 Fluid Status Monitoring, Conexus® Wireless Telemetry	yes	no	yes	yes	yes	no	yes
VIVA™ QUAD XT			Digital implantable cardioverter defibrillator with cardiac resynchronization therapy (DDE-DDDR),PhysioCurve™ Design, AdaptivCRT™ Algorithm, CardioSync™ Optimization, VectorExpress™ LV Automated Test, SmartShock™ Technology (RV Lead Noise Discrimination, RV Lead Integrity Alert, TWave Discrimination, Confirmation+, Wavelet, PR Logic®), and ATP programmable in RV/LV/BIV and ATP During Charging™ Feature, Active Can and SVC coil programmable, Complete Capture Management® Diagnostic (ACM, RVCM, LVCM), OptiVol® 2.0 Fluid Status Monitoring, Conexus® Wireless Telemetry	yes	no	yes	yes	yes	yes	yes
Viva S			Digital implantable cardioverter defibrillator with cardiac resynchronization therapy (DDE-DDDR),PhysioCurve™ Design, CardioSync™ Optimization, SmartShock™ Technology (RV Lead Noise Discrimination, RV Lead Integrity Alert, TWave Discrimination, Confirmation+, Wavelet, PR Logic®), and ATP programmable in RV/LV/BIV and ATP During Charging™ Feature, Active Can and SVC coil programmable, Complete Capture Management® Diagnostic (ACM, RVCM, LVCM),Conexus® Wireless Telemetry	yes	no	yes	no	yes	no	no
Maximo II CRT-D	no atrial therapies	The system is indicated for use in patients who are at high risk of sudden death due to ventricular tachyarrhythmias and	Digital implantable cardioverter defibrillator with cardiac resynchronization therapy (DDE-DDDR), RV Lead Integrity Alert, Wavelet, PR Logic®, and ATP programmable in RV/LV/BIV and ATP During Charging™ Feature, Active Can and SVC coil programmable, Conexus® Wireless Telemetry	yes	no	yes	no	yes	no	no

Model	Indication		Functions	Remote Monitoring (follow up)	MRI conditional	ATP in FV zone	Diagnostics for heart failure	Inappropriate ICD shock diagnosis	Quadripolar	Automatic Optimization of Cardiac Resynchronization Therapy (AV and VV intervals optimization)
Cardia CRT-D		who have heart failure with ventricular dyssynchrony. The device is intended to provide ventricular antitachycardia pacing, cardioversion, and defibrillation for automated treatment of life-threatening ventricular tachyarrhythmias.	Digital implantable cardioverter defibrillator with cardiac resynchronization therapy (DDE-DDDR), RV Lead Integrity Alert, Wavelet, PR Logic®, and ATP programmable in RV/LV/BIV and ATP During Charging™ Feature, Active Can and SVC coil programmable,	yes	no	yes	no	yes	no	no
Brava			Digital implantable cardioverter defibrillator with cardiac resynchronization therapy (DDE-DDDR),PhysioCurve™ Design, CardioSync™ Optimization, SmartShock™ Technology (RV Lead Noise Discrimination, RV Lead Integrity Alert, TWave Discrimination, Confirmation+, Wavelet, PR Logic®), and ATP programmable in RV/LV/BIV and ATP During Charging™ Feature, Active Can and SVC coil programmable, Complete Capture Management® Diagnostic (ACM, RVCM, LVCM), Conexus® Wireless Telemetry	yes	no	yes	no	yes	no	no
Brava Quad			Digital implantable cardioverter defibrillator with cardiac resynchronization therapy (DDE-DDDR),PhysioCurve™ Design, CardioSync™ Optimization, VectorExpress™ LV Automated Test, SmartShock™ Technology (RV Lead Noise Discrimination, RV Lead Integrity Alert, TWave Discrimination, Confirmation+, Wavelet, PR Logic®), and ATP programmable in RV/LV/BIV and ATP During Charging™ Feature, Active Can and SVC coil programmable, Complete Capture Management® Diagnostic (ACM, RVCM, LVCM), Conexus® Wireless Telemetry	yes	no	yes	no	yes	no	yes

Tab 4 CRT-D produced and actually commercialized in the Italian market by Sorin Group

Model	Indication	Functions	Remote Monitoring (follow up)	MRI conditional	ATP in FV zone	Diagnostics for heart failure	Inappropriate ICD shock diagnosis	Quadripolar	Automatic Optimization of Cardiac Resynchronization Therapy (AV and VV intervals optimization)
PARADYM RF CRT-D 9750	— Patients who are survivors of cardiac arrest due to ventricular fibrillation or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes. — Patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable. — Patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or ventricular fibrillation induced at electrophysiological study. — Patients with reduced LVEF due to prior myocardial infarction who are at least 40 days post--myocardial infarction and with symptomatic heart failure or LV dysfunction. — Patients with non-ischemic dilated cardiomyopathy and reduced LVEF with symptomatic heart failure. — Patients with non-sustained VT due to prior myocardial infarction, reduced LVEF and inducible ventricular fibrillation or sustained VT at electrophysiological study. Biventricular pacing therapy is indicated in patients with symptomatic heart failure despite optimal pharmacological therapy, with reduced LVEF and wide QRS. For further details please refer to "ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities" or "ACC/AHA/ESC 2006 Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death". For biventricular pacing therapy,	**Remote Monitoring and wireless telemetry enabled** Single sensor system: **Accelerometer** (Rate Responsive function) **PARAD+ algorithm**: 7 enhanced criteria for arrhytmia discrimination (heart rate, rhythm stability, AV association, AV stability, Sudden onset, Sudden onset origin, Long ventricular cycle analysis) **ATP** fully and indipently programmable in **VF zone** based on **stability criterion** to by-pass not-necessary shocks. Automatic ATP reprogrammation on therapeutic efficacy base. **Brady-Tachy overlap (BTO)**: CRT pacing applied in VT zone **SafeR** ↔ CRT switch: automatic switch between RV pacing minimization and CRT pacing in case of AV block	yes	no	yes	no	yes	no	no
PARADYM RF CRT-D SONR 9770		**Remote Monitoring and wireless telemetry enabled** **Dual sensor system:** SonR (CRT optimization and HF monitoring) + Accelerometer (Rate Responsive function) **SonR - Automatic and continuous haemodynamic CRT optimization** (AV and VV delay) **HF diagnostic**: SonR signal trend linked to contractility changes **PARAD+ algorithm**: 7 enhanced criteria for arrhytmia discrimination (heart rate, rhythm stability, AV association, AV stability, Sudden onset, Sudden onset origin, Long ventricular cycle analysis) **ATP** fully and indipently programmable in **VF zone** based on **stability criterion** to by-pass not-necessary shocks. Automatic ATP reprogrammation on therapeutic efficacy base. **Brady-Tachy overlap (BTO)**: CRT pacing applied in VT zone **SafeR** ↔ CRT switch: automatic switch between RV pacing minimization and CRT pacing in case of AV block	yes	no	yes	yes	yes	no	yes
PARADYM CRT-D 8750		Single sensor system: **Accelerometer** (Rate Responsive function) **PARAD+ algorithm**: 7 enhanced criteria for arrhytmia discrimination (heart rate, rhythm stability, AV association, AV stability, Sudden onset, Sudden onset origin, Long ventricular cycle analysis) **ATP** fully and indipently programmable in **VF zone** based on **stability criterion** to by-pass not-necessary shocks. Automatic ATP reprogrammation on therapeutic efficacy base. **Brady-Tachy overlap (BTO)**: CRT pacing applied in VT zone **SafeR** ↔ CRT switch: automatic switch between RV pacing minimization and CRT pacing in case of AV block	no	no	yes	no	yes	no	no
PARADYM 2 CRT-D 8752			no	no	yes	no	yes	no	no
INTENSIA SONR CRT-D184		**Remote Monitoring and wireless telemetry enabled** **Dual sensor system**: SonR (CRT optimization and HF monitoring) + **Accelerometer** (Rate Responsive function) **SonR**: Automatic and continuous haemodynamic CRT optimization (AV and VV delay) **HF diagnostic**: SonR signal trend linked to contractility changes **PARAD+ algorithm**: 7 enhanced criteria for arrhytmia discrimination (heart rate, rhythm stability, AV association, AV stability, Sudden onset, Sudden onset origin, Long ventricular cycle analysis) **ATP** fully and indipently programmable in **VF zone** based on **stability criterion** to by-pass not-necessary shocks. Automatic ATP reprogrammation on therapeutic efficacy base. **Brady-Tachy overlap (BTO)**: CRT pacing applied in VT zone **SafeR** ↔ CRT switch: automatic switch between RV pacing minimization and CRT pacing in case of AV block connessione quadripolare in linea - **DF-4**	yes	no	yes	yes	yes	no	yes

Model	Indication	Functions	Remote Monitoring (follow up)	MRI conditional	ATP in FV zone	Diagnostics for heart failure	Inappropriate ICD shock diagnosis	Quadripolar	Automatic Optimization of Cardiac Resynchronization Therapy (AV and VV intervals optimization)
PARADYM 2 CRT-D SONR 8772	please also refer to "2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy".	**Dual sensor system:** SonR (CRT optimization and HF monitoring) + **Accelerometer** (Rate Responsive function) **SonR:** Automatic and continuous haemodynamic CRT optimization (AV and VV delay) **HF diagnostic**: SonR signal trend linked to contractility changes **PARAD+ algorithm**: 7 enhanced criteria for arrhytmia discrimination (heart rate, rhythm stability, AV association, AV stability, Sudden onset, Sudden onset origin, Long ventricular cycle analysis) **ATP** fully and indipently programmable in **VF zone** based on **stability criterion** to by-pass not-necessary shocks. Automatic ATP reprogrammation on therapeutic efficacy base. **Brady-Tachy overlap (BTO)**: CRT pacing applied in VT zone **SafeR** ↔ CRT switch: automatic switch between RV pacing minimization and CRT pacing in case of AV block	no	no	yes	yes	yes	no	yes
PARADYM SONR TRIV 8970		**Multipoint pacing (Triventricular)** **Dual sensor system**: SonR (CRT optimization and HF monitoring) + **Accelerometer** (Rate Responsive function) **SonR**: Automatic and continuous haemodynamic CRT optimization (AV and VV delay) **HF diagnostic**: SonR signal trend linked to contractility changes **PARAD+ algorithm**: 7 enhanced criteria for arrhytmia discrimination (heart rate, rhythm stability, AV association, AV stability, Sudden onset, Sudden onset origin, Long ventricular cycle analysis) **ATP** fully and indipently programmable in **VF zone** based on **stability criterion** to by-pass not-necessary shocks. Automatic ATP reprogrammation on therapeutic efficacy base. **Brady-Tachy overlap (BTO)**: CRT pacing applied in VT zone **SafeR** ↔ CRT switch: automatic switch between RV pacing minimization and CRT pacing in case of AV block	no	no	yes	yes	yes	yes* (* multipoint pacing with three dedicated ventricular pacing channels)	yes

Tab 5 CRT-D produced and actually commercialized in the Italian market by St Jude Medical

Model	Indication	Functions	Remote Monitoring (follow up)	MRI conditional	ATP in FV zone	Diagnostics for heart failure	Inappropriate ICD shock diagnosis	Quadripolar	Automatic Optimization of Cardiac Resynchronization Therapy (AV and VV intervals optimization)
Promote +		Remote monitoring, Algorithms for maintaining the BiV stimulation, AV and VV optimization QuickOPT, patient alert, Diagnostics (episodes, rhythm).	yes	no	no	yes	yes	no	yes
Promote Quadra		Remote monitoring, Algorithms for maintaining the BiV stimulation, AV and VV optimization QuickOPT, patient alert, Diagnostics (episodes, rhythm), Automatic management pacing thresholds, advanced diagnostics (FA HF), ShockGuard, ATP during charging (shock-PainFree reduction), lead quadrapolar, CRT toolkit VectSelect.	yes	no	yes	yes	yes	yes	yes
Unify Quadra		Remote monitoring, Algorithms for maintaining the BiV stimulation, AV and VV optimization QuickOPT, patient alert, Diagnostics (episodes, rhythm), Automatic management pacing thresholds, advanced diagnostics (FA HF), ShockGuard, ATP during charging (shock-PainFree reduction), lead quadrapolar, CRT toolkit VectSelect.	yes	no	yes	yes	yes	yes	yes
Unify Assura		Remote monitoring, Algorithms for maintaining the BiV stimulation, AV and VV optimization QuickOPT, patient alert, Diagnostics (episodes, rhythm), Automatic management pacing thresholds, advanced diagnostics (FA HF), ShockGuard, ATP during charging (shock-PainFree reduction), Advanced Features of discrimination, DynamicTX, Parylene coating	yes	no	yes	yes	yes	no	yes
Quadra Assura		Remote monitoring, Algorithms for maintaining the BiV stimulation, AV and VV optimization QuickOPT, patient alert, Diagnostics (episodes, rhythm), Automatic management pacing thresholds, advanced diagnostics (FA HF), ShockGuard, ATP during charging (shock-PainFree reduction), lead quadrapolar, CRT toolkit VectSelect, Advanced Features of discrimination, DynamicTX, Parylene coating	yes	no	yes	yes	yes	yes	yes
Quadra Assura MP		Remote monitoring, Algorithms for maintaining the BiV stimulation, AV and VV optimization QuickOPT, patient alert, Diagnostics (episodes, rhythm), Automatic management pacing thresholds, advanced diagnostics (FA HF), ShockGuard, ATP during charging (shock-PainFree reduction), lead quadrapolar, CRT toolkit VectSelect, Advanced Features of discrimination, DynamicTX, Parylene coating, MultiPoint stimulation	yes	no	yes	yes	yes	yes	yes

Appendix 2 - LITERATURE SEARCH

"Implantable cardiac resynchronization therapy and defibrillator (CRT-D) in patient with heart failure"

MEDLINE

Date: 24 Febrary 2014

Filters: *Language:* English, Italian - *Species:* humans - *Time range:* none (2004-2014) - *Study design:* Clinical Trial; Comparative Study; Controlled Clinical Trial; Evaluation Studies; Observational Study; Meta-Analysis; Randomized Controlled Trial

POPULATION		TECHONOLOGY				COMPARATOR
Heart failure [Mesh] OR "Intraventricular conduction delay" [Text Word] OR "Cardiac dyssynchrony" [Text Word] OR Ventricular tachycardia [Mesh] OR Ventricular fibrillation [Mesh] OR Ventricular dysfunction [Mesh] OR cardiac asynchrony [Text Word] OR QRS interval [Text Word]	AND	cardiac resynchronization therapy [Mesh] OR cardiac resynchronization [Title/Abstrac] OR CRT [Title/Abstrac] OR biventricular stimulation [Title/Abstrac] OR biventricular pacing [Title/Abstrac]	AND	Defibrillator [Title/Abstract] OR implantable cardioverter defibrillators [Mesh] OR ICD [Title/Abstract] OR "automatic internal defibrillator" [Title/Abstract] OR "implantable defibrillator" [Title/Abstract] OR Automatic implantable cardioverter defibrillator	AND	cardiac resynchronization therapy [Mesh] OR cardiac resynchronization [Title/Abstract] OR CRT [Title/Abstract] OR CRT-P [Title/Abstract] OR biventricular stimulation [Title/Abstract] OR biventricular pacing [Title/Abstract] OR (cardiac resynchronization therapy [Mesh] OR cardiac resynchronization) AND pacemaker [Title/Abstract]

				[Title/Abstract] OR AICD[Title/Abstract]		
		OR				
		(CRT-D OR CRT-ICD OR Lumax OR Iforia OR Ilesto OR Idova OR Livian OR "Contak Renewal" OR Incepta OR Energen OR Punctua OR Ovatio OR Consulta OR Maximo OR Insync OR Protecta OR Viva OR Brava OR Cardia OR Paradym OR Promote OR Epic OR Atlas OR Unify OR Quadra) [Title/Abstract]				
		OR				
		Pacemaker-defibrillator [Title/Abstract]				
		OR				
		cardiac resynchronization therapy, devices [Mesh]				

Yield: 376

EMBASE

Date: 27 February 2014

Filters: *Language:* English, Italian - *Species:* humans - *Time range:* none (2004-2014) - *Study design:* ('clinical trial'/de OR 'clinical trial (topic)'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'major clinical study'/de OR 'meta-analysis'/de OR 'multicenter study'/de OR 'observational study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'retrospective study'/de)

POPULATION		TECHONOLOGY				COMPARATOR
'heart failure'/exp OR 'heart ventricle tachycardia'/exp OR 'heart ventricle fibrillation'/exp OR	AND	'cardiac resynchronization therapy'/exp OR (cardiac AND resynchronization:ab,ti)	AND	defibrillator:ab,ti OR 'implantable cardioverter defibrillator'/exp OR icd:ab,ti OR	AND	'cardiac resynchronization therapy'/exp OR (cardiac AND resynchronization:ab,ti) OR

'heart ventricle function'/exp OR 'intraventricular conduction delay' OR 'cardiac dyssynchrony' OR (cardiac AND asynchrony) OR 'heart ejection fraction'/exp OR 'qrs interval'		OR crt:ab,ti OR (biventricular AND stimulation: ab,ti) OR (biventricular AND pacing:ab,t)		(automatic AND internal AND defibrillator: ab,ti) OR (implantable AND defibrillator: ab,ti) OR (automatic AND implantable AND cardioverter AND defibrillator: ab,ti) OR aicd:ab,ti		crt:ab,ti OR 'crt p':ab,ti OR (biventricular AND stimulation:ab,ti) OR (biventricular AND pacing:ab,ti) OR ('cardiac resynchronization therapy'/exp OR (cardiac AND resynchronization: ab,ti) AND pacemaker:ab,ti)
		OR				
		'crt d':ab,ti OR 'crt icd':ab,ti OR lumax:dn OR iforia:dn OR ilesto:dn OR idova:dn OR livian:dn OR 'contak renewal':dn OR incepta:dn OR energen:dn OR punctua:dn OR ovatio:dn OR consulta:dn OR maximo:dn OR insync:dn OR protecta:dn OR viva:dn OR brava:dn OR cardia:dn OR paradym:dn OR promote:dn OR epic:dn OR atlas:dn OR unify:dn OR quadra:dn				
		OR				
		'pacemaker defibrillator':ab,ti				
		OR				
		'cardiac resynchronization therapy device'/exp				

Yield: 630

Cochrane Library

Date: 28 febbraio 2014

Filters: *Time range:* 2004-2014 - *Study design:* trials

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<tr><td rowspan="3">Heart failure [Mesh descriptor]
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“Intraventricular conduction delay”
OR
“Cardiac dyssynchrony”
OR
Tachycardia, Ventricular [Mesh descriptor]
OR
Ventricular fibrillation [Mesh descriptor]
OR
Ventricular dysfunction [Mesh descriptor]
OR
cardiac asynchrony [Text Word]
OR
“Ejection fraction”:ti,ab,kw
OR
QRS interval:ti,ab,kw</td><td rowspan="3">AND</td><td>cardiac resynchronization therapy [Mesh descriptor]
OR
cardiac resynchronization:ti,ab,kw
OR
CRT:ti,ab,kw
OR
biventricular stimulation [Title/Abstrac]
OR
biventricular pacing [Title/Abstrac]</td><td>AND</td><td>Defibrillator:ti,ab,kw
OR
Defibrillators, Implantable [Mesh descriptor]
OR
ICD:ti,ab,kw
OR
automatic internal defibrillator:ti,ab,kw
OR
“implantable defibrillator”:ti,ab,kw
OR
Automatic implantable cardioverter defibrillator:ti,ab,kw
OR
AICD:ti,ab,kw</td><td rowspan="3">AND</td><td rowspan="3">cardiac resynchronization therapy [Mesh descriptor]
OR
cardiac resynchronization:ti,ab,kw
OR
CRT:ti,ab,kw
OR
CRT-P:ti,ab,kw
OR
biventricular stimulation:ti,ab,kw
OR
biventricular pacing:ti,ab,kw
OR
(cardiac resynchronization therapy [Mesh descriptor] OR cardiac resynchronization) AND pacemaker:ti,ab,kw</td></tr>
<tr><td colspan="3">OR</td></tr>
<tr><td colspan="3">(CRT-D OR CRT-ICD OR Lumax OR Iforia OR Ilesto OR Idova OR Livian OR “Contak Renewal” OR Incepta OR Energen OR Punctua OR Ovatio OR Consulta OR Maximo OR Insync OR Protecta OR Viva OR Brava OR Cardia OR Paradym OR Promote OR Epic OR Atlas OR Unify OR</td></tr>
</table>

		Quadra):ti,ab,kw		
		OR		
		Pacemaker-defibrillator:ti,ab,kw		
		OR		
		cardiac resynchronization therapy devices [Mesh descriptor]		

Yield: 110

Appendix 3 - Excluded studies

References to excluded studies

Prognostic studies (n=49)

Brenyo A, Barsheshet A, Rao M et al. Brain natriuretic peptide and cardiac resynchronization therapy in patients with mildly symptomatic heart failure. Circ Heart Fail 2013; 6(5):998-1004.

Diab IG, Hunter RJ, Kamdar R et al. Does ventricular dyssynchrony on echocardiography predict response to cardiac resynchronisation therapy? A randomised controlled study. Heart (British Cardiac Society) 2011; 97(17):1410-6.

Diaz-Infante E, Mont L, Leal J et al. Predictors of lack of response to resynchronization therapy. Am J Cardiol 2005; 95(12):1436-40.

El-Saed A, Voigt A, Shalaby A. Usefulness of brain natriuretic peptide level at implant in predicting mortality in patients with advanced but stable heart failure receiving cardiac resynchronization therapy. Clin Cardiol 2009; 32(11):E33-8.

Ellenbogen KA, Gold MR, Meyer TE et al. Primary results from the smartdelay determined AV optimization: A comparison to other AV delay methods used in cardiac resynchronization therapy (SMART-AV) trial: A randomized trial comparing empirical, echocardiography- guided, and algorithmic atrioventricular delay programming in cardiac resynchronization therapy. Circulation 2010; 122(25):2660-8.

Ellims AH, Pfluger H, Elsik M, Butler MJ, Hare JL, Taylor AJ. Utility of cardiac magnetic resonance imaging, echocardiography and electrocardiography for the prediction of clinical response and long-term survival following cardiac resynchronisation therapy. Int. J. Card. Imaging 2013; 29(6):1303-11.

Fantoni C, Regoli F, Ghanem A et al. Long-term outcome in diabetic heart failure patients treated with cardiac resynchronization therapy. Eur J Heart Fail 2008; 10(3):298-307.

Fauchier L, Poret P, Robin I et al. Different criteria of cardiac resynchronization therapy and their prognostic value for worsening heart failure or major arrhythmic events in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 2006; 97(3):393-9.

Gasparini M, Lunati M, Landolina M et al. Electrical storm in patients with biventricular implantable cardioverter defibrillator: Incidence, predictors, and prognostic implications. Am. Heart J. 2008; 156(5):847-54.

Gasparini M, Menozzi C, Proclemer A et al. A simplified biventricular defibrillator with fixed long detection intervals reduces implantable cardioverter defibrillator (ICD) interventions and heart failure hospitalizations in patients with non-ischaemic cardiomyopathy implanted for primary

prevention: the RELEVANT [Role of long detection window programming in patients with LEft VentriculAr dysfunction, Non-ischemic eTiology in primary prevention treated with a biventricular ICD] study. Eur Heart J 2009; 30(22):2758-67.

Gasparini M, Regoli F, Ceriotti C et al. Remission of left ventricular systolic dysfunction and of heart failure symptoms after cardiac resynchronization therapy: temporal pattern and clinical predictors. Am Heart J 2008; 155(3):507-14.

Giraldi F, Cattadori G, Roberto M et al. Long-term effectiveness of cardiac resynchronization therapy in heart failure patients with unfavorable cardiac veins anatomy: Comparison of surgical versus hemodynamic procedure. J. Am. Coll. Cardiol. 2011; 58(5):483-90.

Goldenberg I, Hall WJ, Beck CA et al. Reduction of the risk of recurring heart failure events with cardiac resynchronization therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). J Am Coll Cardiol 2011; 58(7):729-37.

Goldenberg I, Moss AJ, Hall WJ et al. Predictors of response to cardiac resynchronization therapy in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011; 124(14):1527-36.

Goldenberg I, Moss AJ, McNitt S et al. Relation between renal function and response to cardiac resynchronization therapy in Multicenter Automatic Defibrillator Implantation Trial--Cardiac Resynchronization Therapy (MADIT-CRT). Heart Rhythm : the Official Journal of the Heart Rhythm Society 2010; 7(12):1777-82.

Guha K, Mantziari L, Sharma R, McDonagh TA, Gibson D, Duncan AM. A reduction in total isovolumic time with cardiac resynchronisation therapy is a predictor of clinical outcomes. Int. J. Cardiol. 2013; 168(1):382-7.

Hsu JC, Solomon SD, Bourgoun M et al. Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) study. J. Am. Coll. Cardiol. 2012; 59(25):2366-73.

Knebel F, Schattke S, Bondke H et al. Implementation of seven echocardiographic parameters of myocardial asynchrony to improve the long-term response rate of cardiac resynchronization therapy (CRT). Cardiovasc. Ultrasound 2008; 6.

Kostic T, Perisic Z, Milic D et al. Long-term benefits of cardiac resynchronization therapy in heart failure patients. HealthMED 2012; 6(12):4113-9.

Kutyifa V, Kloppe A, Zareba W et al. The influence of left ventricular ejection fraction on the effectiveness of cardiac resynchronization therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). J Am Coll Cardiol 2013; 61(9):936-44.

Kutyifa V, Pouleur AC, Knappe D et al. Dyssynchrony and the risk of ventricular arrhythmias. JACC Cardiovasc Imaging 2013; 6(4):432-44.

Kutyifa V, Solomon SD, Bourgoun M et al. Effects of cardiac resynchronization therapy on left ventricular mass and wall thickness in mild heart failure patients in MADIT-CRT. Heart Rhythm 2013; 10(3):354-60.

Lepillier A, Piot O, Gerritse B et al. Relationship between New York Heart Association class change and ventricular tachyarrhythmia occurrence in patients treated with cardiac resynchronization plus defibrillator. Europace 2009; 11(1):80-5.

Leyva F, Foley PW, Chalil S, Irwin N, Smith RE. Female gender is associated with a better outcome after cardiac resynchronization therapy. Pacing Clin Electrophysiol 2011; 34(1):82-8.

Lim P, Donal E, Lafitte S et al. Multicentre study using strain delay index for predicting response to cardiac resynchronization therapy (MUSIC study). Eur. J. Heart Fail. 2011; 13(9):984-91.

Manfredi JA, Al-Khatib SM, Shaw LK et al. Association between left ventricular ejection fraction post-cardiac resynchronization treatment and subsequent implantable cardioverter defibrillator therapy for sustained ventricular tachyarrhythmias. Circ Arrhythm Electrophysiol 2013; 6(2):257-64.

Martin DT, McNitt S, Nesto RW, Rutter MK, Moss AJ. Cardiac resynchronization therapy reduces the risk of cardiac events in patients with diabetes enrolled in the multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy (MADIT-CRT). Circ. Heart Fail. 2011; 4(3):332-8.

Molhoek SG, Bax JJ, Boersma E et al. QRS duration and shortening to predict clinical response to cardiac resynchronization therapy in patients with end-stage heart failure. PACE Pacing Clin. Electrophysiol. 2004; 27(3):308-13.

Morani G, Gasparini M, Zanon F et al. Cardiac resynchronization therapy-defibrillator improves long-term survival compared with cardiac resynchronization therapy-pacemaker in patients with a class IA indication for cardiac resynchronization therapy: Data from the Contak Italian Registry. Europace 2013; 15(9):1273-9.

Olshansky B, Day JD, Sullivan RM, Yong P, Galle E, Steinberg JS. Does cardiac resynchronization therapy provide unrecognized benefit in patients with prolonged PR intervals? The impact of restoring atrioventricular synchrony: an analysis from the COMPANION Trial. Heart Rhythm 2012; 9(1):34-9.

Ouellet G, Huang DT, Moss AJ et al. Effect of cardiac resynchronization therapy on the risk of first and recurrent ventricular tachyarrhythmic events in MADIT-CRT. J Am Coll Cardiol 2012; 60(18):1809-16.

Pan W, Su Y, Zhu W, Shu X, Ge J. Notched QRS complex in lateral leads as a novel predictor of response to cardiac resynchronization therapy. Ann. Noninvasive Electrocardiol. 2013; 18(2):181-7.

Penn J, Goldenberg I, Moss AJ et al. Improved outcome with preventive cardiac resynchronization therapy in the elderly: A MADIT-CRT substudy. J. Cardiovasc. Electrophysiol. 2011; 22(8):892-7.

Pires LA, Abraham WT, Young JB, Johnson KM. Clinical predictors and timing of New York Heart Association class improvement with cardiac resynchronization therapy in patients with advanced chronic heart failure: Results from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) trials. Am. Heart J. 2006; 151(4):837-43.

Qiao Q, Ding L-G, Hua W, Chen K-P, Wang F-Z, Zhang S. Potential predictors of non-response and super-response to cardiac resynchronization therapy. Chin. Med. J. 2011; 124(9):1338-41.

Reynolds MR, Joventino LP, Josephson ME. Relationship of baseline electrocardiographic characteristics with the response to cardiac resynchronization therapy for heart failure. PACE Pacing Clin. Electrophysiol. 2004; 27(11):1513-8.

Rossi L, Malagoli A, Piepoli M et al. Indexed maximal left atrial volume predicts response to cardiac resynchronization therapy. Int. J. Cardiol. 2013; 168(4):3629-33.

Ruschitzka F, Abraham WT, Singh JP et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. New Engl. J. Med. 2013; 369(15):1395-405.

Schuchert A, Muto C, Maounis T et al. One-year outcome after CRT implantation in NYHA class IV in comparison to NYHA class III patients. Clin. Res. Cardiol. 2013; 102(7):505-11.

Shah RV, Altman RK, Park MY et al. Usefulness of hemoglobin A(1c) to predict outcome after cardiac resynchronization therapy in patients with diabetes mellitus and heart failure. Am J Cardiol 2012; 110(5):683-8.

Steffel J, Milosevic G, Hurlimann A et al. Characteristics and long-term outcome of echocardiographic super-responders to cardiac resynchronisation therapy: 'real world' experience from a single tertiary care centre. Heart 2011; 97(20):1668-74.

Taylor AJ, Elsik M, Broughton A et al. Combined dyssynchrony and scar imaging with cardiac magnetic resonance imaging predicts clinical response and long-term prognosis following cardiac resynchronization therapy. Europace 2010; 12(5):708-13.

Tian Y, Zhang P, Li X et al. True complete left bundle branch block morphology strongly predicts good response to cardiac resynchronization therapy. Europace 2013; 15(10):1499-506.

Versteeg H, van den Broek KC, Theuns DA et al. Effect of cardiac resynchronization therapy-defibrillator implantation on health status in patients with mild versus moderate symptoms of heart failure. Am J Cardiol 2011; 108(8):1155-9.

Wikstrom G, Blomstr^m-Lundqvist C, Andren B et al. The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE-HF trial. Eur Heart J 2009; 30(7):782-8.

Woo GW, Petersen-Stejskal S, Johnson JW, Conti JB, Aranda JA, Curtis AB. Ventricular reverse remodeling and 6-month outcomes in patients receiving cardiac resynchronization therapy: analysis of the MIRACLE study. Journal of Interventional Cardiac Electrophysiology : an International Journal of Arrhythmias and Pacing 2005; 12(2):107-13.

Ypenburg C, van Erven L, Bleeker GB et al. Benefit of Combined Resynchronization and Defibrillator Therapy in Heart Failure Patients With and Without Ventricular Arrhythmias. J. Am. Coll. Cardiol. 2006; 48(3):464-70.

Zareba W, Klein H, Cygankiewicz I et al. Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011; 123(10):1061-72.

Zhang Q, Chan Y-S, Liang Y-J et al. Comparison of left ventricular reverse remodeling induced by cardiac contractility modulation and cardiac resynchronization therapy in heart failure patients with different QRS durations. Int. J. Cardiol. 2013; 167(3):889-93.

Non comparative studies (n=38)

Achilli A, Turreni F, Gasparini M et al. Efficacy of cardiac resynchronization therapy in very old patients: The insync/insync ICD Italian registry. Europace 2007; 9(9):732-8.

Ahsan SY, Saberwal B, Lambiase PD et al. An 8-year single-centre experience of cardiac resynchronisation therapy: procedural success, early and late complications, and left ventricular lead performance. Europace 2013; 15(5):711-7.

Akyol A, Alper AT, Cakmak N et al. Long-term effects of cardiac resynchronization therapy on heart rate and heart rate variability. Tohoku J. Exp. Med. 2006; 209(4):337-46.

Alpendurada F, Guha K, Sharma R et al. Right ventricular dysfunction is a predictor of non-response and clinical outcome following cardiac resynchronization therapy. J. Cardiovasc. Magn. Reson. 2011; 13(1).

Ammann P, Kiencke S, Schaer B et al. Cardiac resynchronization in severe heart failure and left bundle branch block: A single centre experience. Swiss Med. Wkly 2004; 134(19-20):277-82.

Bhavnani SP, Pavuluri V, Coleman CI et al. The gender-paradox among patients with implantable cardioverter-defibrillators: a propensity-matched study. Pacing Clin Electrophysiol 2013; 36(7):878-84.

Boriani G, Biffi M, Muller CP et al. A prospective randomized evaluation of VV delay optimization in CRT-D recipients: echocardiographic observations from the RHYTHM II ICD study. Pacing Clin Electrophysiol 2009; 32 Suppl 1:S120-5.

Botto GL, Dicandia CD, Mantica M et al. Clinical characteristics, mortality, cardiac hospitalization, and ventricular arrhythmias in patients undergoing CRT-D implantation: results of the ACTION-HF study. J Cardiovasc Electrophysiol 2013; 24(2):173-81.

Boven NV, Bogaard K, Ruiter J et al. Functional response to cardiac resynchronization therapy is associated with improved clinical outcome and absence of appropriate shocks. J. Cardiovasc. Electrophysiol. 2013; 24(3):316-22.

Brambatti M, Guerra F, Matassini MV et al. Cardiac resynchronization therapy improves ejection fraction and cardiac remodelling regardless of patients' age. Europace 2013; 15(5):704-10.

Cabrera-Bueno F, Fernandez-Pastor J, Molina-Mora MJ et al. Combined resynchronization therapy and automatic defibrillator in advanced non-ischaemic heart failure: The importance of QRS width. Europace 2010; 12(1):92-5.

Carson P, Anand I, O'Connor C et al. Mode of death in advanced heart failure: the Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial. J Am Coll Cardiol 2005; 46(12):2329-34.

Chen JY, Tsai WC, Liu YW et al. Long-term effect of septal or apical pacing on left and right ventricular function after permanent pacemaker implantation. Echocardiography 2013; 30(7):812-9.

Cobb V, Thomas M, Ellery S et al. Cardiac resynchronisation therapy: A randomised trial of factory or echocardiographic settings for optimum response. Heart Lung Circul. 2013; 22(9):717-23.

Cortes Garcia M, Hernandez I, De La Cruz E et al. Results of cardiac resynchronisation therapy in a very elderly population. Eur. Heart J. 2013; 34:584.

Cortes M, Avila P, De La Cruz E et al. Usefulness of implantable cardioverter defibrillator therapy in patients aged over 75 years as compared with optimal medical therapy. J. Am. Coll. Cardiol. 2013; 61(10):E398.

Davis DR, Krahn AD, Tang ASL et al. Long-term outcome of cardiac resynchronization therapy in patients with severe congestive heart failure. Can. J. Cardiol. 2005; 21(5):413-7.

Faran A, Lewicka-Nowak E, Dabrowska-Kugacka A et al. Cardiac resynchronisation therapy in patients with end-stage heart failure - Long-term follow-up. Kardiol. Pol. 2008; 66(1):19-26.

Forleo GB, Mantica M, Di Biase L et al. Clinical and procedural outcome of patients implanted with a quadripolar left ventricular lead: early results of a prospective multicenter study. Heart Rhythm 2012; 9(11):1822-8.

Froehlich GM, Holzmeister JH, Hubler MH et al. Prophylactic implantable cardioverter-defibrillator treatment in patients with endstage heart failure listed for heart transplantation. Eur. J. Heart Fail. Suppl. 2012; 11:S88.

Fung JWH, Zhang Q, Yip GWK, Chan JYS, Chan HCK, Yu CM. Effect of cardiac resynchronization therapy in patients with moderate left ventricular systolic dysfunction and wide QRS complex: A prospective study. J. Cardiovasc. Electrophysiol. 2006; 17(12):1288-92.

Gasparini M, Lunati M, Santini M et al. Long-term survival in patients treated with cardiac resynchronization therapy: A 3-year follow-up study from the InSync/InSync ICD Italian registry. PACE Pacing Clin. Electrophysiol. 2006; 29(SUPPL. 2):S2-S10.

Gilliam FR 3rd, Kaplan AJ, Black J, Chase KJ, Mullin CM. Changes in heart rate variability, quality of life, and activity in cardiac resynchronization therapy patients: results of the HF-HRV registry. Pacing Clin Electrophysiol 2007; 30(1):56-64.

Herweg B, Ilercil A, Cutro R et al. Cardiac resynchronization therapy in patients with end-stage inotrope-dependent class IV heart failure. Am J Cardiol 2007; 100(1):90-3.

Jensen CJ, Liadski A, Bell M et al. Echocardiography versus intracardiac electrocardiography-based optimization for cardiac resynchronization therapy: A comparative clinical long-term trial. Herz 2011; 36(7):592-9.

Leon AR, Abraham WT, Brozena S et al. Cardiac resynchronization with sequential biventricular pacing for the treatment of moderate-to-severe heart failure. J. Am. Coll. Cardiol. 2005; 46(12):2298-304.

Marfella R, Di Filippo C, Potenza N et al. CirculatingmicroRNA changes in heart failure patients treated with cardiac resynchronization therapy: Responders vs. non-responders. Eur. J. Heart Fail. 2013; 15(11):1277-88.

Mullens W, Kepa J, De Vusser P et al. Importance of adjunctive heart failure optimization immediately after implantation to improve long-term outcomes with cardiac resynchronization therapy. Am J Cardiol 2011; 108(3):409-15.

Nazeri A, Massumi A, Rasekh A et al. Cardiac resynchronization therapy may improve symptoms of congestive heart failure in patients without electrical or mechanical dyssynchrony. Europace 2009; 11(1):86-8.

Reant P, Zaroui A, Donal E et al. Identification and characterization of super-responders after cardiac resynchronization therapy. Am J Cardiol 2010; 105(9):1327-35.

Saxon LA, Greenfield RA, Crandall BG, Nydegger CC, Orlov M, Van Genderen R. Results of the multicenter RENEWAL(registered trademark) 3 AVT clinical study of cardiac resynchronization defibrillator therapy in patients with paroxysmal atrial fibrillation. J. Cardiovasc. Electrophysiol. 2006; 17(5):520-5.

Shahrzad S, Soleiman NK, Taban S et al. The effect of Left Ventricular (LV) remodeling on ventricular arrhythmia in cardiac resynchronization therapy (CRT-D) patients (Antiarrhythmic Effect of CRT). PACE Pacing Clin. Electrophysiol. 2012; 35(5):592-7.

Soliman OI, Theuns DA, van Dalen BM et al. Prediction of appropriate defibrillator therapy in heart failure patients treated with cardiac resynchronization therapy. Am J Cardiol 2010; 105(1):105-11.

Theodorakis G, Katsikis A, Livanis E et al. Long term effects of cardiac resynchronization therapy in non-ambulatory NYHA IV heart failure patients. PACE Pacing Clin. Electrophysiol. 2011; 34(11):1553-60.

Theuns DA, Thornton AS, Klootwijk AP et al. Outcome in patients with an ICD incorporating cardiac resynchronisation therapy: differences between primary and secondary prophylaxis. Eur J Heart Fail 2005; 7(6):1027-32.

Thijssen J, Borleffs CJW, Delgado V et al. Implantable cardioverter-defibrillator patients who are upgraded and respond to cardiac resynchronization therapy have less ventricular arrhythmias compared with nonresponders. J. Am. Coll. Cardiol. 2011; 58(22):2282-9.

van Bommel RJ, Tanaka H, Delgado V et al. Association of intraventricular mechanical dyssynchrony with response to cardiac resynchronization therapy in heart failure patients with a narrow QRS complex. Eur Heart J 2010; 31(24):3054-62.

van Bommel RJ, van Rijnsoever E, Borleffs CJ et al. Effect of cardiac resynchronization therapy in patients with New York Heart Association functional class IV heart failure. Am J Cardiol 2010; 106(8):1146-51.

Studies with comparators not fitting inclusion criteria (n=22)

Adelstein E, Bhattacharya S, Simon MA, Gorcsan J 3rd, Saba S. Comparison of outcomes for patients with nonischemic cardiomyopathy taking intravenous inotropes versus those weaned from or never taking inotropes at cardiac resynchronization therapy. Am J Cardiol 2012; 110(6):857-61.

Albertsen AE, Mortensen PT, Jensen HK, Poulsen SH, Egeblad H, Nielsen JC. Adverse effect of right ventricular pacing prevented by biventricular pacing during long-term follow-up: a randomized comparison. Eur J Echocardiogr 2011; 12(10):767-72.

Beshai JF, Grimm RA, Nagueh SF et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. New Engl. J. Med. 2007; 357(24):2461-71.

Bhattacharya S, Abebe K, Simon M, Saba S, Adelstein E. Role of cardiac resynchronization in end-stage heart failure patients requiring inotrope therapy. J. Card. Fail. 2010; 16(12):931-7.

Boriani G, Kranig W, Donal E et al. A randomized double-blind comparison of biventricular versus left ventricular stimulation for cardiac resynchronization therapy: the Biventricular versus Left Univentricular Pacing with ICD Back-up in Heart Failure Patients (B-LEFT HF) trial. Am Heart J 2010; 159(6):1052-8.e1.

Boriani G, M¸ller CP, Seidl KH et al. Randomized comparison of simultaneous biventricular stimulation versus optimized interventricular delay in cardiac resynchronization therapy. The

Resynchronization for the HemodYnamic Treatment for Heart Failure Management II implantable cardioverter defibrillator (RHYTHM II ICD) study. Am Heart J 2006; 151(5):1050-8.

Boriani G, Rapezzi C, Diemberger I et al. Trial-generated profiles for implantation of electrical devices in outpatients with heart failure: real-world prevalence and 1-year outcome. J Eval Clin Pract 2010; 16(1):82-91.

Borleffs CJW, Ypenburg C, van Bommel RJ et al. Clinical importance of new-onset atrial fibrillation after cardiac resynchronization therapy. Heart Rhythm 2009; 6(3):305-10.

Burger H, Kempfert J, van Linden A et al. Endurance and performance of two different concepts for left ventricular stimulation with bipolar epicardial leads in long-term follow-up. Thorac Cardiovasc Surg 2012; 60(1):70-7.

Castel MA, Magnani S, Mont L et al. Survival in New York Heart Association class IV heart failure patients treated with cardiac resynchronization therapy compared with patients on optimal pharmacological treatment. Europace 2010; 12(8):1136-40.

Curtis AB, Worley SJ, Adamson PB et al. Biventricular versus right ventricular pacing in patients with left ventricular dysfunction and atrioventricular block (BLOCK HF study). Circulation 2012; 126(23):2785.

Daubert C, Gold MR, Abraham WT et al. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. J Am Coll Cardiol 2009; 54(20):1837-46.

De Marco T, Wolfel E, Feldman AM et al. Impact of cardiac resynchronization therapy on exercise performance, functional capacity, and quality of life in systolic heart failure with QRS prolongation: COMPANION trial sub-study. J Card Fail 2008; 14(1):9-18.

Gasparini M, Bocchiardo M, Lunati M et al. Comparison of 1-year effects of left ventricular and biventricular pacing in patients with heart failure who have ventricular arrhythmias and left bundle-branch block: The Bi vs Left Ventricular Pacing: An International Pilot Evaluation on Heart Failure Patients with Ventricular Arrhythmias (BELIEVE) multicenter prospective randomized pilot study. Am. Heart J. 2006; 152(1):155.e1-155.e7.

Grosu A, Senni M, Iacovoni A et al. CArdiac resynchronization in combination with beta blocker treatment in advanced chronic heart failure (CARIBE-HF): the results of the CARIBE-HF study. Acta Cardiol 2011; 66(5):573-80.

Landolina M, Lunati M, Gasparini M et al. Comparison of the effects of cardiac resynchronization therapy in patients with class II versus class III and IV heart failure (from the InSync/InSync ICD Italian Registry). Am J Cardiol 2007; 100(6):1007-12.

Leclercq C, Gras D, Tang A, Alonso C, Thomas-Revault D'Allones F, Mabo P. Comparative effects of ventricular resynchronization therapy in heart failure patients with or without coronary artery disease. Ann. Cardiol. Angeiol. 2004; 53(4):171-6.

Lee DS, Gula L, Mangat I et al. Outcomes of primary prevention implantable cardioverter defibrillator (ICD) recipients with vs without clinical trial entry criteria: Observations from a comprehensive provincial icd registry. Can. J. Cardiol. 2011; 27(5):S294.

Linde C, Abraham WT, Gold MR, Daubert C. Cardiac resynchronization therapy in asymptomatic or mildly symptomatic heart failure patients in relation to etiology: Results from the reverse (REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction) study. J. Am. Coll. Cardiol. 2010; 56(22):1826-31.

Martin DO, Day JD, Lai PY et al. Atrial support pacing in heart failure: results from the multicenter PEGASUS CRT trial. J Cardiovasc Electrophysiol 2012; 23(12):1317-25.

Padeletti L, Muto C, Maounis T et al. Atrial fibrillation in recipients of cardiac resynchronization therapy device: 1-year results of the randomized MASCOT trial. Am. Heart J. 2008; 156(3):520-6.

Tereshchenko LG, Henrikson CA, Stempniewicz P, Han L, Berger RD. Antiarrhythmic effect of reverse electrical remodeling associated with cardiac resynchronization therapy. Pacing Clin Electrophysiol 2011; 34(3):357-64.

Retrospective studies (n=17)

Agarwal SK, Singla I, Hreybe H, Saba S. Predictors of mortality amongst recipients of implantable cardioverter defibrillators for secondary prevention of cardiac arrest. Indian Pacing Electrophysiol. J. 2007; 7(4):218-24.

Ajijola OA, Macklin EA, Moore SA et al. Inpatient vs. elective outpatient cardiac resynchronization therapy device implantation and long-term clinical outcome. Europace 2010; 12(12):1745-9.

Bank AJ, Burns KV, Gage RM et al. Cardiac resynchronization therapy in the real world: comparison with the COMPANION study. J Card Fail 2012; 18(2):153-8.

Bonanno C, Ometto R, Pasinato S, Finocchi G, La Vecchia L, Fontanelli A. Effects of cardiac resynchronization therapy on disease progression in patients with congestive heart failure. Ital Heart J 2004; 5(5):364-70.

Chen Z, Kotecha T, Crichton S et al. Lower incidence of inappropriate shock therapy in patients with combined cardiac resynchronisation therapy defibrillators (CRT-D) compared with patients with non-CRT defibrillators (ICDs). Int. J. Clin. Pract. 2013; 67(8):733-9.

Curtis AB, Yancy CW, Albert NM et al. Cardiac resynchronization therapy utilization for heart failure: findings from IMPROVE HF. Am Heart J 2009; 158(6):956-64.

Ermis C, Lurie KG, Zhu AX et al. Biventricular implantable cardioverter defibrillators improve survival compared with biventricular pacing alone in patients with severe left ventricular dysfunction. J. Cardiovasc. Electrophysiol. 2004; 15(8):862-6.

Frohlich GM, Holzmeister J, Hubler M et al. Prophylactic implantable cardioverter defibrillator treatment in patients with end-stage heart failure awaiting heart transplantation. Heart 2013; 99(16):1158-65.

Ghali JK, Boehmer J, Feldman AM et al. Influence of diabetes on cardiac resynchronization therapy with or without defibrillator in patients with advanced heart failure. J Card Fail 2007; 13(9):769-73.

Killu AM, Wu J-H, Friedman PA et al. Outcomes of cardiac resynchronization therapy in the elderly. PACE Pacing Clin. Electrophysiol. 2013; 36(6):664-72.

Leong DP, Hoke U, Delgado V et al. Right ventricular function and survival following cardiac resynchronisation therapy. Heart 2013; 99(10):722-8.

Lin G, Rea RF, Hammill SC, Hayes DL, Brady PA. Effect of cardiac resynchronisation therapy on occurrence of ventricular arrhythmia in patients with implantable cardioverter defibrillators undergoing upgrade to cardiac resynchronisation therapy devices. Heart 2008; 94(2):186-90.

Markowitz SM, Lewen JM, Wiggenhorn CJ et al. Relationship of reverse anatomical remodeling and ventricular arrhythmias after cardiac resynchronization. J. Cardiovasc. Electrophysiol. 2009; 20(3):293-8.

Palmieri V, Pezzullo S, Coltorti F et al. Cardiac resynchronization therapy: Mortality, rehospitalization and implant-related complications. Three-year single-center observational study within the National Health System: Resincronizzazione cardiaca: Morte, riospedalizzazione e complicanze correlate all'impianto. Studio osservazionale triennale in un singolo centro del Sistema Sanitario Nazionale. G. Ital. Cardiol. 2012; 13(5):369-76.

Pescariu S, Brie D, Dumitrescu A et al. Is cardiac resynchronization therapy useful in patients with end-stage heart failure patients inotrope-supported? Eur. J. Heart Fail. Suppl. 2011; 10:S122.

Peterson PN, Greiner MA, Qualls LG et al. QRS duration, bundle-branch block morphology, and outcomes among older patients with heart failure receiving cardiac resynchronization therapy. JAMA 2013; 310(6):617-26.

Tabereaux PB, Doppalapudi H, Kay GN, McElderry HT, Plumb VJ, Epstein AE. Limited response to cardiac resynchronization therapy in patients with concomitant right ventricular dysfunction. J. Cardiovasc. Electrophysiol. 2010; 21(4):431-5.

Studies reporting no data (n=7)

Achilli A, Sassara M, Pontillo D et al. In the light of trials data on CRT, should the defibrillator be always associated with a biventricular stimulator? Mediterr. J. Pacing Electrophysiol. 2006; 8(1-2):1-6.

Aronow WS. CRT plus ICD in congestive heart failure: Use of cardiac resynchronization therapy and an implantable cardioverter-defibrillator in heart failure patients with abnormal left ventricular dysfunction. Geriatrics 2005; 60(2):24-8.

Cleland JGF, Coletta AP, Freemantle N, Clark AL. Clinical trials update from the American College of Cardiology Meeting 2011: STICH, NorthStar, TARGET, and EVEREST II. Eur. J. Heart Fail. 2011; 13(7):805-8.

Cleland JGF, Coletta AP, Lammiman M et al. Clinical trials update from the European Society of Cardiology meeting 2005: CARE-HF extension study, ESSENTIAL, CIBIS-III, S-ICD, ISSUE-2, STRIDE-2, SOFA, IMAGINE, PREAMI, SIRIUS-II and ACTIVE. Eur. J. Heart Fail. 2005; 7(6):1070-5.

Cleland JGF, Coletta AP, Yassin A, Buga L, Torabi A, Clark AL. Clinical trials update from the European Society of Cardiology Meeting 2009: AAA, RELY, PROTECT, ACTIVE-I, European CRT survey, German pre-SCD II registry, and MADIT-CRT. Eur. J. Heart Fail. 2009; 11(12):1214.

Cleland JGF, Coletta AP, Yassin A et al. Clinical trials update from the American College of Cardiology 2008: CARISMA, TRENDS, meta-analysis of Cox-2 studies, HAT, ON-TARGET, HYVET, ACCOMPLISH, MOMENTUM, PROTECT, HORIZON-HF and REVERSE. Eur. J. Heart Fail. 2008; 10(6):614-20.

Dichtl W, Strohmer B, Fruhwald F. Clinical outcome after 1 year of cardiac resynchronisation therapy: National results from the European CRT survey. Wien. Klin. Wochenschr. 2013; 125(23-24):750-4.

Secondary pubblication studies (n=6)

Cleland JGF, Freemantle N, Erdmann E et al. Long-term mortality with cardiac resynchronization therapy in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial. Eur. J. Heart Fail. 2012; 14(6):628-34.

Elanchenny M, Moss AJ, McNitt S et al. Effectiveness of cardiac resynchronization therapy with defibrillator in at-risk black and white cardiac patients. Ann Noninvasive Electrocardiol 2013; 18(2):140-8.

Gold MR, Daubert J-C, Abraham WT et al. Implantable defibrillators improve survival in patients with mildly symptomatic heart failure receiving cardiac resynchronization therapy analysis of the long-term follow-up of remodeling in systolic left ventricular dysfunction (reverse). Circ. Arrhythmia Electrophysiol. 2013; 6(6):1163-8.

Kron J, Aranda JM, Miles WM et al. Benefit of cardiac resynchronization in elderly patients: results from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) trials. Journal of Interventional Cardiac Electrophysiology : an International Journal of Arrhythmias and Pacing 2009; 25(2):91-6.

Lindenfeld J, Feldman AM, Saxon L et al. Effects of cardiac resynchronization therapy with or without a defibrillator on survival and hospitalizations in patients with New York Heart Association class IV heart failure. Circulation 2007; 115(2):204-12.

Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). Circulation 2006; 113(2):266-72.

Economic evaluations (n=4)

Aidelsburger P, Grabein K, Klauss V, Wasem J. Cost-effectiveness of cardiac resynchronization therapy in combination with an implantable cardioverter defibrillator (CRT-D) for the treatment of chronic heart failure from a German health care system perspective. Clin Res Cardiol 2008; 97(2):89-97.

Linde C, Mealing S, Hawkins N, Eaton J, Brown B, Daubert JC. Cost-effectiveness of cardiac resynchronization therapy in patients with asymptomatic to mild heart failure: insights from the European cohort of the REVERSE (Resynchronization Reverses remodeling in Systolic Left Ventricular Dysfunction). Eur Heart J 2011; 32(13):1631-9.

Wells GA, Coyle D, Coyle K, Talajic M, Tang A. Cost effectiveness of cardiac resynchronization therapy (CRT) for mild to moderate heart failure. Can. J. Cardiol. 2012; 28(5):S419.

Wells GA, Coyle D, Nichol G, Coyle K, Talajic M, Tang A. Cost effectiveness of cardiac resynchronization therapy (CRT) for mild to moderate heart failure. Heart Rhythm 2012; 9(5):S71.

Studies with missing abstract (n=2)

Breithardt G. MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy): Cardiac resynchronization therapy towards early management of heart failure. Eur. Heart J. 2009; 30(21):2551-3.

Gasparini M, Auricchio A, Regoli F et al. Four-year efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: the importance of performing atrioventricular junction ablation in patients with atrial fibrillation. J Am Coll Cardiol 2006; 48(4):734-43.

Imaging studies (n=2)

Alikhani Z, Li J, Merchan JA, Nijhof N, Mendel J, Orlov MV. Coronary sinus anatomy by computerized tomography, overlaid on live fluoroscopy can be successfully used to guide left

ventricular lead implantation: a feasibility study. J Interv Card Electrophysiol 2013; 36(3):217-22.

Bleeker GB, Schalij MJ, Boersma E et al. Relative Merits of M-Mode Echocardiography and Tissue Doppler Imaging for Prediction of Response to Cardiac Resynchronization Therapy in Patients With Heart Failure Secondary to Ischemic or Idiopathic Dilated Cardiomyopathy. Am. J. Cardiol. 2007; 99(1):68-74.

Upgrading study (n=1)

Bogale N, Witte K, Priori S et al. The European Cardiac Resynchronization Therapy Survey: comparison of outcomes between de novo cardiac resynchronization therapy implantations and upgrades. Eur J Heart Fail 2011; 13(9):974-83.

Earlier version of previous study (n=1)

Linde C, Abraham WT, Gold MR, John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008; 52(23):1834-43.

Appendix 4 – Primary studies

Abraham WT, Young JB, Leon AR et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. Circulation 2004; 110(18):2864-8.

Anand IS, Carson P, Galle E et al. Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure: results from the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial. Circulation 2009; 119(7):969-77.

Arshad A, Moss AJ, Foster E et al. Cardiac resynchronization therapy is more effective in women than in men: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. J Am Coll Cardiol 2011; 57(7):813-20.

Arslan Z, Tanabe K, Bhamre S et al. Percent pacing in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) study. Heart Rhythm 2012; 9(5):S374.

Auricchio A, Metra M, Gasparini M et al. Long-term survival of patients with heart failure and ventricular conduction delay treated with cardiac resynchronization therapy. Am J Cardiol 2007; 99(2):232-8.

Bai R, Biase L, Elayi C et al. Mortality of heart failure patients after cardiac resynchronization therapy: identification of predictors. J Cardiovasc Electrophysiol 2008; 19(12):1259-65.

Barsheshet A, Goldenberg I, Moss AJ et al. Response to preventive cardiac resynchronization therapy in patients with ischaemic and nonischaemic cardiomyopathy in MADIT-CRT. Eur Heart J 2011; 32(13):1622-30.

Barsheshet A, Moss AJ, Eldar M et al. Time-dependent benefit of preventive cardiac resynchronization therapy after myocardial infarction. Eur Heart J 2011; 32(13):1614-21.

Barsheshet A, Moss AJ, McNitt S et al. Long-term implications of cumulative right ventricular pacing among patients with an implantable cardioverter-defibrillator. Heart Rhythm : the Official Journal of the Heart Rhythm Society 2011; 8(2):212-8.

Barsheshet A, Wang PJ, Moss AJ et al. Reverse remodeling and the risk of ventricular tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). J Am Coll Cardiol 2011; 57(24):2416-23.

Becker M, Erdmann N, Stegemann E et al. Survival and quality of life in patients with cardiac resynchronization therapy for severe heart failure and in heart transplant recipients within a contemporary heart failure management program. J Heart Lung Transplant 2008; 27(7):746-52.

Birnie DH, Ha A, Higginson L et al. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: Results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). Circ Heart Fail 2013; 6(6):1190-8.

Blaschke F, Knaus T, Celebi O et al. Ventricular tachycardia or ventricular fibrillation occurs less often in patients with left bundle branch block and combined resynchronization and defibrillators than in patients with narrow QRS and conventional defibrillators. Europace 2012; 14(2):224-9.

Bllchlck KC, Stukenborg GJ. Comparative effectiveness of CRT-D in medicare patients strongly depends on heart failure class. Heart Rhythm 2013; 10(5):S368-S369.

Boidol J, Sredniawa B, Kowalski O et al. Many response criteria are poor predictors of outcomes after cardiac resynchronization therapy: validation using data from the randomized trial. Europace 2013; 15(6):835-44.

Brenyo A, Goldenberg I, Moss AJ et al. Baseline functional capacity and the benefit of cardiac resynchronization therapy in patients with mildly symptomatic heart failure enrolled in MADIT-CRT. Heart Rhythm 2012; 9(9):1454-9.

Brenyo A, Kutyifa V, Moss AJ et al. Atrioventricular delay programming and the benefit of cardiac resynchronization therapy in MADIT-CRT. Heart Rhythm 2013; 10(8):1136-43.

Brenyo A, Link MS, Barsheshet A et al. Cardiac resynchronization therapy reduces left atrial volume and the risk of atrial tachyarrhythmias in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). J Am Coll Cardiol 2011; 58(16):1682-9.

Brenyo A, Rao M, Barsheshet A et al. QRS axis and the benefit of cardiac resynchronization therapy in patients with mildly symptomatic heart failure enrolled in MADIT-CRT. J. Cardiovasc. Electrophysiol. 2013; 24(4):442-8.

Bristow MR, Saxon LA, Boehmer J et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004; 350(21):2140-50.

Buber J, Klein H, Moss AJ et al. Clinical course and outcome of patients enrolled in US and non-US centres in MADIT-CRT. Eur Heart J 2011; 32(21):2697-704.

Cleland JGF, Daubert J-C, Erdmann E et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. New Engl. J. Med. 2005; 352(15):1539-49.

Cleland JG, Daubert JC, Erdmann E et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. Eur Heart J 2006; 27(16):1928-32.

Curtis AB, Worley SJ, Adamson PB et al. Biventricular pacing for atrioventricular block and systolic dysfunction. New Engl. J. Med. 2013; 368(17):1585-93.

Healey JS, Hohnloser SH, Exner DV et al. Cardiac resynchronization therapy in patients with permanent atrial fibrillation: results from the Resynchronization for Ambulatory Heart Failure Trial (RAFT). Circulation. Heart Failure 2012; 5(5):566-70.

Knappe D, Pouleur AC, Shah AM et al. Dyssynchrony, contractile function, and response to cardiac resynchronization therapy. Circ Heart Fail 2011; 4(4):433-40.

Moss AJ, Hall WJ, Cannom DS et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. New Engl. J. Med. 2009; 361(14):1329-38.

Muto C, Solimene F, Gallo P et al. A randomized study of cardiac resynchronization therapy defibrillator versus dual-chamber implantable cardioverter-defibrillator in ischemic cardiomyopathy with narrow QRS: the NARROW-CRT study. Circ Arrhythm Electrophysiol 2013; 6(3):538-45.

Pinter A, Mangat I, Korley V et al. Assessment of resynchronization therapy on functional status and quality of life in patients requiring an implantable defibrillator. Pacing and Clinical Electrophysiology : PACE 2009; 32(12):1509-19.

Pouleur AC, Knappe D, Shah AM et al. Relationship between improvement in left ventricular dyssynchrony and contractile function and clinical outcome with cardiac resynchronization therapy: the MADIT-CRT trial. Eur Heart J 2011; 32(14):1720-9.

Schuchert A, Muto C, Maounis T et al. Lead complications, device infections, and clinical outcomes in the first year after implantation of cardiac resynchronization therapy-defibrillator and cardiac resynchronization therapy-pacemaker. Europace 2013; 15(1):71-6.

Tang AS, Wells GA, Talajic M et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010; 363(25):2385-95.

van Geldorp IE, Vernooy K, Delhaas T et al. Beneficial effects of biventricular pacing in chronically right ventricular paced patients with mild cardiomyopathy. Europace 2010; 12(2):223-9.

Veazie PJ, Noyes K, Li Q et al. Cardiac resynchronization and quality of life in patients with minimally symptomatic heart failure. J Am Coll Cardiol 2012; 60(19):1940-4.

Appendix 5 - Included Systematic reviews and Meta Analysis

Abdulla J, Haarbo J, Kober L, Torp-Pedersen C. Impact of implantable defibrillators and resynchronization therapy on outcome in patients with left ventricular dysfunction - A meta-analysis. Cardiology 2006; 106(4):249-55.

Bertoldi EG, Polanczyk CA, Cunha V, Ziegelmann PK, Beck-Da-Silva L, Rohde LE. Mortality reduction of cardiac resynchronization and implantable cardioverter-defibrillator therapy in heart failure: An updated meta-analysis. does recent evidence change the standard of care? J. Card. Fail. 2011; 17(10):860-6.

Chen S, Ling Z, Kiuchi MG, Yin Y, Krucoff MW. The efficacy and safety of cardiac resynchronization therapy combined with implantable cardioverter defibrillator for heart failure: A meta-analysis of 5674 patients. Europace 2013; 15(7):992-1001.

Chen S, Yin Y, Krucoff MW. Effect of cardiac resynchronization therapy and implantable cardioverter defibrillator on quality of life in patients with heart failure: A meta-analysis. Europace 2012; 14(11):1602-7.

Cleland JGF, Abraham WT, Linde C et al. An individual patient meta-analysis of randomized trials assessing the effects of CRT and CRT-D in heart failure in sinus rhythm with a prolonged QRS duration and left ventricular systolic dysfunction. Eur. J. Heart Fail. 2013; 12:S8.

Jiang M, He B, Zhang Q. Comparison of CRT and CRT-D in heart failure: Systematic review of controlled trials. Int. J. Cardiol. 2012; 158(1):39-45.

Lam SKH, Owen A. Combined resynchronisation and implantable defibrillator therapy in left ventricular dysfunction: Bayesian network meta-analysis of randomised controlled trials. Br. Med. J. 2007; 335(7626):925-8.

Wells G, Parkash R, Healey JS et al. Cardiac resynchronization therapy: a meta-analysis of randomized controlled trials. CMAJ 2011; 183(4):421-9.

Appendix 6 - Synopsis of included systematic reviews and meta-analysis

Serial	Study ID	Population	Intervention	Control	Outcome	Design (date of searches)	Results	Conclusion	Quality AMSTAR	Notes
1	Abdulla J et al. Cardiology 2006;106:249–255	LVSD	CRT ICD ICD+CRT	CRT vs No CRT (univentricular pacemaker or conventional pharmacologic therapy) primary prophylactic ICD vs. No ICD (conventional pharmacologic or antiarrhythmic therapy) ICD+CRT vs no ICD	Mortality and Hospitalization for Heart Failure Functional Status	Meta-analysis of parallel or cross-over randomized controlled or controlled studies: only studies with a treatment period of at least one month were selected. (June 2005)	20 parallel or cross-over controlled trials (two studiesw were not randomised) (10853 participants)	CRT reduced all cause mortality and hospitalization for heart failure and improved New York Heart Association class . Implantation of ICD reduced all-cause mortality and cardiac mortality. Adding ICD to CRT reduced all cause mortality.	11/11	Brief reporting but ICD benefits may in part be due to the young age group of recipients in the ten relevant trials
2	Lam SKH et al, 2007 doi:10.1136/bmj.39343.511389.BE	LVSD (ejection fraction <35%);	ICD CRT CRT-D	ICD vs CRT-D CRT vs CRT-D CRT-D vs medical therapy	Mortality	Bayesian network meta-analysis. (June 2006)	12 studies including 1636 events in 8307 patients	Evidence is insufficient to show the superiority of combined cardiac resynchronisation and implantable cardioverter defibrillator therapy over cardiac resynchronisation therapy alone in patients with left ventricular impairment.	11/11	
3	Wells G et al. CMAJ 2011. DOI:10.1503/cmaj.101685	mildly symptomatic or advanced heart failure, with a QRS interval of more than 120 ms.	CRT CRT-D	CRT vs optimal medical therapy CRT-D vs ICD	mortality	randomized trials using a parallel or crossover design. (December 2010)	12 studies (n = 7538) were included in meta-analysis.	the addition of cardiac resynchronization to optimal medical therapy or defibrillator therapy significantly reduces mortality among patients with heart failure. Superiority of CRT+ICD vs ICD remained significant among patients with New York Heart Association (NYHA) class I or II disease (RR 0.80, 95% CI 0.67–0.96) but not among those with class III or IV disease (RR 0.84, 95% CI 0.69–1.07).	11/11	
4	Bertoldi J et al Cardiac Fail 2011;17:860	LVSD and HF		CRT CRT-D ICD Medical therapy	all-cause mortality.	all randomized controlled trials reported in Medline, Embase, and the	Twelve studies were included, with a total of 8,284 randomized patients.	Combined CRT and ICD therapy reduces overall mortality in HF patients when compared with ICD alone.	11/11	

Serial	Study ID	Population	Intervention	Control	Outcome	Design (date of searches)	Results	Conclusion	Quality AMSTAR	Notes
	e866					Cochrane Library databases. (NR in main text)				
5	Chen S et al Europace 2012; 14, 1602–1607 doi:10.1093/europace/eus168	HF, LVEF ≤35%, QRS duration ≥120 ms;	ICD CRT-D	CRT-D vs ICD	QoL	randomized controlled trials (RCTs) published studies up to 31 December 2011 in Medline, Embase, The Cochrane Library, and US Food and Drug Administration website. (December 2011)	Four RCTs with 1655 patients were included in this meta-analysis.	CRT-D therapy improves the QoL compared with ICD therapy alone, especially in patients with moderate to severe heart failure.	11/11	
6	Jiang M et al, International Journal of Cardiology 158 (2012) 39–45	LVSD(ejection fraction >35%) and a wide QRS complex (QRS duration N120 ms)	CRT CRT-D	CRT-D vs CRT	all-cause death rate.	randomised and non-randomised trials of Medline database from 1970 to September 2010. (September 2010)	A total of 3404 patients were retrieved from seven studies	Superiority of CRT-D over CRT, such as all-cause death rate after one-year follow-up	11/11	However, these findings must be verified in larger, randomised, prospective trials, including with extended patient follow-up.
7	Cleland JG European Heart Journal (2013) 34, 3547–3556	LVSD HF	CRT CRT-D	CRT-D vs CRT	all-cause mortality hospitalization for HF.	An individual patient meta-analysis of five randomized trials, funded by Medtronic Inc>6months of follow up. (CARE-HF, MIRACLE, REVERSE or CRT-D with ICD, RAFT) (Studies published 2002-2010)	3782 patients	QRS duration is a powerful predictor of the effects of CRT on morbidity and mortality in patients with symptomatic HF and left ventricular systolic dysfunction who are in sinus rhythm. QRSmorphology did not provide additional information about clinical response.	11/11	Funded by Medtronic Inc.
8	Chen S et al. Europace 2013; 15 (7): 1532-2092	HF, LVEF <=35% and QRS duration >= 120	ICD CRT-D	CRT-D vs ICD	Mortality, hospitalization, improvement clinical conditions, pre-implantation adverse events	From Medline, Embase, The Cochrane Library, and US Food and Drug Administration: Randomized trials enrolling > 50 Pts. (May 2012)	8 randomized study selected: 5674 Participants included.	CRT-D had less hospitalizations and all-cause mortality	11/11	

Appendix 7 - Search Strategy – Economic literature

MEDLINE

Date: 11 March 2014
Limits: Humans, Publication Date from 2004/01/01 to date, English and Italian

<table>
<tr><th colspan="3">Health technology</th><th></th><th>Study design</th></tr>
<tr><td>cardiac resynchronization therapy [Mesh]
OR cardiac resynchronization therapy, devices [Mesh]
OR
CRT [Title/Abstract]
OR
“biventricular stimulation” [Title/Abstract]
OR
“biventricular pacing” [Title/Abstract]</td><td>AND</td><td>Defibrillator [Title/Abstract]
OR
implantable cardioverter defibrillators [Mesh]
OR
ICD [Title/Abstract]
OR
“automatic internal defibrillator” [Title/Abstract]
OR
“implantable defibrillator” [Title/Abstract]
OR
Automatic implantable cardioverter defibrillator [Title/Abstract]
OR
AICD[Title/Abstract]</td><td rowspan="3">AND</td><td rowspan="3">(Cost [title/abstract] AND analysis [title/abstract])
OR
(“cost minimization” [title/abstract] OR CMA [title/abstract])
OR
(“cost effectiveness” [title/abstract] OR CEA [title/abstract])
OR
(“cost utility” [title/abstract] OR CUA [title/abstract])
OR
(“health care” [Text Word] AND cost*[Text Word])
OR
(economic [Text Word] AND (evaluation OR analysis OR aspect OR assessment) [Text Word])
OR
“Budget Impact Analysis” [title/abstract]
OR
BIA [title/abstract]</td></tr>
<tr><td colspan="3">OR</td></tr>
<tr><td colspan="3">(CRT-D OR CRT-ICD OR Pacemaker-defibrillator OR Lumax OR Iforia OR Ilesto OR Idova OR Livian OR “Contak Renewal” OR Incepta OR Energen OR Punctua OR Ovatio OR Consulta OR Maximo OR Insync OR Protecta OR Viva OR Brava OR Cardia OR Paradym OR Promote OR Epic OR Atlas OR Unify OR Quadra) [Title/Abstract]</td></tr>
</table>

Yield: 23

EMBASE

Date: 12 March 2014
Limits: Humans, Publication Date from 2004 to date, English and Italian

Health technology				Study design
'cardiac resynchronization therapy'/exp OR 'cardiac resynchronization therapy, devices'/exp OR CRT:ab,ti OR 'biventricular stimulation':ab,ti OR 'biventricular pacing':ab,ti	AND	defibrillator:ab,ti OR 'implantable cardioverter defibrillator'/mj OR ICD:ab,ti OR 'automatic internal defibrillator':ab,ti OR 'implantable defibrillator':ab,ti OR (automatic AND implantable AND cardioverter AND defibrillator:ab,ti) OR AICD:ab,ti	AND	'cost analysis'/exp OR ('cost minimization':ab,ti OR CMA:ab,ti) OR ('cost effectiveness':ab,ti OR cea:ab,ti) OR ('cost utility':ab,ti OR cua:ab,ti) OR 'health care'/exp AND cost* OR (economic AND ('evaluation'/exp OR 'analysis'/exp OR aspect OR assessment)) OR ('budget impact analysis':ab,ti OR bia:ab,ti)
OR				
('crt d':ab,ti OR 'crt icd':ab,ti OR 'pacemakerdefibrillator':ab,ti) OR (lumax:dn OR iforia:dn OR ilesto:dn OR idova:dn OR livian:dn OR 'contak renewal':dn OR incepta:dn OR energen:dn OR punctua:dn OR ovatio:dn OR consulta:dn OR maximo:dn OR insync:dn OR protecta:dn OR viva:dn OR brava:dn OR cardia:dn OR paradym:dn OR promote:dn OR epic:dn OR atlas:dn OR unify:dn OR quadra:dn)				

Yield: 289

Cochrane library

Date: 13 March 2014
Limits: Publication Date from 2004 to date

<table>
<tr><th colspan="3">Health technology</th><th></th><th>Study design</th></tr>
<tr><td>MeSH descriptor: [Cardiac Resynchronization Therapy] explode all trees
OR
MeSH descriptor: [Cardiac Resynchronization Therapy Devices] explode all trees
OR
CRT:ti,ab,kw
OR
'biventricular stimulation':ti,ab,kw
OR
'biventricular pacing':ti,ab,kw</td><td>AND</td><td>'defibrillator':ti,ab,kw
OR
MeSH descriptor: [Defibrillators, Implantable] explode all trees
OR
ICD:ti,ab,kw
OR
'automatic internal defibrillator':ti,ab,kw
OR
'implantable defibrillator':ti,ab,kw
OR
automatic implantable cardioverter defibrillator:ti,ab,kw
OR
AICD:ti,ab,kw</td><td rowspan="3">AND</td><td rowspan="3">'cost analysis':ti,ab,kw
OR
('cost minimization': ti,ab,kw OR cma)
OR
('cost effectiveness': ti,ab,kw OR cea)
OR
('cost utility': ti,ab,kw OR cua)
OR
'health care' and cost*:ti,ab,kw
OR
economic and (evaluation or analysis or aspect or assessment):ti,ab,kw
OR
('budget impact analysis': ti,ab,kw OR bia)</td></tr>
<tr><td colspan="3">OR</td></tr>
<tr><td colspan="3">(CRT-D or CRT-ICD or pacemaker-defibrillator or Lumax or Iforia or Ilesto or Idova or Livian or "Contak Renewal" or Incepta or Energen or Punctua or Ovatio or Consulta or Maximo or Insync or Protecta or Viva or Brava or Cardia or Paradym or Promote or Epic or Atlas or Unify or Quadra):ti,ab,kw</td></tr>
</table>

Yield: 27

Appendix 8 - Extraction sheet

Economic studies

General information			
Reviewer name:			
Date of extraction:			
Author/Year:			
Title:			
Journal:			
Source of funding:			
Study Characteristics			
Objective of study:			
Study population:			
Intervention:			
Comparator:			
Economic Study Type		***Perspective***	
Cost-effectiveness Analysis	□	NHS	□
Cost-utility Analysis	□	Societal	□
Cost-benefit Analysis	□	Hospital	□
Cost-Consequence Analysis	□	Not Stated	□
Cost-Study	□	Other	□
Other (specify)	□		
Not reported	□		
Modelling			
Was a model used?			
Yes	□		
No	□		
If yes, state purpose and type:			
Source of Data			
Source of effectiveness data		*Source of Cost Data*	
Single study	□	Actual source (survey, direct contact, etc.)	□
Synthesis of Previous Publication	□	Literature source	□

Source of effectiveness data	
Effectiveness data from a single study	
Study design	
RCT	☐
Non-RCT with concurrent controls	☐
Cohort study	☐
Historical control	☐
Before and after study	
Case series	☐
Other (specify)	☐
Not reported	☐
Study population Number of patients in intervention group Number subject in control group Number excluded from study **Methods of sample selection:** **Follow-up** Duration of follow-up: Loss to follow-up: **Number of centres:** **Any blinding for assessment of outcomes:** **Analysis of clinical studies:**	
Treatment completers	☐
Intention to treat	☐

Study inclusion criteria:	**Study exclusion criteria reported:**
Effectiveness results: **Study designs included:** RCT ☐ Non-RCT with concurrent controls ☐ Cohort study ☐ Historical control ☐ Before and after study ☐ Case seies ☐ Other ☐ Not reported	**Number of primary studies included:**
Sources searched reported:	**Method of combination of primary study:** Meta-analysis ☐ Narrative methods ☐ Other (specify) ☐
Criteria used to judge validity: Concealment of randomisation ☐ Blind assessment ☐ Low drop out rates ☐ Other (specify) ☐ Not reported ☐	
Results of the review (Effectiveness results):	
Economic evaluation	
Measures of Benefits used in the Economic Analysis yes ☐ no ☐	
If yes, specify:	
Side effect considered yes ☐ no ☐	
Direct costs: Health service Estimation based on: A guess ☐ Actual data ☐ Derived using Modelling ☐ Other ☐ Not reported ☐	

Direct costs: Patients

Estimation based on:

A guess	☐
Actual data	☐
Derived using Modelling	☐
Other	☐
Not reported	☐

Source of Direct costs Data:	**Discounting Undertaken?**
Price Year:	Yes ☐
Currency:	No ☐
	Discount rate:

Indirect costs:

Estimation based on:

A guess	☐
Actual data	☐
Derived using Modelling	☐
Other	☐
Not reported	☐

Source of Indirect costs Data:	**Discounting Undertaken?**
Price Year:	Yes ☐
Currency:	No ☐
Conversion rates used:	**Discount rate:**

Statistical / sensitivity analyses

Statistical tests carried out?	Types of tests used in analysis of costs:
yes ☐	
no ☐	

Type of sensitivity analysis	**Areas of uncertainty tested:**
One-way analysis ☐	
Two-way analysis ☐	
Multi-way analysis ☐	
Threshold analysis ☐	
Analysis of Extremes ☐	
Probabilistic analysis ☐	
Not reported ☐	
Not carried out ☐	
Other:	

Results of study
Clinical Outcome/Benefit: Duration of benefits **Costs results:** **Cost of adverse events considered** yes ☐ No ☐ Not relevant ☐
How were the estimates of costs and benefits combined? Cost-Life saved ☐ Cost/Life gained ☐ Cos/QALY ☐ Not benefit ☐ Incremental net benefit ☐ Other ☐ Not combined ☐
Results of Synthesis of costs and benefits:
Author's conclusion:
Reviewer's conclusion:
Overall assessment of study quality (CHEERS):

Adapted from Bamford J, et al. Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen. *Health Technol Assess 2007;11(32).*

Appendix 9 - Excluded studies

List of excluded studies with reasons for exclusion

Not available (n=3):

Biffi, M.; Bertini, M.; Ziacchi, M.; Moschini, C.; Maztotti, A.; Mantovani, V.; Gardini, B.; Cervi, E.; Martignani, C.; Diembtrger, I.; Vaizanta, C.; Domenickini, G., and Boriani, G. Health economy: The true cost oe ICDs as based on their longevity in the real-life scenario. Europace. 2010; 12i100; ISSN: 1099-5129.

Bruggenjurgen, B.; Israel, C. W.; Klesius, A. A.; Ezzat, N., and Willich, S. N. Health services research in heart failure patients treated with a remote monitoring device in Germanya retrospective database analysis in evaluating resource use. J. Med. Econ. 2012; 15(4):737-745; ISSN: 1369-6998. 1941-837X .

Medical technology advances must be rapidly made available to patients. Expert Rev. Pharmacoecon. Outcomes Res. 2005; 5(4):373-375; ISSN: 1473-7167. 1744-8379.

Earlier version of previous study (n=1):

Bertoldi, E.G.; Rohde, L.E.; Zimerman, L.I.; Pimentel, M., and Polanczyk, C.A. Cost-effectiveness of cardiac resynchronization therapy in patients with heart failure: the perspective of middle-income country's public health system. Europace. 2011; 13; ISSN: 1099-5129.

No technology (n=3):

Wang, P. J. and Al-Ahmad, A. Advances in ICD Therapy. Card. Electrophysiol. Clin. 2011; 3(3):xv; ISSN: 1877-9182. 1877-9190.

Whang, W. Single-lead, shock-only ICD therapy reduces sudden death in people with congestive heart failure. Evid.-Based Cardiovasc. Med. 2005; 9(2):112-114; ISSN: 1361-2611.

Williams, I. Viewpoint: ICD cost-effectiveness. Circulation. 2006; 114(6):f121-f122; ISSN: 0009-7322.

No comparison (n=9):

Aidelsburger, P.; Grabein, K.; Klauss, V., and Wasem, J. Cost-effectiveness of cardiac resynchronization therapy in combination with an implantable cardioverter defibrillator (CRT-D) for the treatment of chronic heart failure from a German health care system perspective. Clin Res Cardiol. 2008 Feb; 97(2):89-97.

Banz, K. Cardiac resynchronization therapy (CRT) in heart failure: a model to assess the economic vlue of this new medical technology (Structured abstract). Value in Health. 2005; 8(2):128-139;ISSN:NHSEED-22005007704.

Linde, C.; Mealing, S.; Hawkins, N.; Eaton, J.; Brown, B., and Daubert, J. C. Cost-effectiveness of cardiac resynchronization therapy in patients with asymptomatic to mild heart failure: insights from the European cohort of the REVERSE (Resynchronization Reverses remodeling in Systolic Left Ventricular Dysfunction) (Structured abstract). European Heart Journal. 2011; 32(13):1631-1639; ISSN: NHSEED-22011001279.

Ondrackova, B.; Miklik, R.; Parenica, J.; Spinar, J.; Sticha, M., and Sulcova, A. In hospital costs of acute heart failure patients in the Czech Republic. Cent. Eur. J. Med. 2009; 4(4):483-489; ISSN: 1895-1058. 1644-3640.

Ondrackova, B.; Parenica, J.; Felsoci, M.; Miklik, R.; Horakova, K.; Spinar, J., and Sulcova, A. Cost comparison study in acute coronary syndromes and acute heart failure patients. Value Health. 2010; 13(7):A348; ISSN: 1098-3015.

Reynolds, M. R.; Cohen, D. J.; Kugelmass, A. D.; Brown, P. P.; Becker, E. R.; Culler, S. D., and Simon, A. W. The Frequency and Incremental Cost of Major Complications Among Medicare Beneficiaries Receiving Implantable Cardioverter-Defibrillators. J. Am. Coll. Cardiol. 2006; 47(12):2493-2497; ISSN: 0735-1097.

Shah, P.; Rongione, A. J.; Hewitt, P. D.; Rosner, C. M.; May, C. W.; Burton, N. A., and Desai, S. S. Is cardiac resynchronization therapy a cost-effective strategy in patients whose ultimate destination is a left ventricular assist device? J. Heart Lung Transplant. 2012; 31(4):S50-S51; ISSN: 1053-2498.

Swindle, J.; Burroughs, T. E.; Schnitzler, M. A., and Hauptman, P. J. Short-term mortality and cost associated with cardiac device implantation in patients hospitalized with heart failure. Am. Heart J. 2008; 156(2):322-328; ISSN: 0002-8703. 1097-6744.

Thijssen, J.; Van Den Akker, M. E.; Borleffs, C. J. W.; Van Rees, J. B.; De Bie, M. K.; Van Der Velde, E. T.; Van Erven, L., and Schalij, M. J. Cost-effectiveness of prophylactic cardioverter defibrillator implantation in a large single center cohort. Eur. Heart J. 2011; 32312; ISSN: 0195-668X.

No study design (n=21):

Alan, K. and Jeffrey, G. Selecting patients for ICD implantation: Are clinicians choosing appropriately? J. Am. Med. Assoc. 2011; 305(1):91-92;ISSN:0098-7484. 1538-3598.

Berisso, M.Z.; Canonero, D.; Caruso, D.; Setti, S., and Domenicucci, S. [Cardiac resynchronization therapy with defibrillation capability: considerations on a not yet proven therapeutic superiority]. G Ital Cardiol (Rome). 2010 Apr; 11(4):295-305.

Bernard, M.L. and Gold, M.R. Economic Implications and Cost-effectiveness of Implantable Cardioverter Defibrillator and Cardiac Resynchronization Therapy. Heart Fail. Clin. 2011; 7(2):241-250; ISSN:1551-7136.

Biffi, M.; Ziacchi, M.; Bertini, M.; Sangiorgi, D.; Corsini, D.; Martignani, C.; Diemberger, I., and Boriani, G. Longevity of implantable cardioverter-defibrillators: Implications for clinical practice and health care systems. Europace. 2008; 10(11):1288-1295; ISSN: 1099-5129. 1532-2092.

Boriani, G. and Diemberger, I. Identifying the patient who FADES away prior to appropriate ICD intervention. Heart. 2012; 98(11):833-834; ISSN: 1355-6037.1468-201X.

Boriani, G.; Biffi,M.; Martignani, C.; Valzania, C.; Diemberger,I.; Bertini, M.; Domenichini, G.; Ziacchi, M., and Branzi, A. Is cardiac resynchronization therapy cost-effective? Europace. 2009 Nov; 11 Suppl 5:v93-7.

Boriani, G.; Mantovani, L.G.; Biffi, M.; Schalij, M.J.; Martignani, C.; Leclercq, C.; Bax,J.J., and Auricchio, A. Cardiac resynchronization therapy: a cost or an investment? Europace. 2011 May; 13 Suppl 2:ii32-8.

Cannom, D.S. and Prystowsky, E.N. The evolution of the implantable cardioverter defibrillator. Heart Rhythm. 2004; 1(5SUPPL.):102C-114C; ISSN: 1547-5271.

Cutro, R.; Rich, M. W., and Hauptam, P.J. Device therapy in patients with heart failure and advanced age: Too much too late? Int. J. Cardiol. 2012; 155(1):52-55; ISSN: 0167-5273. 1874-1754.

Epstein, A.E. Benefits of the Implantable Cardioverter-Defibrillator. J. Am. Coll. Cardiol. 2008; 525(14):1122-1127; ISSN: 0735-1097.

Field, M. E. and Sweeney, M. O. Socio-economic analysis of cardiac resynchronization therapy. J. Intervent. Card. Electrophysiol. 2006; 17(3):225-236; ISSN: 1383-875X. 1572-8595.

Fox, D.J.; Davidson, N.C., and Fitzpatrick, A.P. How should we cost ICD therapy? Int. J. Cardiol. 2007; 118(1):1-3; ISSN: 0167-5273.

Freeman, J. V.; Ullal, A., and Turakhia, M. P. Cost-effectiveness of Implantable Cardioverter-Defibrillators and Cardiac Resynchronization Therapy. Card. Electrophysiol. Clin. 2011; 3(3):421-440; ISSN: 1877-9182. 1877-9190.

Kremers, M.S.; Hammill, S.C:; Berul, C.I.; Koutras, C.; Curtis, J.S.; Wang, Y.; Beachy, J.; Blum Meisnere, L.; Conyers, D.M.; Reynolds, M.R.; Heidenreich, P.A.; Al-Khatib, S.M.; Pina, I.L.; Blake, K.; Norine Walsh, M.; Wilkoff, B.L.; Shalaby, A.; Masoudi, F.A., and Rumsfeld, J. The National ICD Registry Report: Version 2.1 including leads and pediatrics for years 2010 and 2011. Heart Rhythm. 2013; 10(4):e59-e65;ISSN: 1547-5271. 1556-3871.

Lehmann, M.H. and Aaronson, K.D. CRT-D therapy in heart failure. How much do NYHA class IV patients benefit? J. Cardiovasc. Electrophysiol. 2006; 17(5):491-494; ISSN: 1045-3873. 1540-8167.

Linde, C.; Curtis, A.; Fonarow, G.; Lee, K.; Little, W.; Tang, A.; Levys, F.; Momomura, S.; Bergmann, T., and Cowie, M. Is CRT-P beneficial in heart failure patients with LBBB and LVEF 36-50%? The design of the MIRACLE EF study. Europace. 2013; 15ii46; ISSN: 1099-5129.

Lindsay, B. D. Perspective on cost-effective utilization of cardiac resynchronization therapy. J. Cardiovasc. Electrophysiol. 2013; 24(1):75-76; ISSN: 1045-3873. 1540-8167.

Panescu, D. Cardiac resynchronization therapy. IEEE Eng. Med. Biol. Mag. 2005; 24(2):22-26; ISSN: 0739-5175.

Reddy, M.; Mahankali Sridhar, A. R.; Vallakati, A.; Lakkireddy, D., and Dawn, B. Gender differences in the utilization of the type of cardiac resynchronization therapy: Data from the nationwide inpatient sample 2003-2009. J. Am. Coll. Cardiol. 2013; 61(10):E669; ISSN: 0735-1097.

Russo, A. M. The reality of implantable cardioverter-defibrillator longevity: What can be done to improve cost-effectiveness? Heart Rhythm. 2012; 9(4):520-521; ISSN: 1547-5271. 1556-3871.

Sedlacek, K. ; Jurkuvenas, P.; Hoskova, L.; Malek, I., and Kautzner, J. Patterns of ICD use in patients enlisted for heart transplantation: A single centre retrospective analysis 2006-2010. PACE Pacing Clin. Electrophysiol. 2011; 34(11):1337; ISSN: 0147-8389.

No full text available (n=8):

Abraham, W.T.; Birgersdotter-Green, U., and Bolinger, K. Health care burden of cardiac resynchronization therapy (CRT) non-responders: An analysis from the freedom randomized controlled trail. Heart Rhythm. 2013; 10(5):S360; ISSN: 1547-5271.

Betts, T.R.; Jones, M.A.; Wong, K.C.K.; Qureshi, N.; Rajappan, K., and Bashir, Y.. Cost effectiveness of using a plugged LV port in ICD recipients with low EF, dyssynchrony and mild heart failure symptoms. Europace. 2011; 13; ISSN: 1099-5129.

Gold, M. R.; Tsintzos, S. I.; Sidhu, M. K.; Mealing, S.; Fortier, K. A.; Padhiar, A., and Abraham, W. T. Economic impact and cost-effectiveness of cardiac resynchronization therapy versus optimal medical therapy in mild heart failure: Long-term follow-up and projections from reverse. Circulation. 2013; 128(22): ISSN: 0009-7322.

Jones, M. A.; Betts, T. R.; Rajappan, K.; Bashir, Y.; Wong, K. C. K., and Qureshi, N. Is it cost effective to use a plugged LV port? Heart. 2011; 97A88; ISSN: 1355-6037.

Kirkfeldt, R.; Nielsen, H.; Johnsen, S.P.; Gerdes, J.C., and Nielsen, J.C. Myocardial infarction in Danish ICD patients: Risk, predictors and healthcare costs. Eur. Heart J. 2013; 34259; ISSN: 0195-668X.

Kutyifa, V.; Aidelsburger, P.; Schauer, S.; Merkely, B.; Klein, H.; Kuniss, M.; Kloppe, A.; Kayser, T.; Peppa, R., and Moss, A. J. Cost-effectiveness of cardiac resynchronization therapy in combination with an implantable cardioverter defibrillator in mild heart failure based on Markov modeling using UK cost approach in MADIT CRT. Eur. Heart J. 2012; 33896; ISSN: 0195-668X.

Umar, F.; Taylor, R.; Vakharia, A.; Marshall, H., and Leyva, F. Implantable cardioverter defibrillator therapy or cardiac resynchronisation therapy with defibrillation in patients with left ventricular dysfunction: A cost-impact study. Europace. 2013; 15ii50; ISSN: 1099-5129.

Wells, G. A.; Coyle, D.; Coyle, K.; Talajic, M., and Tang, A. Cost effectiveness of cardiac resynchronization therapy (CRT) for mild to moderate heart failure. Can. J. Cardiol. 2012; 28(5):S419; ISSN: 0828-282X.

Appendix 10 - Included studies

Cost-effectiveness, cost-utility analysis:

Bertoldi, E. G.; Rohde, L. E.; Zimerman, L. I.; Pimentel, M., and Polanczyk, C. A. Cost-effectiveness of cardiac resynchronization therapy in patients with heart failure: the perspective of a middle-income country's public health system. Int J Cardiol. 2013 Mar 10; 163(3):309-15.

Feldman, A. M.; de Lissovoy, G.; Bristow, M. R.; Saxon, L. A.; De Marco, T.; Kass, D. A.; Boehmer, J.; Singh, S.; Whellan, D. J.; Carson, P.; Boscoe, A.; Baker, T. M., and Gunderman, M. R. Cost effectiveness of cardiac resynchronization therapy in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. J Am Coll Cardiol. 2005 Dec 20; 46(12):2311-21.

Fox, M.; Mealing, S.; Anderson, R.; Dean, J.; Stein, K.; Price, A., and Taylor, R. S. The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model. Health Technol Assess. 2007 Nov; 11(47):iii-iv, ix-248.

Neyt, M.; Stroobandt, S.; Obyn, C.; Camberlin, C.; Devriese, S.; De Laet, C., and Van Brabandt, H. Cost-effectiveness of cardiac resynchronisation therapy for patients with moderate-to-severe heart failure. Value Health. 2011; 14(7):A253; ISSN: 1098-3015.

Noyes, K.; Veazie, P.; Hall, W. J.; Zhao, H.; Buttaccio, A.; Thevenet-Morrison, K., and Moss, A. J. Cost-effectiveness of cardiac resynchronization therapy in the MADIT-CRT trial. J. Cardiovasc. Electrophysiol. 2013; 24(1):66-74; ISSN: 1045-3873. 1540-8167.

Yao, G.; Freemantle, N.; Calvert, M. J.; Bryan, S.; Daubert, J. C., and Cleland, J. G. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. Eur Heart J. 2007 Jan; 28(1):42-51.

Cost analysis:

Bentkover, J. D.; Dorian, P.; Thibault, B., and Gardner, M. Economic analysis of a randomized trial of biventricular pacing in Canada. Pacing Clin Electrophysiol. 2007 Jan; 30(1):38-43.

Boriani, G.; Braunschweig, F.; Deharo, J. C.; Leyva, F.; Lubinski, A., and Lazzaro, C. Impact of extending device longevity on the long-term costs of implantable cardioverter-defibrillator therapy: A modelling study with a 15-year time horizon. Europace. 2013; 15(10):1453-1462; ISSN: 1099-5129. 1532-2092.