# *Cardiac resynchronisation therapy for severe heart failure*

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Phil Hider, Dr Robert Weir, Mrs Sarah Hogan, Mrs Susan Bidwell, Mr Peter Day, Dr Katherine Hall and Dr Ray Kirk from New Zealand Health Technology Assessment, University of Otago. The report was edited by Carol Webb. The report was endorsed by the Minister for Health and Ageing on 28 November 2005.

Publication approval number: 3800

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## The procedure

Cardiac resynchronisation therapy (CRT) is proposed as a treatment for severe heart failure. The treatment aims to restore the synchronous contraction of the left and right ventricles and thereby improve cardiac function. The application involves specialised techniques and cardiac catheterisation equipment to gain access to the venous system of the ventricle via the coronary sinus. A specially designed guide catheter is inserted into the coronary sinus and retrograde venography is performed using balloon-tipped catheters. The balloon catheter is then removed and a specially designed pacing lead is advanced into a branch of the coronary sinus. Threshold testing is then performed on the implanted lead. Standard atrial and ventricular pacing leads are placed in both the right atrium and the right ventricle. The three leads are attached to a cardiac synchronisation device, which is similar to a conventional pacemaker with the capability of sensing and pacing in the three – one atrial and both ventricular – chambers. The procedure is usually conducted under local anaesthetic and an inpatient stay in hospital is required.

## Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the New Zealand Health Technology Assessment Unit was engaged to conduct a systematic review of literature on treatment of heart failure by permanent cardiac resynchronisation therapy. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

## MSAC's assessment of treatment of heart failure by permanent cardiac resynchronisation therapy

### Clinical need

Based on United States data it is estimated that about 325,000 Australians may be affected by heart failure and about 30,000 new cases are diagnosed annually. Heart failure is a major cause of mortality and hospitalisation in Australia. More than 2,700 deaths (2% of all deaths) and 41,884 hospitalisations in 2001/02 (0.7% of all hospitalisations) were attributed to the condition. The economic burden associated with heart failure is

significant and it has been estimated that direct health-care costs in 2000 were close to $1 billion.

Assuming that the prevalence of heart failure in Australia is 1 per cent of the total population, and about 20 per cent of patients with the condition are moderate to severely affected (NYHA III – IV), while 10 per cent of these patients have a QRS (quasi-random signal) >150 msec on an electrocardiograph assessment, then it can be estimated that in Australia approximately 3,860 people may be potentially eligible for cardiac resynchronisation therapy.

## Safety

CRT is associated with an acceptable short-term safety profile. Implantation is successful in about 90 per cent of patients. Fatalities at implantation are rare (<1%) and although complications may arise in approximately 6 per cent of implantations, most – with the exception of perforation (2% of implantations) – are unlikely to be serious. Postoperative complications occur among about 7 per cent of patients over two years of follow-up. These commonly involve lead problems such as dislodgement and infection that require the patient to undergo a repeat procedure, but are usually not life threatening. Reliable data about the longer term safety of CRT is not available. The incidence of complications increases over the length of follow-up and is reduced as operators gain experience with the procedure.

## Effectiveness

Four well-designed, multi-centre, randomised controlled trials have consistently reported similar favourable benefits from CRT plus OPT in relation to patient quality of life and a number of measures of exercise performance and functional ability (Abraham et al 2002, Cazeau et al 2001, Bristow et al 2004, Cleland et al 2005b). The largest trial, COMPANION (Bristow et al 2004), assessed the impact of CRT plus OPT using a composite endpoint that included all-cause mortality and hospitalisation. The trial was stopped early and although the intervention group was associated with a 24 per cent reduction in all-cause mortality, the result was not statistically significant (hazard ratio = 0.76, p=0.06, 95% CI: 0.58-1.01). In another large trial, the MIRACLE study (Abraham et al 2002), the mortality rates during follow-up appear to be lower in the CRT plus OPT group compared with the OPT alone group . However, this trial, along with the third study (Cazeau et al 2001), lacked sufficient statistical power to reliably assess this issue. The fourth major trial had sufficient statistical power to assess mortality and the study recorded a significant 36 per cent (hazard ratio: 0.64, 95% CI: 0.48-0.85, p<0.001) reduction in all-cause mortality over a relatively long duration of follow-up (mean 29 months).

The results from a meta-analysis that included 6-12 month mortality data from the four randomised controlled trials indicated that CRT was associated with a statistically significant reduction of 21 percent in the relative risk of mortality (RR=0.79, 95% CI: 0.63-0.98). This result suggests that there is 95 per cent probability that the therapy may reduce the risk of mortality by as much as 37 per cent, or it may have no effect.

In the MIRACLE study, CRT plus OPT was associated with a 51 per cent reduction in the relative risk and an 11 per cent reduction in the absolute risk of hospitalisation after

implantation. Separate hospitalisation data has not yet been published from the COMPANION study. The reduction in absolute risk in the MIRACLE trial suggests that only nine patients would need to be treated over six months in order to prevent one hospitalisation for heart failure after implantation. Hospitalisation data was reported in the CARE-HF study in relation to admissions for just cardiovascular events and worsening heart failure. Both types of admissions were significantly reduced by the intervention over the 29-month duration of the trial – cardiovascular events by 39 per cent and heart failure by 52 per cent. Quality of life as measured by the Minnesota Living with Heart Failure Questionnaire was significantly improved ($p<0.001$) among patients who received CRT in all four trials after three to six months of follow-up. In the CARE-HF trial the intervention group was associated with a 22 per cent improvement in quality of life after just 90 days follow-up (40 points versus 31 points). In two large trials (COMPANION and MIRACLE) the mean or median decrease among those in the intervention group was 100 per cent greater than the decrease among the control group (24 points versus 12 points COMPANION and 18 points versus nine points MIRACLE, both $p<0.001$). Exercise performance among participants in the intervention groups was also significantly improved after six months' follow-up in all three trials. Six-minute walk results were improved by a mean of 40 metres in the COMPANION trial and a median distance of 39 metres in the MIRACLE trial among the groups receiving CRT compared to a one-metre or ten-metre improvement for members of the control groups in COMPANION and MIRACLE studies respectively ($p<0.001$ and $p<0.01$).

The benefits from CRT plus OPT appear to be clinically significant in appropriately selected patients, especially in relation to quality of life, reduction in mortality and improvements in the rate of hospitalisation, particularly for cardiovascular events and worsening heart failure. Long-term data supporting the benefits of therapy are available up to a mean 29 months follow-up period.

## Cost-effectiveness

Currently available evidence suggests that CRT reduces the total number of days of hospitalisation relative to optimal pharmacological treatment alone, due to a substantial reduction in hospitalisation for major cardiovascular events. Over approximately 29.4 months – the mean follow-up time in the CARE-HF study – CRT is associated with an incremental cost of $13,774 per patient, based on public hospital costs, and $22,419 per patient, based on private hospital costs. The associated reduction in hospitalisation for the total number of hospital days is 2.39 days in public hospitals and 2.85 days in private hospitals. For the number of hospital days post-implantation, it is 7.65 days in both public and private hospitals. In terms of cost-effectiveness, this implies an incremental cost per post-implantation hospital day avoided of $1,801 in public hospitals and $2,931 in private hospitals.

Mortality data at two years of follow-up and data on quality of life allowed the estimation of incremental cost per life year saved and incremental cost per quality-adjusted life year saved. Over a patient's lifetime, CRT is expected to be associated with an increase of 1.52 discounted (2.74 undiscounted) life years and 1.54 discounted (2.63 undiscounted) quality-adjusted life years. The expected five-year incremental cost per life year saved was estimated to be $35,436, based on public hospital data, and $63,861, based on private hospital data. The expected 15-year incremental cost per quality-adjusted life year (QALY) saved was estimated to be $25,362, based on public hospital data, and $45,706, based on private hospital data. These estimates are based on conservative projections,

which do not allow for changes in mortality rates beyond two years or changes in quality of life beyond 90 days. Longer term data on these variables are not currently available.

Sensitivity analysis showed that the conclusion of the analysis is robust to plausible variations in key parameters of the model. That is, the conclusion that adding CRT to optimal pharmacological treatment is expected to be associated with a favourable incremental cost-effectiveness ratio. However, the ratio is sensitive to variations, suggesting that an incremental cost-effectiveness ratio in the range of up to $29,000 per life year saved, or per QALY saved, is plausible.

The total incremental annual cost of adding CRT to optimal pharmacological treatment was estimated under various assumptions regarding initial and long-term take-up. Long-term incremental annual costs are expected to be between $2,230,019 and $11,969,378, based on 97 to 290 new patients annually. However, first-year incremental annual costs could be as low as $3,142,890, if only 200 of the existing stock of eligible patients receive CRT, or as high as $35,695,875 if 1,500 existing eligible patients receive CRT.

## Recommendation

On the strength of evidence pertaining to safety, effectiveness and cost-effectiveness, MSAC recommends that public funding should be supported for the use of cardiac resynchronisation therapy in patients who have moderate to severe chronic heart failure (NYHA class III or IV) despite optimised medical therapy and who meet all of the following criteria-sinus rhythm, a left ventricular ejection fraction of less than or equal to 35% and a QRS duration greater than or equal to 120ms

- The Minister for Health and Ageing accepted this recommendation on 28 November 2005 -

# Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of cardiac resynchronisation therapy, which is a therapeutic procedure for severe heart failure. The initial application was for the consideration of cardiac synchronisation therapy for severe heart failure. During the course of the review the Advisory Panel decided to rename the topic cardiac resynchronisation therapy in order to remain consistent with international literature. The scope of the review did not change. Specifically, it did not include cardiac resynchronisation therapy with an implantable defibrillator. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are given in Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for cardiac resynchronisation therapy, without an implantable cardiac defibrillator, for severe heart failure.

# Background

## Heart failure

Heart failure is a complex syndrome resulting from any structural or functional cardiac disorder that reduces the ability of the heart to function as a pump (Cowie and Zaphirou 2002). The condition is characterised by dyspnoea, fatigue, and fluid retention (Cowie and Zaphirou 2002). Patients with heart failure have limited exercise capacity, frequent need for hospitalisation, high rates of mortality and an impaired quality of life (Hare 2002). The most common cause in the developed world is coronary heart disease although hypertension often co-exists (Fox et al 2001). Guidelines for the diagnosis and management of the condition have recently been published by the National Heart Foundation of Australia in conjunction with the Cardiac Society of Australia and New Zealand (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002).

## Pacing therapies for heart failure

Pacing therapies for heart failure have rapidly progressed over the last 10 years (Haywood 2001). Early interest in pacing therapy for heart failure centred on the reduction of the atrioventricular (AV) delay in patients who were implanted with a dual chamber pacemaker using right atrial and right ventricular leads (Haywood 2001). Shortening the AV delay was associated with promising results in several cardiac laboratory-based studies that included patients with first degree AV block and in those with doppler evidence of pre-systolic mitral regurgitation (Hochleitner et al 1990, Brecker et al 1992, Nishimura et al 1995). However, little benefit was found among patients with severe heart failure (New York Heart Association classes III and IV) enrolled in longer term controlled randomised trials (Linde et al 1995, Gold et al 1995).

During the 1990s, some small clinical studies including (Cazeau et al 1994, Foster et al 1995) and cardiac laboratory-based assessments (Blanc et al 1997, Leclercq et al 1998) demonstrated that clinical and haemodynamic benefits could be obtained from the combination of atrial and biventricular pacing.

Early studies of biventricular pacing used epicardial leads placed on both ventricles (Haywood 2001). The first report of left ventricular pacing using a transvenous technique was published in 1998. The technique involved introducing a lead via the coronary sinus and positioning its tip on the wall of the left ventricle (Daubert et al 1998). Transvenous implantation of the lead is an important innovation that has enabled the potential benefits of biventricular therapy to be employed without the intraoperative morbidity and difficult postoperative recovery associated with a thoracotomy (Ritter et al 1994, Cazeau et al 1996, Daubert et al 1998, Haywood 2001). The transvenous approach is facilitated by the development of new instrumentation and new purpose-built left ventricular leads with a lower profile and some degree of pre-formed curve (Gras et al 2002a).

## Rationale for cardiac resynchronisation therapy

Patients with heart failure often have a dysynchronous contraction of the cardiac chambers (Conti 2001). Cardiac dysynchrony can occur in two ways: due to either ineffective synchronisation between the atria and ventricles (AV dysnchrony) or lack of synchronisation within the two ventricles (ventricular dysnchrony) (Luqman et al 2001). Intraventricular and interventricular conduction delays can also cause an inefficient uncoordinated pattern of left ventricular activation with segments contracting at different times (Barold 2001). Consequently, there is a shorter diastole and/or overlapping systole/diastole and aggravation of functional mitral regurgitation (Barold 2000).

Conduction system abnormalities are common among patients with systolic heart failure. Up to 50 per cent of patients with systolic heart failure may have conduction delays such as first-degree atrial-ventricular block, or intraventricular conduction delays such as left bundle branch block (Shamim et al 1999, Schoeller et al 1993, Aaronson et al 1997). These conduction delays result in abnormal electrical depolarisation of the heart. Approximately one-third of patients with heart failure may exhibit intraventricular conduction delay characterised by a wide QRS complex on electrocardiography (Stevenson et al 1995). Prolonged QRS duration or ventricular dysynchrony results in abnormal interventricular septal wall motion, decreased contractility, reduced diastolic filling times, and prolonged duration of mitral regurgitation. These factors all place the failing heart at a significant mechanical disadvantage (Xiao et al 1992, Xiao et al 1993, Panidis et al 1986) (Xiao et al 1991, Grines et al 1989). Ventricular dyssynchrony has been shown to be an independent prognostic risk factor for increased mortality among patients with heart failure (Xiao et al 1996, Aaronson et al 1997). The underlying rationale for synchronisation therapy is to improve the sequence of electrical activation (synchronisation) of the two atria, followed by the two ventricles and thereby improve the mechanical efficiency of the heart by creating a more coordinated and efficient systolic contraction (Barold 2000). Whereas dual chamber pacing may further delay left ventricular activation and result in more contraction and relaxation dysnchrony, simultaneous pacing of both ventricles may ameliorate this problem (Wong et al 2001).

## Terminology

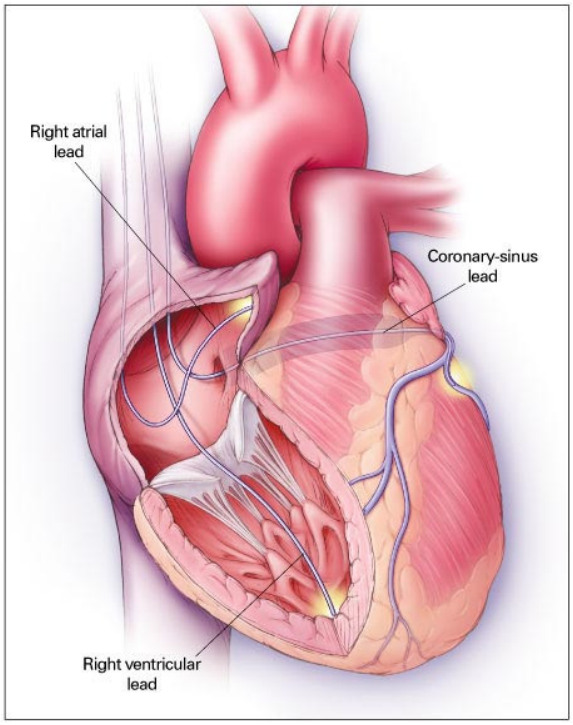
Pacing therapies for heart failure that involve pacing the left ventricle in addition to the right ventricle and the right atrium are referred to as biventricular therapy, resynchronisation therapy or synchronisation therapy (Auricchio and Spinelli 2000). Therapy involving just the right atrium and one ventricle is known as dual-chamber pacing and is not the subject of this review. The normal sequence of atrial depolarisation and contraction followed by ventricular depolarisation and contraction is termed atrioventricular synchrony.

## The procedure

Cardiac resynchronisation therapy (CRT) is proposed as a treatment for severe heart failure. The treatment aims to restore the synchronous contraction of the left and right ventricles and thereby improve cardiac function. The application involves specialised techniques and cardiac catheterisation equipment to gain access to the venous system of the ventricle via the coronary sinus. A specially designed guide catheter is then inserted into the coronary sinus and retrograde venography is performed using balloon-tipped

catheters. A balloon is temporarily inflated to occlude the flow in the coronary sinus and then non-ionised contrast is injected to opacify the left ventricle venous system and map out the anatomy. The balloon catheter is removed and a specially designed pacing lead is advanced into a branch of the coronary sinus. Threshold testing is then performed on the implanted lead (Conti 2001). Standard atrial and ventricular pacing leads are placed in both the right atrium and the right ventricle. The three leads are attached to a cardiac synchronisation device, which is similar to a conventional pacemaker with the capability of sensing and pacing in the three (one atrial and both ventricular) chambers (Tang 2001) (See Figure 1). The procedure is usually conducted under local anaesthetic and at least a night in hospital is required (Gras et al 2002a).

**Figure 1 Position of the leads in cardiac resynchronisation therapy**

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## Intended purpose

The procedure is indicated for use with patients with:

- severe heart failure (NYHA grades III-IV); and

- sinus rhythm; and

- QRS > 120 ms; and

- LVEF < 0.35; and

- already receiving optimal pharmacological therapy, including treatment with an angiotensin converting enzyme (ACE) inhibitor and a beta-blocker, all in optimal or maximally tolerated doses and usually also treated with a loop diuretic.

Other optional pharmacological therapies may include spironolactone, booster diuretics, angiotensin receptor blockers/angiotensin II inhibitors, digoxin, certain calcium-channel blockers and other alternate vasodilators.

# Clinical need/burden of disease

## Heart failure

No national data are available about the number of Australians who have heart failure or the severity of their disease (Australian Institute of Health & Welfare (AIHW) 2004, National Centre for Monitoring Cardiovascular Disease 2004). The following section presents estimates based on the most up-to-date published formation available.

The prevalence of heart failure in Western countries is estimated to be 1 per cent of the total population (Cleland 2001a). The prevalence of heart failure increases with age such that 50 per cent of people aged 85 years and older may have the condition (Kannel and Cupples 1988). Information about the incidence and prevalence of heart failure in Australia is mainly derived from extrapolation from overseas studies (Australian Institute of Health & Welfare (AIHW) 2004, National Centre for Monitoring Cardiovascular Disease 2004). Based on United Kingdom data, it is estimated that in 2000 about 325,000 Australians were affected by heart failure and that there were approximately 22,000 incident hospital admissions (Clark et al 2004). An estimated 30,000 new cases of heart failure are diagnosed annually (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002).

Heart failure is an important cause of mortality and hospitalisation in Australia. Heart failure accounted for more than 2,729 deaths (2 % of all deaths) in 2002 and 41,884 hospitalisations (0.7 % of all hospitalisations) in 2001-02 (Australian Institute of Health & Welfare (AIHW) 2004, National Centre for Monitoring Cardiovascular Disease 2004). Rates of hospitalisation for heart failure in Australia increase markedly with age, especially among males (see Table 1).

**Table 1 Rates of heart failure hospital separations by age and gender in Australia (1997-98)**

| Heart failure (ICD-9CM code 428) | Age group | | | | | |
|---|---|---|---|---|---|---|
| | <15 | 15-34 | 35-54 | 55-74 | 75+ | All ages |
| Males | 2.8 | 5.0 | 47.8 | 596.7 | 2980.3 | 226.7 |
| Females | 3.3 | 1.7 | 23.1 | 364.4 | 2452.6 | 220.8 |

Table based on (Australian Institute of Health & Welfare et al 2001).

Heart failure is also a common reason for general practitioner contact. Approximately, 899,000 consultations (or 0.6 % of all problems managed) for heart failure occurred in general practice in 1998-99 (Australian Institute of Health & Welfare 2001).

There are no precise data for the economic burden associated with heart failure. It was estimated that heart failure accounted for $411 million of direct health care costs in 1993-94. The largest single proportion of this money ($157 million) was spent on inpatient care, while nursing home costs amounted to $135 million (Australian Institute of Health & Welfare 1999). Recent estimates put the direct health care cost of heart failure in 2000 at close to $1 billion (Clark et al 2004).

The burden associated with heart failure is expected to rise due to pressures associated with an ageing population and an increase in the number of people with hypertension, coronary heart disease, obesity and diabetes mellitus (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002, Australian Institute of Health & Welfare (AIHW) 2003).

Assuming that the estimated prevalence of heart failure in Europe (1% of the total population) can be translated to the Australian population in 2000, then approximately 192,800 people may be affected (Australian Institute of Health & Welfare et al 2001). If about 20 per cent of patients with heart failure remain severely or moderately symptomatic (NYHA III and IV), and 10 per cent of these patients have QRS >150 msec, (Xiao et al 1996, Shamim et al 1999, Wilensky et al 1988, Schoeller et al 1993, Cianfrocca et al 1992) then it can be estimated that in Australia approximately 3,860 people may be potentially eligible for cardiac resynchronisation therapy.

This estimate is in broad agreement with a recent United Kingdom-based study of hospital admissions for heart failure in which 3 per cent to 10 per cent of patients exhibited severe heart failure (NYHA III or IV) and had a QRS duration > 120 msecs, and were considered to be candidates for cardiac resynchronisation therapy (Farwell et al 2000). About 41,884 separations for heart failure occurred in Australia during 2001-02 (National Centre for Monitoring Cardiovascular Disease 2004), although it is not known how many patients were involved in these separations as they are a count of episodes of care. If 3 per cent to 10 per cent of these separations involved individual patients with clinical features amenable to cardiac resynchronisation therapy, then approximately 1,260 to 4,190 patients may be eligible for the treatment in Australia.

## Prognosis for patients with severe heart failure

Clinical studies provide information about prognosis for well defined patient groups with documented severe heart failure. Participants in the study by Packer et al (2001) had symptoms at rest or at minimal exercise and an ejection fraction of less than 25 per cent. Cumulative risks of mortality at one year in the active and placebo groups were 11.4 per cent and 18.5 per cent. The risk of death was higher among patients with recent evidence of cardiac decompensation and in this group the risk of death at one year in the placebo group was 24 per cent. This result equates to an annual mortality rate of 28.5 per cent per patient-year of follow-up. These risks are comparable to the rates reported for patients with similarly advanced disease in other studies (CIBIS-II Investigators 1999, MERIT-HF Triallists Group 1999, Packer et al 1996).

# Existing procedures

## Heart transplantion

Seventy-two heart transplants were performed in Australia during 1998 (Australian Institute of Health & Welfare et al 2001). The main reason for heart transplantation is coronary heart disease and cardiomyopathy (Australian Institute of Health & Welfare 2002). The availability of suitable donor hearts, along with significant mortality, morbidity and costs associated with the procedure, limit the use of this intervention for the treatment of heart failure in Australia (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002).

## Ventricular assist devices

Mechanical support with left ventricular assist devices has mostly been used as a bridge to cardiac transplantation or for recovery following cardiac surgery (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002). While they may be used as a medium-term alternative to cardiac transplantation, no device is currently approved for this indication in Australia (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002) The prohibitive cost, large size, and the risk of complications limits the use of currently available ventricular assist devices (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002).

## Other surgical procedures

Other surgical procedures, such as left ventricular free wall excision, are the subject of ongoing international trials and are not yet available for routine patient care (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002)

# Comparator

The advisory panel determined that the appropriate comparative treatment is optimal pharmacological therapy alone, as defined above in the scope for the evaluation. The comparison is therefore between CRT with optimal pharmacological therapy evaluated against treatment with only optimal pharmacological therapy. That is, this report examines the incremental benefit of CRT in addition to optimal pharmacological treatment.

## Current pharmacological therapy

### Recommended agents

Current guidelines recommend that ACE inhibitors and beta-blockers are first-line agents that should be used for all patients with severe systolic heart failure, unless contraindicated or not tolerated (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002). Diuretics may be employed where necessary

for symptom relief (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002).

### Angiotensin converting enzyme inhibitors (ACE inhibitors)

Angiotensin converting enzyme inhibitors (ACE inhibitors), if tolerated, are mandatory in patients with severe systolic heart failure (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002). ACE inhibitors have been shown to prolong survival (SOLVD Investigators 1991, CONSENSUS Trial Study Group 1987) for people with NYHA class II-IV heart failure. In clinical trials they also have been shown to improve symptoms and exercise tolerance while reducing the need for hospitalisation (Pflugfelder et al 1993). The optimal dose of ACE inhibitor therapy has not been clearly established, but there is general agreement that therapy should be provided with a low dose of ACE inhibitor. If it is tolerated, an effort should be made to increase the dose (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002).

### Beta-blockers

Beta-blockers, notably carvedilol, have been shown to improve survival among people with severe systolic heart failure while also providing symptomatic benefits (CIBIS-II Investigators 1999, MERIT-HF Triallists Group 1999, Packer et al 1996). Guidelines recommend beta-blocker therapy, unless contraindicated or not tolerated, for patients who remain moderately symptomatic despite appropriate doses of ACE inhibitors and diuretics (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002).

### Diuretics

The principle use of diuretic therapy is to provide symptomatic relief (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002). Diuretics can effectively reduce the physical symptoms of fluid overload, such as swelling and shortness of breath, among patients with heart failure (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002).

### Other optional agents

Treatment with digoxin, spironolactone, ACE II receptor antagonists, certain calcium-channel blockers and other alternate vasodilators may be used in the management of patients with severe heart failure.

### Digoxin

Digoxin may be a useful agent to provide some symptomatic relief and reduce the need for hospitalisation among patients with advanced heart failure, although there may be no effect on mortality (Digitalis Investigation Group 1997).

### Spironolactone

Spironolactone can reduce all-cause mortality and may give symptomatic improvement among selected people with advanced systolic heart failure (Pitt et al 1999).

### Angiotensin II receptor antagonists (AII)

Comparative studies between ACE inhibitors and AII inhibitors have usually demonstrated similar levels of effectiveness between the two agents. However, it is possible that combination therapy with ACE inhibitors and AII antagonists may

maximise the benefits of these agents (Pitt et al 1997). Current guidelines recommend that AII antagonists should be used when a patient is intolerant to ACE inhibitors due to kinin-mediated adverse effects such as coughs (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002).

### Calcium antagonists

Non-dihydropyridine calcium antagonists that are negative inotropes are usually contraindicated for patients with systolic heart failure (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002). However, dihydropyridine calcium antagonists may be used to treat co-morbidities such as hypertension and ischaemic heart disease in patients with heart failure, as they have been shown not to increase mortality (Cohn et al 1997).

### Other vasodilators (eg, hydralazine)

Hydralazine and isosorbide dinitrate may be used for patients intolerant of ACE inhibitors or when these agents are contraindicated and no other therapeutic option exists (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002).

### Other pharmacological agents

### Inotropic infusions

Episodic inpatient intravenous infusions of an inotropic agent remain an effective treatment to gain haemodynamic optimisation for inpatients with severe heart failure (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002). Current evidence does not support the use of intermittent outpatient infusions (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002).

## Limitations of current pharmacological therapy

Although current pharmacological agents can dramatically modify the natural history of heart failure, many patients remain symptomatic despite maximal medical therapy (Garg and Yusuf 1995, Dracup et al 1992). Patients with heart failure are still at high risk of death, despite optimal medical therapy (Cleland et al 1998, Goldman et al 1993). Observers have also noted that in contrast to the positive results from clinical trials, the evidence from epidemiological studies suggest there may not have been any major improvement in the prognosis of heart failure during the past 40 years (Khand et al 2000, Cleland and Clark 1999).

Several of the medications currently used for the treatment of heart failure are associated with potentially serious side effects. For example, treatment with diuretic therapy requires that the patient should be monitored for the development of dehydration or electrolyte disturbances (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002).

Finally, it appears that pharmacological therapy cannot normalise atrioventricular intervals or intraventricular delays. It is therefore unable to address the mechanical asynchrony that reduces the effectiveness of cardiac contraction among a significant proportion of patients with heart failure (Auricchio and Spinelli 2000).

## Marketing status of the device

The following products are listed on the Australian Register of Therapeutic Goods (ARTG) with the Therapeutic Goods Administration (TGA).

Products and ARTG listing numbers are presented in Table 2.

**Table 2 ARTG listing number, by product**

| Product name | AUST R number | ARTG ID number |
|---|---|---|
| Contak Renewal TR, Model H120 | | 101574 |
| Contak Renewal TR, Model H125 | | 101572 |
| Contak Renewal TR2, Model H140 | | 101571 |
| Contak Renewal TR2, Model H145 | | 101573 |
| Easytrak Lead | 74514, 74515, 74516 | |
| Easytrak 2 Lead | | 99579 |
| Easytrak IS-1 Lead | | 112809 |
| Easytrak 2 IS-1 Lead | | 112810 |
| Easytrak 3 Lead | | 114811 |

It should be noted that this report does not include an assessment of cardiac resynchronisation therapy with an implantable defibrillator.

## Current reimbursement arrangement

Currently, the insertion of permanent biventricular (triple chamber) transvenous electrodes is not specifically funded under the Medical Benefits Scheme. Table 3 lists relevant procedures funded under the November 2004 edition of the Medical Benefit Scheme (Australian Department of Health & Ageing 2002) including funding for cardiac pacemaker insertion and for coronary venography. Reimbursements are available for the insertion, removal or replacement of single-chamber or dual-chamber permanent transvenous electrodes (Items: 38278, 38284). The scheme lists separate references for the injection of opaque material into any coronary vessel (Item 38243) and the insertion, removal or replacement of a permanent cardiac pacemaker (38281).

**Table 3 Current procedures funded under the Medical Benefits Scheme**

| Code | Procedure | Amount |
|---|---|---|
| 38243<br>(T8.33<br>T8.35) | Placement of catheter and injection of opaque material into any coronary vessel(s) or graft(s) prior to any coronary interventional procedure, not being a service associated with a service to which item 38246 applies (Anaes.) | $376.40 |
| 38278 | Single chamber permanent transvenous electrode, insertion, removal or replacement of (Anaes.) | $541.95 |
| 38281<br>(T8.39) | Permanent cardiac pacemaker, insertion, removal or replacement of (Anaes.) | $216.75 |
| 38284<br>(T8.39) | Dual-chamber permanent transvenous electrodes, insertion, removal or replacement of (Anaes.) | $710.50 |
| 61109 | Fluoroscopy in an angiography suite with image intensification, in conjunction with a surgical procedure, using interventional techniques, not being a service associated with a service to which another item in this table applies (R) | $258.90 |

# Approach to assessment

## Review questions

The advisory panel determined that the review questions were:

1. What is the safety of CRT and optimal pharmacological therapy, compared to optimal pharmacological therapy alone, for people with severe heart failure?

2. What is the effectiveness of CRT and optimal pharmacological therapy, compared to optimal pharmacological therapy alone, for people with severe heart failure?

3. What is the clinical need for CRT and optimal pharmacological therapy, compared to optimal pharmacological therapy alone, for people with severe heart failure?

4. What is the cost-effectiveness of CRT and optimal pharmacological therapy, compared to optimal pharmacological therapy alone, for people with severe heart failure?

## Review of literature

### Databases searched and search terms used

The medical literature was searched to identify relevant studies and reviews (see Table 4). Retrieval was limited to information in English. There was no restriction by date of publication. The search of all sources was completed in April 2005.

**Table 4 Databases accessed and major search terms used in the literature search**

| Database | Platform | Edition | Major search terms |
|---|---|---|---|
| Medline | Ovid<br>Pubmed | 1966 to March Week 2 2002<br>2002 – March Week 4 2005 | (heart failure/ or heart failure.mp.) AND (cardiac pacing, artificial/ OR pacemarker, artificial/ OR pacing.mp OR pacemaker.mp) AND (resynchroni$ OR re-synchroni$ OR biventricular OR bi-ventricular OR synchron$).mp. |
| Premedline | Ovid | March 12 2002<br>April 6 2005 | (pacing or pacemaker$) AND (resynchron$ OR re-synchron$ OR bi-ventricular OR biventricular) AND (heart OR cardio$ OR cardiac) |
| Embase | Ovid | 1988 – 2002 Week 10<br>2002 – 2005 Week 14 | (exp heart disease/ OR heart failure.mp. OR cardiac failure.mp.) AND (exp pacemaker OR exp heart pacing OR pacing.mp. OR pacemaker.mp.) AND (resynchroni$ OR re-synchroni$ OR biventricular OR bi-ventricular OR synchron$).mp. |
| Current Contents | Web of Science | 1993 week 26- 2002 week 11<br>April 6 2005 | (pacing or pacemaker$) AND (resynchron$ OR re-synchron$ OR bi-ventricular OR biventricular) AND (heart OR cardio$ OR cardiac) |
| Science Citation Index | Web of Science | 1987 – 2002 March<br>2002 – 6 April 2002 | (pacing or pacemaker*) AND (resynchron* OR re-synchron* OR bi-ventricular OR biventricular) AND (heart OR cardio* OR cardiac) |
| Cochrane Database of Systematic Reviews | Ovid | Issue 1 2002 -<br>Issue 1 2005 | (biventricular or bi-ventricular OR re-synchroni$ or resynchroni$ or synchroni$).mp. AND (heart OR cardiac).mp. |
| Cochrane Controlled Trials Register | Ovid | Issue 1 2002<br>1st Issue 2005 | (biventricular or bi-ventricular OR re-synchroni$ or resynchroni$ or synchroni$).mp. AND (heart OR cardiac).mp. AND (pacing OR pacemaker).mp |
| DARE; NHS EED; HTA databases | CRD website | 12 March 2002<br>6 April 2005 | (biventricular OR bi-ventricular OR re-synchroni$ OR resynchroni$ OR synchroni? OR dual chamber).mp. AND (heart OR cardiac).mp. |

## Other sources of information

- Reference lists of papers retrieved were searched for additional relevant citations and background references, along with material supplied by the applicant.
- Clinical trials registers.
- Websites and publications of Health Technology Assessment agencies (see Appendix F).
- Websites of major professional cardiology associations and societies (see Appendix F).
- Government agencies for information relating to the burden of heart disease.

## Results from the search strategy

### Existing reviews

Four systematic reviews were located, but only one primarily addressed the aims of this review. The only systematic review that specifically considered the effects of CRT alone was published in 2003 and it included just the results from one study, MIRACLE.

### Published literature

The search was completed in April 2005 and retrieved a total of 1,445 non-duplicate citations. The numbers of non-duplicate citations retrieved from each database are listed in Table 5.

**Table 5 Results from the search**

| No. of Citations | Medline | Embase | Current Contents | Science Citation Index | Cochrane Controlled Trials Register | Total |
|---|---|---|---|---|---|---|
| Total | 878 | 294 | 242 | | 31 | 1,445 |

From the citations, 560 articles (39%) were obtained and formally considered against the inclusion criteria (see Table 8).

### Criteria for selecting studies

The non-duplicate citations were evaluated to determine whether they met agreed eligibility criteria. The eligibility criteria were defined for review question 1 (what is the safety of CRT and optimal pharmacological therapy, compared to optimal pharmacological therapy alone, for people with severe heart failure) and slightly modified for the other review questions according to defined parameters. For all review questions, the same criteria were applied to abstracts and full papers.

### Review question 1: Safety

The safety of CRT was assessed in relation to the frequency and severity of short-term and long-term adverse events related to the treatment.

Human studies that assessed the safety of the intervention were selected for inclusion using information provided in the title/abstract located by the search, or by an evaluation of the full study. The selection criteria are outlined in Table 6.

**Table 6 Selection criteria for a review of the safety of CRT**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Studies were included whether or not they had a comparison or control group (corresponding to studies outlined by NHMRC levels I – IV, See Table 9).<br>Any number of human subjects.<br>English language articles.<br>Studies that clearly describe their methods and results.<br>Important non-published studies or abstracts of studies identified by expert members of the advisory panel. | Letters, comments and articles published in abstract form only.<br>Non-published work.<br>Studies that have not reported primary data obtained in a clinical setting (eg, reviews).<br>Studies that have been superseded by another publication using the same patient group with the same purpose. |

In addition:

- Safety information was presented from trials with patients in atrial fibrillation, if these trials included *any* patients in sinus rhythm.

- Safety information was presented from trials using combined biventricular pacing devices with an implantable cardiac defibrillator, if the trial included *any* patients receiving a biventricular pacing device alone.

- Safety information was presented from trials including patients who received epicardial or transseptal left ventricular leads, if these trials included *any* patients who received transvenous leads.

The justification for these inclusions were that excluding trials that contained some patients with atrial fibrillation and/or an implantable defibrillator and/or transseptal or epicardial leads would eliminate information relevant to the review. Also, the potential safety issues may be independent of the underlying heart rhythm/presence of a defibrillator/type of leads. However, in many studies when an undesirable outcome was described, the type of rhythm, device or method of lead insertion was not specifically stated. Where this information was provided, it has been included in the tables.

## Criteria for review question 2: Effectiveness

The assessment of effectiveness used the same methods as the assessment of safety but with the following important differences:

- Only randomised controlled trials or systematic reviews of randomised trials relevant to the research questions (corresponding to studies outlined by NHMRC levels I – II, see Table 9) were included. It should be noted that data from non-randomised studies that considered postoperative survival and hospitalisations related to the procedure are presented in the safety section. Information about survival and hospitalisations provided by randomised studies is presented under effectiveness.

- Studies were limited to those with 20 or more human subjects.

### Review question 3: Need

Studies that described the clinical need for the intervention were identified and included. Burden of disease data relevant to Australia was specifically sought from a number of websites listed in Appendix F.

### Review question 4: Economic evaluation

Economic evaluations examining CRT in the treatment of severe heart failure that involved both costs and consequences for the intervention and its comparator were eligible for inclusion and assessment. Potential study types included: cost-minimisation analysis, cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis. NHMRC criteria were available to evaluate the quality of the evaluations (National Health and Medical Research Council 2001).

## Reasons for exclusion

Based on the preceding criteria 462 (82%) retrieved papers were excluded from this review (see Table 8). The reasons for exclusion are listed in Table 7. Three hundred and fifty eight studies (78% overall) were excluded because they did not present any randomised trial or non-randomised comparative study data relevant to the assessment of effectiveness. Some 312 studies (68%) failed to provide any primary data relevant to the review questions. Appendix E tabulates each paper retrieved and the reason(s) for its exclusion.

**Table 7 Reasons for exclusion**

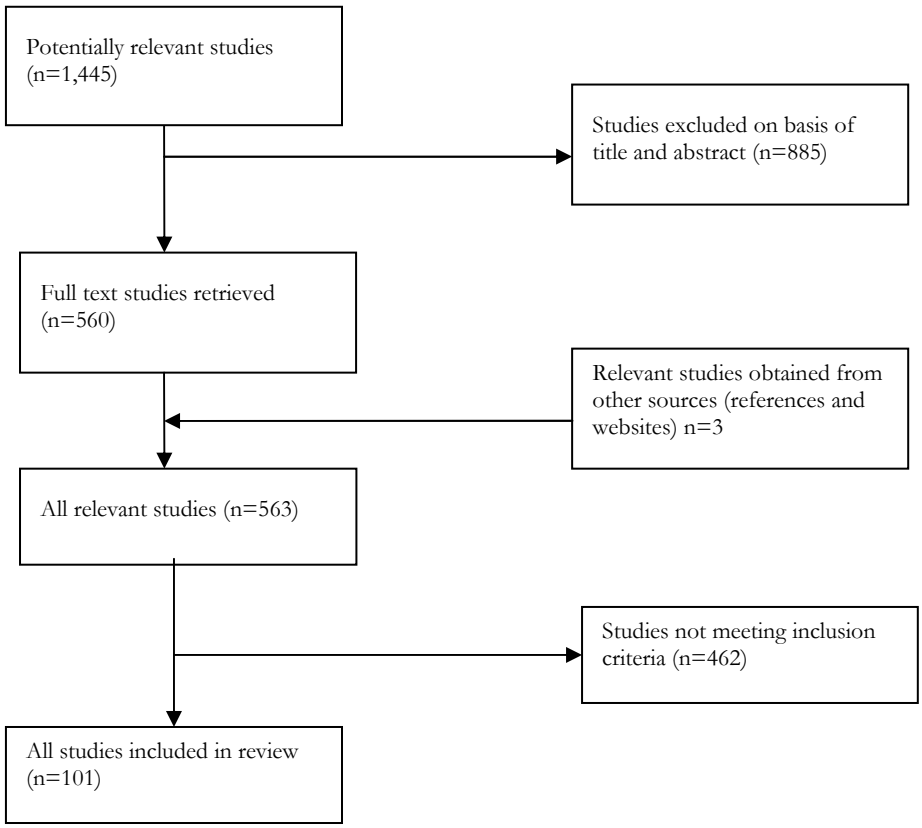
| Reason for exclusion | Number (%) * |
|---|---|
| Not systematic review/ randomised trial or non-randomised comparative study (effectiveness criteria only) | 358 (78) |
| <20 subjects (effectiveness criteria only) | 112 (24) |
| Background paper/ no primary data/ expert opinion/ electrophysiological or haemodynamic outcomes only | 312 (68) |
| Letters/comments/ abstract only published | 38 (8) |
| All participants not in sinus rhythm | 7 (2) |
| All participants received non-transvenous leads | 19 (4) |
| All participants received an ICD | 29 (6) |

*Note: more than one reason is possible per paper and % corresponds to proportion of 461

## Included studies

Data from 101 studies were included in this review (see Table 8) and the studies are described in Appendix C.

**Table 8 Flow diagram of studies through the review**



# Assessment methods

## Study methodology appraisal

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (National Health and Medical Research Council 2000). Evidence tables are presented that describe the characteristics of the study participants, the intervention, the magnitude of effect in relation to key outcome(s) along with the level of evidence and the quality of the study. The highest level of evidence was regarded as primary evidence in relation to decision making and other levels were considered supplementary evidence.

The assessment of the study quality involved a series of questions designed to ascertain the potential for bias in the study (see (Medicare Services Advisory Committee 2000), pages 29-31). An indication was provided of whether the questions were based on information that was stated and adequate, stated but inadequate, or not stated. These dimensions (see Table 9) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect, and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

**Table 9 Evidence dimensions**

| Type of evidence | Definition |
|---|---|
| Strength of the evidence | |
| Level | The study design used, as an indicator of the degree to which bias has been eliminated by design.* |
| Quality | The methods used by investigators to minimise bias within a study design. |
| Statistical precision | The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect. |
| Size of effect | The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval. |
| Relevance of evidence | The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used. |

*See Table 10

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 10.

**Table 10 Designations of levels of evidence***

| Level of evidence | Study design |
|---|---|
| I | Evidence obtained from a systematic review of all relevant randomised controlled trials |
| II | Evidence obtained from at least one properly-designed randomised controlled trial |
| III-1 | Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method) |
| III-2 | Evidence obtained from comparative studies, including systematic reviews of such studies, with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group |
| III-3 | Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group |
| IV | Evidence obtained from case series, either post-test or pre-test/post-test |

*Modified from NHMRC, (2000).

## Data extraction

Data extraction was undertaken by two independent reviewers using a standardised instrument created for this review. Disagreements between reviewers were resolved by consensus.

Where available, the following information was extracted:

- year of study/publication;
- subject selection;
- study location;
- setting;
- study design;
- intervention description;
- description of comparator;
- definition of how diagnosis of heart failure was established and definition of severity;
- sample size and power;
- eligibility criteria for study subjects;
- age/gender of participants;
- co-morbid conditions;
- estimate of compliance;
- percentage in control group who received intervention (contamination) ;
- other treatment(s) provided to both groups;

- length of follow-up and completeness of follow-up in both groups;
- outcomes measured;
- magnitude of effect;
- reported adverse effects (frequency and severity).

## Outcomes measures

A hierarchy of outcomes was used in this review. Studies that assessed clinical and patient-oriented outcomes, such as mortality, quality of life, costs and aspects of morbidity such as rates of hospitalisation, were regarded as primary evidence. Research that included surrogate clinical outcomes, such as oxygen consumption at peak exercise and at anaerobic threshold, and the six-minute walk test, provided secondary evidence. Research that assessed changes in haemodynamic outcomes was not assessed.

Cardiac resynchronisation therapy (CRT) was evaluated taking into account the other treatments provided. CRT was usually performed in addition to optimal pharmacological therapy, so its incremental value was assessed.

### Description of outcome measures

#### NYHA classification

The NYHA classification system was first introduced in 1948 and subsequently has been used extensively in heart failure research. The classification system assesses functional capacity by using a patients' own assessment of their exercise ability. NYHA class I indicates that the patient has no limitations to his or her ordinary physical activity due to fatigue, dyspnea or palpitations. Class II indicates that the patient is comfortable at rest but has slight limitation of physical activity, and ordinary physical activity will result in symptoms. By contrast, NYHA class III corresponds to marked limitation of physical activity where less-than-ordinary activity leads to symptoms, while NYHA class IV represents severe limitation with symptoms of heart failure being present at rest and an inability to carry out any physical activity without discomfort. The advantages of the system are that it is simple to use, has been in use for a long time, and is an effective general predictor of outcome (Cowburn et al 1998, Eichhorn 2001, Gibelin 2001). Due to its reliance on self-assessment, some experts have questioned the reliability of the classification system (Gibelin 2001). The severity of symptoms and functional capacity is dependent on the efficacy of treatment, patient expectation, and medical interpretation. There may be a dissonance between symptoms and myocardial dysfunction (Remme et al 2001). Mild symptoms may not equate with minor cardiac dysfunction. Similarly, researchers have also questioned the reproducibility and the sensitivity of the measure to small but sometimes important clinical changes (Selzer and Cohn 1972, Franciosa 1987).

#### Six-minute walk

The six-minute walk is usually conducted according to the recommendations of Guyatt et al ( 1985) and Lipkin et al (1986). Patients are instructed to cover as much ground as possible in six minutes at a brisk walking pace. Baseline evaluation includes a training test

to ensure that the patient can complete the test. Each assessment then includes two tests at least three hours apart. The value recorded is the mean of the results from the two tests. The reproducibility and acceptability of this test have previously been described (Lipkin et al 1986, Opasich et al 1998, Guyatt et al 1985, Zugck et al 2000). The test strongly and independently predicts morbidity and mortality (Lipkin et al 1986, Guyatt et al 1985, Poole-Wilson 2000, Bittner et al 1993). However, the results from some studies suggest there may be a low concordance between NYHA stratification and exercise capacity (Rostagno et al 2000).

### Exercise test

Exercise capacity can be assessed by means of the maximal treadmill exercise test. Patients with heart failure do not always perform well on usual routines so a modified Bruce or Naughton protocol with reduced speed and gradient increments is preferred (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002). The duration of exercise time is an assessment measure of functional capacity and has been used as a prognostic tool (Jafri et al 1986). However, known problems with this measure may include: it may be limited by the motivation of the patient and the physician; results may improve with familiarity with the test; and the relationship between test results and the physical stresses of normal living is not clear (Packer 2001).

### Peak oxygen uptake

Peak oxygen uptake as measured during cardiopulmonary exercise testing can be used to assess the maximal exercise tolerance and has been considered as an objective reference measurement among patients with heart failure (Cowburn et al 1998). This method of assessment has been widely used to assess functional capacity and to reliably predict survival in a variety of patient populations with heart failure (van den Broek et al 1992, Aaronson et al 1997, Szlachcic et al 1985). Its limitations are that it requires sophisticated equipment and specially trained personnel, and readings can be affected by age, gender and the presence of muscle disease (Mancini et al 1991, Stelken et al 1996, Metra et al 1999).

### The Minnesota Questionnaire

The Minnesota Living with Heart Failure Questionnaire (Minnesota Questionnaire) contains 21 questions regarding people's perceptions of the effects of heart failure on their daily lives. Each question is rated on a scale of 0 to 5, producing a total score between 0 and 105. Questions examine the severity of symptoms, aspects of functional ability, patients' need for medical care and their mental wellbeing. The higher the score, the worse the quality of life (Rector et al 1987, Rector and Cohn 1992). The reliability and validity of the questionnaire have been assessed and found to be satisfactory (Rector and Cohn 1992, Rector et al 1987). The questionnaire was designed to be a patient self-assessment measure for use in clinical trials and is not a complete quality of life assessment tool (Rector et al 1987).

### Relationship between outcome measures

Studies comparing patient performance on the preceding outcome measures have recorded varying, and sometimes low, levels of correlation between test results. It is possible that the measures may be assessing different aspects of functional ability (Cowley et al 1991).

### Data analysis and statistical methods

The statistical combination of randomised controlled trials (meta-analysis) was conducted using RevMan (Version 4.2) software. The main measure of effect presented was the relative risk (RR). Tests of heterogeneity were conducted using chi-squared and $I^2$ statistics. A fixed-effect model was used when no statistical heterogeneity was present.

Individual study results were reported with 95 per cent confidence intervals and/or relevant *p* values. The study results were abstracted where possible from published papers. Individual patient data was not obtained. Data was not tabled when it was clear that the results were superseded by subsequent publications.

## Expert advice

An advisory panel with expertise in cardiology, radiology, public health, consumer issues and surgery was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the advisory panel is provided in Appendix B.

# Results of assessment

## Description and methodological quality of included studies

Data was tabulated if it was stated in the text, tables, graphs or figures of an article or it could reliably be extrapolated from the information presented in the article. Where an event was not reported, it was defined as being not stated (ns) rather than inferred that the event did not occur. For example, if the number of septic complications was not stated, then this was documented rather than any inference made that the event(s) had not occurred.

## Designation of levels of evidence

The results from systematic review/meta-analysis are included in this review, although three of them specifically considered the effectiveness of cardiac synchronisation therapy with or without the addition of an implantable cardioverter. Nine RCTs met the inclusion criteria, as did 38 comparative studies and 50 case series studies (see Table 11). Various results from the MIRACLE study were described in seven papers while data from the MUSTIC trial were presented in six publications.

**Table 11 NMHRC levels of evidence**

| Level | Number of studies (%) |
|---|---|
| I | 4 (4) |
| II | 9 (9) |
| III-2 and III-3 | 29 (29) |
| III-3 | 9 (9) |
| IV | 50 (50) |
| Total | 101 |

Note: Percentages do not equal 100 because of rounding.

### Description of included systematic reviews/meta-analyses

Four systematic reviews were included, although only one primarily addressed the aims of this review. Three of the systematic reviews addressed the efficacy and safety of cardiac resynchronisation therapy with and without an implantable defibrillator and only considered the role of CRT alone in relation to sub-group or sensitivity analyses. The only systematic review that specifically considered the effects of CRT alone was published in 2003 and it included the results from only one study, MIRACLE. The systematic review by McAlister et al (2004) was published as a journal article and presented as both a summary report and a full AHRQ publication.

### Description of included individual studies

Nine RCTs, totalling 18 publications, were included in this review. The most important trials were named CARE-HF, COMPANION, MIRACLE and MUSTIC and their results were presented primarily in publications by: Cleland et al (2005), Bristow et al (2004); Abraham et al (2002) and Cazeau et al (2001).

**Individual main randomised trials**

### *CARE-HF study (Cleland 2005)*

The Cardiac Resynchronisation – Heart Failure (CARE-HF) trial was a large study based in 10 countries in Europe that included 82 centres. The study was conducted between January 2001 and March 2003. Two parallel comparison groups were included: one group (treatment group) received optimal pharmacological treatment (OPT) plus biventricular pacing while the control group received only OPT. Patients were randomised in a stratified manner according to NYHA class before implantation. This was similar to COMPANION but unlike MIRACLE and MUSTIC. Inclusion criteria involved the presence of severe heart failure (NYHA III and IV) despite optimal pharmacological treatment, left ventricular ejection fraction no more than 35 per cent, left ventricular end-diastolic diameter of at least 30 mm (indexed to height) and a QRS duration of at least 120 ms. Excluded were patients with a major cardiovascular event in the previous six weeks, those with conventional indications for pacemaker or implantable cardiac defribillator (ICD), patients with heart failure requiring continuous intravenous therapy, and anyone with an atrial arrhythmia. The primary endpoint for the study was a composite composed of death or unplanned hospitalisation for a major cardiovascular event, and only the first event in each patient was included in the analysis. Secondary outcomes were: death from any cause; a composite of death from any cause and unplanned hospitalisation with heart failure; quality of life at 90 days and also NYHA class at 90 days. In total, 813 patients were included in the trial with 409 randomised to receive cardiac resynchronisation therapy plus OPT while 404 were randomised to receive only OPT. The two patient groups were similar at baseline with respect to demographic, electrophysiological, haemodynamic and functional characteristics. Implantation and activation of a pacemaker was successful in 390 (95%) of the patients included in the treatment group. Neither patients nor clinicians were blinded to treatment assignment during the trial although the endpoints assessment committee was unaware of the patients' treatment assignment during the study. Outcome assessments were made at one, three, six, nine, 12 and 18 months of follow-up, and every six months thereafter. Survival status was ascertained for all patients by the end of the study. In the OPT group, a pacing device was inserted and activated in 50 patients. The device was activated in 19 patients (5%) before they reached the primary endpoint. However, the results of the trial were assessed using an intention-to-treat method of analysis.

### *COMPANION study (Bristow 2004)*

The Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) study was a large multi-site RCT undertaken in 128 centres in the United States between January 2000 and November 2002. The trial had three parallel arms with patients allocated to the comparison groups in a 1:2:2 ratio. It simultaneously compared OPT with OPT plus CRT, and OPT plus CRT plus an implantable cardiac defibrillator. Patients were randomised before implantation, unlike MIRACLE and MUSTIC. Inclusion criteria included the presence of severe heart failure (NYHA III and IV), left ventricular ejection fraction less than 35 per cent, QRS duration greater than 120 ms, PR interval greater than 150 msec, and sinus rhythm. The primary outcome for the study was a composite of deaths or hospitalisations due to any causes, while secondary

outcomes included death from any cause; death or hospitalisation for cardiovascular causes; death or hospitalisation for heart failure and adverse events. Some 617 patients were randomised to receive only a pacemaker in addition to OPT while 308 patients were assigned to the control group and received just medication. Baseline comparisons of the study groups indicated they had similar baseline demographic, electrophysiological, echocardiographic and functional characteristics. Implantation of a pacemaker without a defibrillator was successful in 83 per cent (539/617) of cases. Patients and clinicians were not blinded to study group assignment during the trial. Outcomes were assessed at baseline and during regular intervals throughout follow-up. During the study a relatively large number (26 per cent) of patients withdrew from the medication-only group to join the implant groups. To mitigate this high withdrawal rate, patients who had withdrawn before December 2002 were asked about vital status and hospitalisation for the duration of the study. The trial was stopped early in November 2002 after it was noted that the pacemaker-defibrillator group had crossed the primary and secondary endpoints. Status of the primary endpoint was ascertained for 91 to 99 per cent of the patients in the three study groups. The study employed intention-to-treat analyses.

### *MIRACLE Study (Abraham 2002; Adamson 2003; St John Sutton 2003; Aranda 2004; Woo 2005)*

The Multicentre InSync Randomised Clinical Evaluation (MIRACLE) was a large multi-centre randomised trial involving 45 centres in the United States and Canada. The study used a parallel design to prospectively evaluate the effect of cardiac resynchronisation therapy plus OPT versus no active pacing and OPT. Inclusion criteria included the presence of severe heart failure (NYHA III and IV), ejection fraction less than 35 per cent and a QRS duration greater than 130 msec. Patients were randomised after successful transvenous implantation of a CRT device and three pacing leads. A small group (n=71) of patients was involved in a pilot three-month phase, the results from which were reported elsewhere. For the remaining 453 patients, allocation to active or inactive pacing was undertaken in a double blind manner by an electrophysiologist not otherwise involved in patient care. The active (n=228) and control (n=225) groups were similar at baseline in relation to demographic, electrophysiological, echocardiographic and functional characteristics. Outcomes were assessed at baseline, one, three and six months after randomisation. Thirty-seven people (24 in the control group and 13 in the treatment group) did not complete the trial although there were no losses to follow-up related to worsening heart failure and/or death. The primary outcomes were distance walked in six minutes, quality of life (Minnesota Questionnaire), and change in the NYHA functional class. Secondary outcomes were peak oxygen consumption, total exercise time, patients' view of progress, clinical composite score, left ventricular ejection fraction, end diastolic dimension, and the area of the mitral regurgitant jet. An intention-to-treat analysis was employed.

### MUSTIC Study (Cazeau 2001; Alonso 2003; Linde 2003; Duncan 2003; Linde 2003; Varma 2003)

The Multisite Stimulation in Cardiomyopathy (MUSTIC) was a randomised, controlled crossover trial comparing CRT with no pacing. It involved 58 patients in six European countries. Eligibility requirements included the presence of severe heart failure (NYHA III), an ejection fraction less than 35 per cent, sinus rhythm and a QRS interval greater than 150 msec. All patients had a CRT device implanted and were randomised into two

groups two weeks after implantation. One group had the device switched on and the other had it switched off for three months. The method of randomisation and allocation to study groups was not described. The patients were crossed over to the opposite arm for an additional three months, without any 'washout' period. The primary endpoint of MUSTIC was the six-minute hall walk distance. Secondary outcomes included quality of life (Minnesota Living with Heart Failure Questionnaire), peak oxygen consumption, total exercise time and patients' preference. Forty-eight patients completed the study. An intention-to-treat analysis was conducted. Only patients were blinded to treatment allocations.

### Description of included individual studies

Ninety-seven individual studies met the inclusion criteria (see Tables 13 and 14). Although five studies (Abraham et al 2002, Adamson et al 2003, St John Sutton et al 2003, Aranda et al 2004, Woo et al 2005) report the results from the MIRACLE trial, the main publication is provided by Abraham et al (2002). Similarly, six studies (Cazeau et al 2001, Alonso et al 2003, Duncan et al 2003, Linde et al 2002a, Linde et al 2003, Varma et al 2003b) presented data from the MUSTIC trial but the most important publication is provided by Cazeau et al ( 2001). Two studies (Gras et al 1998, Reuter et al 2000) were excluded because they were superseded by later publications. Three publications (Ricci et al 2000, Zardini et al 2000, Porciani et al 2000) report the same trial, InSync, and are presented as one study.

The 97 individual studies included approximately 7,080 participants. However, some double-counting is possible, especially among studies based in the same centre(s). Nine studies are randomised controlled trials, 38 are comparative studies without randomisation and the remaining 50 are case series. All randomised trials were based in either Europe or North America and they included 20 to 925 patients divided between pacemaker and control arms. Of the non-randomised comparative studies 26 were located in Western Europe and four in the United States. Another two studies were jointly based in Europe and North America. Two other studies were based in Hong Kong. One comparative study was undertaken in Australia. Other individual comparative studies were based in Turkey, Japan and the Czech Republic. Seven of the non-randomised comparative studies included more than 100 participants and the largest involved 313 subjects. Among the case series studies, 22 were based in Europe, 10 in the United States, three in both Europe and North America, three in Hong Kong, two in South America, two in Japan, two in Denmark and one each in Southeast Asia, Turkey, Sweden and Saudi Arabia. One case series study was undertaken in Australia and one did not provide information about its location. The case series reports also included a variable number of participants (range: 1 to 198). Overall, 65 of the 97 individual studies (37/50 case series reports and 24/47 randomised or comparative studies) included less than 50 participants. The CARE-HF and COMPANION trials included the largest numbers of participants (813 and 925 respectively) and both reported on safety as a secondary outcome. These two studies primarily reported combined rates of hospitalisation and mortality as composite outcomes, although some single outcomes were also provided. Neither the MIRACLE study nor the MUSTIC trial was sufficiently powered for mortality, although both reported data about this outcome.

All 97 individual studies have included participants with broadly similar characteristics. The reported mean age for participants in the 97 studies was 45 to 78 years. Most studies (81/91) that reported the mean age of participants included patients who were aged 57 to 69 years. Males predominated in nearly every study that provided this information

(4760/6361 patients or 75 per cent in 85 studies). Eighty-three out of 85 studies included more than 50 per cent male while two small case reports with four (Gasparini et al 2003e) and 10 (Nelson et al 2000) participants included equal numbers of both sexes. A single case report concerned one female patient.

The overwhelming majority of patients were in normal sinus rhythm. In total, about 3,838 participants, or 92 per cent of the 4,187 patients included in the 48 studies that provided this information, were in sinus rhythm. The case series by al-Khadra (2003) was the only study to report that participants with sinus rhythm comprised less than 50 per cent of the sample. Twenty-two studies excluded patients who were not in sinus rhythm and 26 included a mixture of patients in either sinus rhythm or atrial fibrillation, while 49 did not provide this information.

The majority of patients (3,754/4,764 or 79 per cent) among the 52 studies that reported this data were in NYHA class III. In 12 studies, the majority of patients were in NYHA class IV and in two studies the majority of patients (58 per cent and 54 per cent) were in NYHA class II (De Cock et al 2005 and Kerwin et al 2000). Across all the studies that reported NYHA class information, only 814 participants, or 17 per cent, were assigned to the most severe degree of symptomatic heart failure. Nine of the 52 studies providing NYHA data included participants in NYHA class II, however, they comprised less than 20 per cent of the total sample in seven of these studies. The average intraventricular conduction delay (QRS interval) was 153 to 197 ms in 62/65 reporting studies. A case series of 102 patients indicated that the mean QRS among the participants was 150 msec (Schuchert et al 2004). One study reported a mean QRS of 123 ms and included seven patients with QRS <120 ms (Hamdan et al 2000). Another study by Sbragia et al (2003) was a single case report that involved a patient with a QRS duration of 100 ms. Mean LVEF was 20 per cent to 32 per cent in all but eight of the 45 studies providing information. In one study the mean LVEF was 42 per cent (al-Khadra 2003) while in seven others the mean LVEF was less than 20 per cent (Daubert et al 1998, Bax et al 2003b, Leclercq et al 1998, Kerwin and Paz 2003, Van Erven et al 2004, Pires et al 2005, Kanhai et al 2004).

Some 66 studies provided data about the underlying aetiology of the heart failure (not shown in Tables 13 and 14). However, variations in the definitions and classifications of the underlying causes prevent valid comparisons beyond noting that on average 45 per cent of patients in the studies were reported to have heart failure that was ischaemic in origin. In the three largest studies, CARE-HF, COMPANION and MIRACLE, the overall proportions of patients with heart failure that were considered to be ischaemic in origin were 38 per cent, 55 per cent and 57 per cent respectively. The smaller studies included wider variation in the proportion of patients with ischaemic cardiomyopathy. For example, all 14 participants in the study by Zagrodzky et al (2001) but only two, or 11 per cent, of the 18 patients included in the Leclercq et al (1998) case series were judged to have an ischaemic origin for their heart failure.

Data about the types of pacemaker and lead systems, the site of implantation and the methods of pacing were often not fully described in the studies. With the rare exceptions of Hansky et al (2002), Ellery et al (2005), and Kautzner et al (2004), most studies have not described the frequency and type of adverse events in relation to the types of equipment used. Similarly, safety and effectiveness data have not usually been attributed to specific sites of implantation or methods of pacing and consequently, this data has generally not been reported in this review.

However, exceptions are provided by two non-randomised comparative studies. Rossillo et al (2004) assessed the effectiveness of placing leads in the anterior or anterolateral branches of the coronary sinus versus the lateral and posterolateral branches and Res et al (2005) examined the impact of placing a lead at different positions in the right ventricle.

Table 12 lists the devices that were implanted in the three largest trials.

**Table 12 Implanted devices**

| Trial | Device |
|---|---|
| CARE-HF | Medtronic InSync or InSync III |
| COMPANION | CONTAK TR models 4510-13, model 1241 (CONTAK CD model 1823 Guidant) |
| MIRACLE | InSync model 8040 Medtronic |

**Table 13 Description of individual randomised trials and comparative studies**

| Study | NHMRC grade | Location | Sample | Mean patient characteristics (medians are presented when means cannot be reported) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Number | Mean Age years | % Male | Mean QRS | Mean LVEF % | % SR | NYHA III % IV % |
| **Randomised controlled trials: CRT versus no active pacing** | | | | | | | | | |
| (Cleland et al 2005b) | II | Europe | 813 | 66.5 | 73 | 160 | 25 | 100 | 94<br>6 |
| (Bristow et al 2004) | II | US | 925 (+595 pacing and ICD) | 67.5 | 68 | 159 | 22 | 100 | 86<br>5 |
| (Abraham et al 2002) | II | US/ Canada | 453 | 63.9 | 68 | 167 | 21.8 | 100 | 91<br>9 |
| (Cazeau et al 2001) | II | Europe | 67 | 63 | 75 | 176 | 23 | 100 | 100<br>0 |
| (Linde et al 2002) | III-2 | Europe | 48 | 63 | 75 | 176 | 22 | 100 | 100<br>0 |
| **Randomised controlled trial: CRT versus RV pacing alone** | | | | | | | | | |
| (Walker et al 2000f) | II | UK | 20 | 60 | 75 | 163 | ns | 60 | 75<br>25 |
| **Randomised controlled trial: testing of different guiding catheter shapes** | | | | | | | | | |
| (Butter et al 2003) | II | Europe | 27 | ns | ns | ns | ns | ns | ns<br>ns |
| **Randomised controlled trials: testing of different venography techniques** | | | | | | | | | |
| (De Martino et al 2005) | II | Italy | 83 | 62 | ns | ns | 24 | ns | ns<br>ns |
| (Sawhney et al 2004) | II | US | 40 | 60 | 70 | 176 | 26 | ns | ns<br>ns |
| **Randomised controlled trial: testing of electrophysiology catheter aided guiding versus conventional guiding** | | | | | | | | | |
| (De Martino et al 2004) | II | Italy | 34 | ns | ns | ns | ns | ns | ns<br>ns |
| **Non-randomised comparative studies: CRT versus LV or RV pacing alone** | | | | | | | | | |
| (O'Donnell et al 2005a) | III-2 | Australia | 50 | 65 | 82 | 167 | 22 | 100 | ns<br>ns |
| (Touiza et al 2001) | III-2 | France | 33 | 67 | 79 | 187 | 22 | 55 | 39<br>61 |
| (Bordachar et al 2004a) | III-2 | France | 33 | 69 | 64 | ns | 26 | ns | ns<br>ns |

**Table 13 Description of individual randomised trials and comparative studies (continued)**

| Study | NHMRC grade | Location | Sample | Mean patient characteristics (medians are presented when means cannot be reported) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Number | Mean age years | % Male | Mean QRS | Mean LVEF % | % SR | NYHA III % IV % |
| (Etienne et al 2001) | III-2 | France | 23 | 68 | 87 | 186 | 23 | 57 | 35<br>65 |
| (Zagrodzky et al 2001) | III-3 | US | 14 | 62 | 100 | ns | 31 | ns | ns<br>ns |
| **Non-randomised comparative studies: Bifocal RV pacing versus right ventricular outflow pacing** | | | | | | | | | |
| (Res et al 2005) | III-2 | Netherlands | 40 | 69 | 78 | 180 | 24 | ns | ns<br>ns |
| **Non-randomised comparative studies: responders to CRT versus non-responders** | | | | | | | | | |
| (Vogt et al 2004b) | III-2 | Germany | 313 | 62 | 75 | ns | 24 | ns | ns<br>ns |
| (Lecoq et al 2005) | III-2 | France | 139 | 68 | 81 | 188 | 21 | 67 | 69<br>31 |
| (Reuter et al 2002) | III-2 | US | 102 | 64 | 85 | 184 | 24 | 81 | 62<br>30 |
| (Bax et al 2004) | III-2 | Netherlands | 85 | 66 | 75 | 178 | 23 | ns | 80<br>20 |
| (Penicka et al 2004) | III-2 | Belgium | 55 | 70 | ns | 182 | ns | 93 | ns<br>ns |
| (Yu et al 2003a) | III-2 | Hong Kong | 30 | 62 | 70 | ns | ns | ns | 60<br>40 |
| (Barbieri et al 2004) | III-2 | Italy | 18 | 68 | 72 | 158 | 23 | 67 | 77<br>23 |
| (Oguz et al 2002b) | III-2 | Turkey | 16 | 59 | 100 | 167 | 26 | ns | 25<br>75 |
| (Capasso et al 2005) | III-2 | Italy | 15 | 69 | 73 | 163 | 25 | ns | 40<br>60 |
| (Lunati et al 2002) | III-3 | Italy | 52 | 61 | 88 | 195 | 26 | ns | 73<br>23 |
| (Tsurugaya et al 2004) | III-3 | Japan | 10 | 62 | 60 | ns | ns | 80 | 30<br>70 |
| **Non-randomised comparative studies: repetitive lead dislocation versus no dislocation** | | | | | | | | | |
| (De Cock et al 2004) | III-2 | Netherlands | 77 | ns | ns | ns | ns | ns | ns<br>ns |
| **Non-randomised comparative studies: testing of over-the-wire technique of lead insertion versus stylet-driven lead** | | | | | | | | | |
| (Ellery et al 2005) | III-2 | Europe | 96 | 68 | 76 | 163 | ns | ns | 83<br>17 |
| **Non-randomised comparative studies: testing of ICD versus pacing alone** | | | | | | | | | |
| (Ermis et al 2004) | III-2 | US | 158 | 69 | 76 | ns | 22 | ns | ns<br>ns |

**Table 13 Description of individual randomised trials and comparative studies (continued)**

| Study | NHMRC grade | Location | Sample | Patient characteristics | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Mean age | % Male | Mean QRS | Mean LVEF % | % SR | NYHA III % IV % |
| (Alonso et al 1999) | III-3 | France | 26 | 66 | 92 | 178 | 23 | 77 | 69<br>31 |
| **Non-randomised comparative studies: coronary heart disease versus non-coronary heart disease (Gasparini also compared lead placement sites in another study involving the same cohort (Gasparini et al 2003b))** | | | | | | | | | |
| (Gasparini et al 2003e) | III-2 | Italy | 158 | 65 | 77 | 174 | 29 | ns | 80<br>20 |
| (Leclercq et al 2004) | III-2 | France<br>Canada | 103 | 67 | 80 | 178 | 22 | 100 | ns<br>ns |
| (Molhoek et al 2004c) | III-2 | Neth-erlands | 74 | 64 | 68 | 177 | 22 | ns | ns<br>ns |
| **Non-randomised comparative studies: QRS duration >120 ms versus <120 ms** | | | | | | | | | |
| (Achilli et al 2003) | III-2 | Italy | 52 | 70 | 60 | 153 | 23 | ns | ns<br>ns |
| **Non-randomised comparative studies: QRS duration 120-150 ms versus >150 ms** | | | | | | | | | |
| (Yu et al 2004a) | III-2 | Hong Kong | 58 | 66 | 66 | ns | ns | ns | 74<br>26 |
| **Non-randomised comparative studies: Baseline perfusion deficit** | | | | | | | | | |
| (Sciagra et al 2004) | III-2 | Italy | 20 | 67 | 85 | ns | ns | ns | 90<br>10 |
| **Non-randomised comparative studies: leads in anterior and anterolateral branches versus lateral and posterolateral branches** | | | | | | | | | |
| (Rossillo et al 2004) | III-2 | Italy<br>US | 233 | 66 | 73 | 169 | 19 | ns | 89<br>11 |
| **Non-randomised comparative studies: epicardial versus transvenous insertion** | | | | | | | | | |
| (Mair et al 2005) | III-2 | Germany<br>?Belgium | 86 | 63 | ns | 182 | 24 | ns | ns<br>ns |
| (Koos et al 2004) | III-2 | Germany | 81 | 65 | 64 | ns | 24 | ns | ns<br>ns |
| (Izutani et al 2002) | III-3 | US | 8 | 69 | 88 | ns | 21 | 100 | 0<br>100 |
| **Non-randomised comparative studies: simultaneous BVP versus individually optimised sequential BVP** | | | | | | | | | |
| (Bordachar et al 2004b) | III-2 | France | 41 | 69 | 80 | 170 | 28 | ns | ns<br>ns |
| **Non-randomised comparative studies: atrial fibrillation versus sinus rhythm** | | | | | | | | | |
| (Molhoek et al 2004a) | III-2 | Netherlands | 60 | 68 | 80 | ns | 23 | 50 | ns<br>ns |
| **Non-randomised comparative studies: comparison of patients with ischameic heart disease before and after implantation** | | | | | | | | | |
| (De Cock et al 2005) | III-3 | Netherlands | 24 | 72 | 79 | 178 | 21 | 75 | 24<br>18 |

**Table 13 Description of individual randomised trials and comparative studies (continued)**

| Study | NHMRC grade | Location | Sample | Patient characteristics | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Mean age | % Male | Mean QRS | Mean LVEF % | % SR | NYHA III % IV % |
| **Non-randomised comparative studies: comparison of patients before and after implantation** | | | | | | | | | |
| (Dixon et al 2004)2} | III-3 | Ireland | 27 | 64 | 89 | 177 | ns | 89 | ns ns |
| (Knaapen et al 2004)5} | III-3 | Netherlands | 16 | 58 | 57 | 173 | 25 | ns | 75 25 |
| **Non-randomised comparative studies: comparison of implantations at different time periods** | | | | | | | | | |
| (Kautzner et al 2004)2} | III-3 | Czech Republic | 46 | 61 | 85 | ns | 22 | ns | ns ns |

**Table 14 Individual non-randomised studies: case series studies**

| | NHMRC | Location | Sample | Mean age | Male % | Mean QRS | Mean LVEF | SR % | NHYA III% IV% |
|---|---|---|---|---|---|---|---|---|---|
| (Mortensen et al 2004) | IV | Europe and Canada | 198 | 66 | 73 | 176 | 24 | ns | 68<br>14 |
| (Ricci et al 2000) | IV | Italy | 190 | 68 | 83 | 172 | 25 | 83 | 61<br>27 |
| (Purerfellner et al 2000) | IV | Europe | 150 | 64 | 78 | 165 | ns | 100 | 70<br>21 |
| (Hansky et al 2002) | IV | Germany | 116 | ns | ns | ns | ns | ns | ns<br>ns |
| (Gras et al 2002b) | IV | Europe/ Canada | 103 | 67 | 79 | 178 | 22 | 100 | 68<br>32 |
| (Alonso et al 2001) | IV | France | 102 | 67 | ns | 185 | 22 | 70 | 70<br>30 |
| (Schuchert et al 2004) | IV | Germany | 102 | 67 | 70 | 150 | ns | 88 | 68<br>32 |
| (Gaita et al 2000) | IV | Italy | 96 | 66 | 92 | ns | 22 | ns | ns<br>ns |
| (Mascioli et al 2002b) | IV | Italy | 96 | 68 | 78 | 177 | 23 | ns | ns<br>ns |
| (Ollitrault et al 2003) | IV | France | 62 | 71 | 81 | ns | ns | 87 | ns<br>ns |
| (Pitzalis et al 2005) | IV | Italy | 60 | 62 | 53 | 171 | 25 | ns | 100<br>0 |
| (Walker et al 2000d) | IV | UK | 54 | 64 | ns | ns | ns | 54 | ns<br>ns |
| (Leclercq et al 2000a) | IV | France | 50 | 68 | 90 | 197 | 20 | 72 | 32<br>68 |
| (Daubert et al 1998) | IV | France | 47 | 68 | 89 | 187 | 17 | ns | 13<br>87 |
| (al-Khadra 2003) | IV | Saudi Arabia | 47 | 57 | 57 | ns | 42 | 30 | ns<br>ns |
| (Ammann et al 2004) | IV | Switzerland | 47 | 65 | 84 | 172 | 20 | 84 | ns<br>ns |
| (Santomauro et al 2004) | IV | Italy | 45 | 64 | 100 | ns | ns | 100 | ns<br>ns |
| (O'Donnell et al 2005b) | IV | Australia | 40 | ns | ns | ns | ns | ns | ns<br>ns |
| (Leclercq et al 2000b) | IV | France | 37 | 67 | ns | 178 | 22 | 59 | 70<br>30 |
| (Chan et al 2003b) | IV | Hong Kong/US | 35 | 57 | 83 | ns | 23 | ns | 60<br>24 |

**Table 14 Individual non-randomised studies: case series studies (continued)**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (Toussaint et al 2003) | IV | France | 34 | 65 | 91 | 179 | 20 | 100 | ns<br>ns |
| (Teo et al 2003) | IV | SE Asia | 29 | 60 | 90 | 161 | 22 | ns | ns<br>ns |
| (Medina-Ravell et al 2003) | IV | Venezuala ?US | 29 | 71 | 79 | 154 | 23 | ns | ns<br>ns |
| (Galvao et al 2002) | IV | Brazil | 28 | 58 | 82 | 187 | 20 | ns | 43<br>57 |
| (O'Cochlain et al 2001b) | IV | US | 26 | 63 | 77 | 160 | ns | ns | 46<br>54 |
| (Sogaard et al 2001) | IV | Denmark | 25 | 61 | 88 | 184 | 23 | 100 | 56<br>44 |
| (Yu et al 2002) | IV | Hong Kong | 25 | 65 | 72 | 162 | 28 | ns | 44<br>56 |
| (Bax et al 2003b) | IV | ? | 22 | 63 | 68 | 172 | 19 | 100 | ns<br>ns |
| (Leclercq et al 1998) | IV | France | 18 | 65 | 94 | 170 | 19 | 100 | 22<br>78 |
| (Braunschweig et al 2000) | IV | Sweden | 16 | 64 | 94 | 181 | 22 | 56 | 88<br>12 |
| (Sayad et al 2003) | IV | US | 15 | 67 | 67 | ns | ns | 73 | ns<br>ns |
| (Pappone et al 2001) | IV | Italy/Israel/ US | 15 | 62 | 80 | ns | 28 | ns | 60<br>27 |
| (Kim et al 2001) | IV | Denmark | 15 | 64 | 100 | 182 | 26 | 100 | 60<br>40 |
| (Kasravi et al 2005) | IV | US | 14 | 72 | 93 | ns | ns | ns | ns<br>ns |
| (Kerwin et al 2000) | IV | US | 13 | 58 | 69 | 156 | 17 | 100 | 46<br>0 |
| (Hamdan et al 2000) | IV | US | 13 | 68 | 100 | 123 | 28 | ns | ns<br>ns |
| (Garrigue et al 2001b) | IV | France | 12 | 64 | 92 | 189 | 24 | 67 | 83<br>17 |
| (Lau et al 2000) | IV | Hong Kong | 11 | 61 | 64 | 165 | 22 | 100 | ns<br>ns |
| (Baker et al 2004) | IV | US | 11 | 62 | 73 | ns | 21 | ns | ns<br>ns |
| (Pires et al 2005) | IV | US | 10 | 66 | 60 | 183 | 19 | ns | ns<br>ns |
| (Nelson et al 2000) | IV | US | 10 | 57 | 50 | 179 | 20 | ns | 80<br>20 |

Note: Percentages are from the data reported in studies and relate to all patients enrolled in the study or those followed up, depending on individual authors

**Table 14 Individual non-randomised studies: case series studies (continued)**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (de Cock et al 2004) | IV | Neth-erlands | 7 | 62 | 71 | ns | ns | ns | ns<br>ns |
| (Ohkusu et al 2003) | IV | Japan | 5 | 69 | 80 | ns | 31 | 100 | ns |
| (Gasparini et al 2003e) | IV | Italy | 4 | ns | 50 | 174 | ns | 75 | 100<br>0 |
| (Akiyama et al 2002) | IV | Japan | 1 | 45 | 100 | 180 | ns | 100 | ns<br>ns |
| (Sbragia et al 2003) | IV | France | 1 | 65 | 100 | 100 | 30 | 100 | ns<br>ns |
| (Van Erven et al 2004) | IV | Netherland | 1 | 53 | 0 | 180 | 14 | 100 | 100<br>0 |
| (Oguz et al 2002a) | IV | Turkey | 1 | 65 | 100 | ns | ns | 100 | ns<br>ns |
| (Kanhai et al 2004)8} | IV | Netherlands | 1 | 78 | 100 | ns | 17 | ns | 100<br>0 |
| (Geske et al 2005)9} | IV | US | 1 | 51 | 100 | 185 | 30 | ns | 100<br>0 |

## Quality of included studies

### Systematic reviews (NHMRC Level I)

None of the four systematic reviews/meta-analyses included in this review sufficiently satisfied quality assessment criteria based on the National Health and Medical Research Council (2000) report to enable them to be useful for this review. Descriptions of the methods and results from these reviews are presented in Appendix C but they are not otherwise considered in this report.

**Table 15 Systematic reviews**

| Study | Inclusion criteria directly related to this review | Adequacy of the search and selection/inclusion processes | Reliable quality assessment | Appropriate summary of results of included studies | Methods of pooling adequate and sources of any heterogeneity explored? |
|---|---|---|---|---|---|
| Odunaye 2004 | Yes | Only located and included MIRACLE study | Unclear | Yes from single study | Not attempted |
| Bradley 2004 | No – included defibrillators<br>Pacemaker CRT examined as sensitivity analysis only | Satisfactory but no data from COMPANION trial available | Yes | Yes but only examined sensitivity analysis in relation to death from progressive heart failure | Yes |
| Brophy 2004 | No – included defibrillators<br>Pacemaker CRT examined as subgroup analysis only | Unclear | Unclear | Unpublished 6-month follow-up data used from COMPANION trial | Yes |
| McAlister 2004 | No – included defibrillators<br>Pacemaker CRT examined as sensitivity analysis only | Satisfactory | Yes | Unpublished 12-month data used from COMPANION trial | Yes |

### Randomised trials (NHMRC Level II)

The six randomised controlled trials included in this review were generally of good quality (see Table 16). The major studies – CARE-HF, COMPANION, MIRACLE, MUSTIC – all employed adequate methods of randomisation, satisfactory follow-up and at least some blinded procedures. Losses to follow-up were generally modest or their impact was well mitigated. Intention-to-treat analyses were conducted in all the studies.

The MIRACLE trial in particular included a relatively large number of participants and employed especially robust design and study methods (Abraham et al 2002). The MIRACLE study used reliable procedures for randomisation and allocation to study groups and it was conducted in a double-blind manner.

The CARE-HF trial was generally well designed, conducted and reported. It involved a large number of participants and more than 80 centres based in 10 European countries. This study was mainly powered to assess the effect of resynchronisation on a composite endpoint of death or hospitalisation for a major cardiovascular event. However, death from any cause was the main secondary outcome and the CARE-HF trial was adequately designed to assess the impact of therapy on survival.

The study was also especially notable because it was able to reliably consider and report the long-term (ie, beyond 12 months) effects of CRT plus OPT on both safety and effectiveness. Follow-up was maintained for a mean duration of 29.4 months and survival status information was available about all participants at the end of the study. Unfortunately, methods of randomisation and group allocation were not fully described and the only form of blinding involved members of the endpoint committee, who were unaware of patients' treatment assignment throughout the study. Although patients in the control group were not scheduled to receive pacing therapy, some crossover occurred and a device was implanted and activated in 50 patients, including 19 (5%) before they reached the primary endpoint.

The COMPANION trial was also relatively well designed and conducted. It used a well described and robust method of randomisation but allocation concealment was unclear, it was not double-blinded, and follow-up was complicated by the high level of withdrawal from the control group. The COMPANION trial was adequately designed to assess the impact of therapy on survival and also consider the long-term (ie, beyond 12 months) effects of CRT plus OPT on both safety and effectiveness. However, as at April 2005, comprehensive and finalised data from this study, including detailed information about all primary and secondary outcomes as well as sub-group analyses, were not yet available.

The MUSTIC trial was conducted with only single blinding and did not provide complete information about allocation concealment, but it did use a satisfactory randomisation procedure and adequate follow-up. Checks for contamination/compliance were reported in both the MUSTIC and MIRACLE studies.

The five remaining studies (Walker et al 2000f, Butter et al 2003) did not provide adequate information to fully assess all aspects of study quality. The small studies by Walker et al (2000f) and Sawhney et al (2004) did not describe methods of randomisation and allocation concealment but did appear to have adequate follow-up and also an intention-to-treat analysis. The report by Butter et al (2003) was only concerned with implantation and failed to provide many details about study design or conduct. Similarly, the two studies by de Martino et al. were largely concerned with issues at implantation.

Finally, the available results from the trials have not yet fully considered all the possible effects of potential confounders, notably the trials have varied in their definition of optimal pharmacological therapy and their use of various medications among study participants. Another general limitation of the major studies except, CARE-HF and COMPANION, is that randomisation occurred after implantation of the device. This design does not compromise the validity of the evidence but it does restrict the generalisability of the findings, as it excluded patients who either cannot tolerate the procedure or in whom implantation is not successful.

### Crossover versus parallel trials

Three parallel trials – CARE-HF, COMPANION, MIRACLE – and one crossover trial, MUSTIC are compared. The crossover trial offers the advantage that each patient is his or her own control, thereby reducing the inter-individual variability in the sample and allowing for a smaller sample size to be used to assess effectiveness. However, smaller patient groups may reduce the applicability of the study's findings to the wider heart failure population. Potential problems can include carry-over or treatment order effects that may confound the analysis. Similarly, the natural history of heart failure, whereby patient health significantly deteriorates over time, may also suggest that treatments

received second may be associated with a worse outcome. In general, a crossover design is best suited to initial evaluation of the effectiveness of a new treatment. A parallel design with larger study groups and longer follow-up periods is required to assess effectiveness conclusively (Narang et al 1996).

**Table 16 Randomised trials**

| Study | Sample | Duration of follow-up (months) | Randomisation described/ allocation concealment | Follow-up | Blinding | Intention to treat |
|---|---|---|---|---|---|---|
| (Cleland et al 2005b) | 813 | 29 | Satisfactory/ Unclear | Satisfactory | Outcome assessment only | Yes |
| (Bristow et al 2004) | 925 | 15 | Satisfactory/ Unclear | Incomplete - high (26%) withdrawal rate in medication group | Single | Yes |
| (Abraham et al 2002) | 453 | 6 | Satisfactory/ Clear | Satisfactory | Double | Yes |
| (Cazeau et al 2001) | 67 | 7 | Satisfactory/ Unclear | Satisfactory | Single | Yes |
| (De Martino et al 2005) | 83 | Not stated but short | Satisfactory/ Clear | Satisfactory | Not stated | Yes |
| (Sawhney et al 2004) | 40 | 3 | Not described/ Unclear | Satisfactory | Single | Yes |
| (De Martino et al 2004) | 34 | Not stated but short | Satisfactory/ Clear | Satisfactory | Not stated | Yes |
| (Butter et al 2003) | 27 | Not stated but short | Not described/ Unclear | Implantation study only | Not stated | Not stated |
| (Walker et al 2000f) | 20 | 7 | Not described/ Unclear | Satisfactory | Single | Yes |

### Non-randomised comparative studies (NHMRC Level III)

Non-randomised studies are generally less able than randomised trials to reduce the potential for bias (NHMRC 2000). In addition, the quality of the included non-randomised comparative studies was generally only moderate (see Table 17). Two large comparative studies were undertaken with more than 200 participants and 17 to 18 months follow-up. However, neither of these studies provided sufficient information to assess all the other quality criteria. Notably, one prospective study was conducted over a relatively long period of follow-up, included 102 participants and met the other quality criteria (Reuter et al 2002). The prospective study by Ermis et al (2004) included more than 150 participants but failed to provide enough information to satisfy all the quality criteria. Similarly, a relatively large prospective study by Gasparini et al (2003e) was also not clear in its description of key methods, such as blinding and the adequacy of follow-up. Two other relatively large retrospective studies with more than 100 participants, by Leclercq et al (2004) and Lecoq et al (2005) also either failed to provide sufficient information or did not satisfy all the quality criteria.

The study by Linde (2002a 2002b) was an extended 12-month and non-randomised follow-up of the participants in the MUSTIC trial. All the other studies involved fewer than 100 participants and/or failed clearly to satisfy the quality criteria. Although the studies used a comparative design in several cases, the comparator was not relevant to this review and the papers actually represent case series studies. The non-randomised comparative studies and the case series studies only provided data relevant to the safety of the procedure. Only the randomised trials primarily considered the effectiveness of the procedure in comparison to optimal pharmacological therapy.

### Case series studies (NHMRC level IV)

Case studies reports are inherently highly prone to the potential for bias related to their design and conduct (NHMRC 2000). Without a control group, these studies were unable to allow for any placebo effect associated with the implantation of CRT. The possibility of publication bias also exists with these studies. Seven studies included sample sizes of more than 100 patients but the quality of most of the studies, determined using criteria suggested by NHMRC (2000,) generally was not high (see Table 18). The large case series reports by Mortensen et al (2004) and Gras et al (2002b) were prospective and involved adequate follow-up. Only one of the 50 included studies satisfied all the quality criteria (Kim et al 2001). The case series studies only provided data relevant to the assessment of the safety of the procedure and did not supply any information about the effectiveness of CRT.

**Table 17 Non-randomised comparative studies (NHMRC Level III)**

| Study | Sample | Duration of follow-up (months) | Prospective or retrospective | Adequacy of follow-up | Blinding | Consecutive or selected |
|---|---|---|---|---|---|---|
| (Vogt et al 2004b) | 313 | 17 | Prospective | Unclear | Unclear | Unclear |
| (Rossillo et al 2004) | 233 | 18 | Retrospective | Unclear | No | Consecutive |
| (Gasparini et al 2003e) | 158 | 11 | Prospective | Unclear | Unclear | Selected defined criteria |
| (Ermis et al 2004) | 158 | 18 | Prospective | Unclear | Unclear | Consecutive |
| (Lecoq et al 2005) | 139 | 6 | Retrospective | Satisfactory | No | Consecutive |
| (Leclercq et al 2004) | 103 | 12 | Retrospective | Unclear | Unclear | Selected defined criteria |
| (Reuter et al 2002) | 102 | 12 | Prospective | Satisfactory | Single | Consecutive |
| (Ellery et al 2005) | 96 | 12 | Prospective | Unclear | Unclear | Unclear |
| (Mair et al 2005) | 86 | 16 | Prospective | Unclear | No | Selected |
| (Bax et al 2004) | 85 | 12 | Prospective | Satisfactory | Unclear | Consecutive |
| (Koos et al 2004) | 81 | 12 | Retrospective | Unclear | No | Selected |
| (De Cock et al 2004) | 77 | 6 | Prospective | Satisfactory | No | Consecutive |
| (Molhoek et al 2004c) | 74 | 14 | Prospective | Satisfactory | Unclear | Consecutive |
| (Molhoek et al 2004d) | 60 | 25 | Retrospective | Unclear | Unclear | Consecutive |
| (Yu et al 2004a) | 58 | 3 | Retrospective | Unclear | No | Unclear |
| (Penicka et al 2004) | 55 | 6 | Prospective | Satisfactory | No | Consecutive |
| (Lunati et al 2002) | 52 | 12 | Retrospective | Not stated | No | Selected undefined criteria |
| (Achilli et al 2003) | 52 | 18 | Prospective | Satisfactory | No | Consecutive |
| (O'Donnell et al 2005a) | 50 | 12 | Retrospective | Unclear | Unclear | Consecutive |
| (Linde et al 2002b) | 48 | 12 | Prospective | Satisfactory | Single | Selected defined criteria |
| (Kautzner et al 2004) | 46 | <1 | Retrospective | Satisfactory | No | Unclear |
| (Bordachar et al 2004b) | 41 | 3 | Prospective | Unclear | No | Unclear |
| (Res et al 2005) | 40 | 7 | Prospective | Unclear | Unclear | Consecutive |
| (Touiza et al 2001) | 33 | 6 | Prospective | Satisfactory | No | Consecutive |

**Table 17 Non-randomised comparative studies (NHMRC Level III) continued**

| Study | Sample | Duration of follow-up (mths) | Prospective or retrospective | Adequacy of follow-up | Blinding | Consecutive or selected |
|---|---|---|---|---|---|---|
| (Bordachar et al 2004a) | 33 | <1 | Retrospective | Unclear | No | Consecutive |
| (Yu et al 2003a) | 30 | 3 | Prospective | Satisfactory | No | Selected defined criteria |
| (Dixon et al 2004) | 27 | 12 | Retrospective | Satisfactory | No | Unclear |
| (Alonso et al 1999) | 26 | 12 | Retrospective | Unclear | No | Unclear |
| (De Cock et al 2005) | 24 | 13 | Prospective | Satisfactory | Unclear | Selected |
| (Etienne et al 2001) | 23 | 6 | Prospective | Satisfactory | No | Consecutive |
| (Sciagra et al 2004) | 20 | 3 | Prospective | Satisfactory | No | Consecutive |
| (Barbieri et al 2004) | 18 | 6 | Prospective | Satisfactory | No | Unclear |
| (Knaapen et al 2004) | 16 | 3 | Retrospective | Satisfactory | Unclear | Consecutive |
| (Oguz et al 2002b) | 16 | 7.6 | Prospective | Satisfactory | No | Consecutive |
| (Capasso et al 2005) | 15 | 12 | Retrospective | Unclear | No | Consecutive |
| (Zagrodzky et al 2001) | 14 | Unclear | Prospective | Unclear | No | Selected with some criteria |
| (Tsurugaya et al 2004) | 10 | 1 | Retrospective | Unclear | Unclear | Unclear |
| (Izutani et al 2002) | 8 | 9 | Retrospective | Satisfactory | No | Selected undefined criteria |

**Table 18 Case series studies (NHMRC level IV)**

| Study | Sample | Retrospective or prospective | Adequacy of follow-up | Blinding | Consecutive or selected |
|---|---|---|---|---|---|
| (Mortensen et al 2004) | 198 | Prospective | Satisfactory | No | Selected with defined criteria |
| (Ricci et al 2000) | 190 | Prospective | Not stated | No | Unclear |
| (Purerfellner et al 2000) | 150 | Prospective | Not stated | No | Selected with some criteria |
| (Hansky et al 2002) | 116 | Retrospective | Not stated | No | Selected no criteria |
| (Gras et al 2002b) | 103 | Prospective | Satisfactory | No | Selected with defined criteria |
| (Alonso et al 2001) | 102 | Unclear | Not stated | No | Consecutive |
| (Schuchert et al 2004) | 102 | Prospective | Not stated | No | Unclear |
| (Gaita et al 2000) | 96 | Unclear | Not stated | No | Selected with defined criteria |
| (Mascioli et al 2002b) | 96 | Retrospective | Incomplete <80% | No | Selected no criteria |
| (Ollitrault et al 2003) | 62 | Prospective | Not stated | Unclear | Selected with limited criteria |
| (Pitzalis et al 2005) | 60 | Prospective | Not stated | No | Unclear |
| (Walker et al 2000d) | 54 | Retrospective | Incomplete < 80% | No | Consecutive |
| (Leclercq et al 2000a) | 50 | Prospective | Not stated | No | Consecutive |
| (Daubert et al 1998) | 47 | Prospective | Satisfactory | No | Selected with defined criteria |
| (al-Khadra 2003) | 47 | Prospective | Not stated | No | Selected with limited criteria |
| (Ammann et al 2004) | 47 | Retrospective | Not stated | No | Selected with defined criteria |
| (Leclercq et al 2000b) | 37 | Prospective | Not stated | No | Selected with defined criteria |
| (Santomauro et al 2004) | 45 | Prospective | Not stated | No | Unclear |
| (O'Donnell et al 2005b) | 40 | Retrospective | Satisfactory | Yes | Consecutive |
| (Chan et al 2003b) | 35 | Retrospective | Not stated | No | Consecutive |
| (Toussaint et al 2003) | 34 | Prospective | Satisfactory | No | Consecutive |
| (Teo et al 2003) | 29 | Prospective | Not stated | No | Selected with defined criteria |
| (Medina-Ravell et al 2003) | 29 | Prospective | Incomplete <80% | Yes | Consecutive |
| (Galvao et al 2002) | 28 | Retrospective | Not stated | No | Unclear |
| (O'Cochlain et al 2001b) | 26 | Prospective | Satisfactory | No | Consecutive |
| (Sogaard et al 2001) | 25 | Prospective | Satisfactory | No | Consecutive |
| (Yu et al 2002) | 25 | Prospective | Satisfactory | No | Consecutive |
| (Bax et al 2003b) | 22 | Prospective | Not stated | No | Consecutive |
| (Leclercq et al 1998) | 18 | Prospective | Satisfactory | No | Selected with defined criteria |
| (Braunschweig et al 2000) | 18 | Prospective | Satisfactory | No | Selected with defined criteria |
| (Pappone et al 2001) | 15 | Prospective | Satisfactory | No | Selected no criteria |
| (Kim et al 2001) | 15 | Prospective | Satisfactory | Single | Consecutive |
| (Sayad et al 2003) | 15 | Retrospective | Not stated | No | Selected no criteria |
| (Kasravi et al 2005) | 14 | Retrospective | Satisfactory | No | Unclear |
| (Kerwin et al 2000) | 13 | Prospective | Not stated | No | Consecutive |
| (Hamdan et al 2000) | 13 | Prospective | Satisfactory | No | Selected with limited criteria |
| (Garrigue et al 2001b) | 12 | Prospective | Satisfactory | No | Selected with defined criteria |
| (Lau et al 2000) | 11 | Prospective | Not stated | No | Consecutive |
| (Baker et al 2004) | 11 | Prospective | Not stated | No | Unclear |
| (Nelson et al 2000) | 10 | Prospective | Satisfactory | No | Selected with defined criteria |
| (Pires et al 2005) | 10 | Retrospective | Not stated | No | Unclear |

**Table 18 Case series studies (NHMRC level IV) continued**

| Study | Sample | Retrospective or prospective | Adequacy of follow-up | Blinding | Consecutive or selected |
|---|---|---|---|---|---|
| (de Cock et al 2004) | 7 | Prospective | Satisfactory | No | Consecutive |
| (Ohkusu et al 2003) | 5 | Prospective | Satisfactory | No | Selected with limited criteria |
| (Gasparini et al 2003d) | 4 | Prospective | Not stated | Unclear | Unclear |
| (Akiyama et al 2002) | 1 | Prospective | Satisfactory | No | Selected no criteria |
| (Sbragia et al 2003) | 1 | Retrospective | Satisfactory | No | Selected no criteria |
| (Van Erven et al 2004) | 1 | Retrospective | Satisfactory | No | Selected no criteria |
| (Geske et al 2005) | 1 | Retrospective | Satisfactory | No | Unclear |
| (Kanhai et al 2004) | 1 | Retrospective | Satisfactory | No | Selected no criteria |
| (Oguz et al 2002a) | 1 | Prospective | Satisfactory | No | Selected no criteria |

# Is it safe?

Studies have described the success of implanting the device along with the occurrence of complications at implantation, and subsequent follow-up.

### Implantation success

Fifty-four studies reported data on whether CRT could be implanted in a range of patients (see Table 19). CRT devices were successfully implanted in 61 per cent to 100 per cent (median= 96%, mean= 93%) of the 5,022 patients included in the 54 studies. The three largest studies – the CARE-HF, COMPANION and MIRACLE trials – concluded that implantation was successful in 95 per cent of 409 patients (Cleland et al 2005b), 87 per cent of 617 patients (Bristow et al 2004) and 92 per cent of 571 patients (Abraham et al 2002). The CARE-HF trial also provided data about the success of implantation with one or two attempts (Cleland et al 2005b). In approximately 85 per cent of cases, the device was implanted successfully on the first attempt. A second attempt at implantation was associated with a 68 per cent success rate (Cleland et al 2005). Fourteen large case series studies involving more than 100 patients consistently reported overall success rates of 80 per cent to 99 per cent of patients (Ricci et al 2000, Purerfellner et al 2000, Gras et al 2002b, Hansky et al 2002, Alonso et al 2001, Reuter et al 2002, Mortensen et al 2004, Gasparini et al 2003e, Rossillo et al 2004, Ermis et al 2004, Kautzner et al 2004, Lecoq et al 2005, Leclercq et al 2004, Schuchert et al 2004). Four studies reported success rates below 80 per cent (61-75%) although these were relatively small studies with only 67, 62, 47 and 30 participants. Conversely, nine out of 10 very small studies with less than 25 participants reported 100 per cent implantation success rates. Many of these very small studies involved highly selected patients (Yu et al 2002, Braunschweig et al 2000, Kerwin et al 2000).

In the MUSTIC trial implantation success was significantly lower at 75 per cent. It is notable that this was an early trial with the procedures occurring during 1998-99. In general, implantation rates appear to be higher in recent studies, ranging from 88 per cent to 100 per cent for studies published in 2005 compared with 75 per cent in the oldest study (Daubert et al 1998), presumably either because of improvements in technology or the the operators' increasing experience. Notable exceptions to the apparent trend of

increasing implantation success with successively more recent publication are the reports published by Ollitrault et al (2003) and Ermis et al (2004). However, both of these studies included patients who were implanted during 1998-99 and they were specifically concerned with the development of new implantation methods.

Further evidence of a learning curve related to the success of implantation is provided in several other studies. Registry data obtained from 63 European centres indicated that those centres that implanted one to two devices had a lower mean success rate (81 per cent) compared to those that inserted three or more devices (mean success rate = 88 per cent) (Purerfellner et al 2000). Similarly a study (Kautzner et al 2004) based in the Czech Republic that examined changes in the implantation success rate during different time periods, noted that implantation was successful in just 82 per cent of 46 early cases while 96 per cent of later implantations were successful. The time for the procedure had decreased from an average of 247 minutes in phase one down to 116 minutes by the end of the study. Consistent with this was a study (Lecoq et al 2005) involving 139 consecutive patients based at a French centre that reported a success rate of only 61 per cent between 1994-6. However, by 2000-1, the success rate had risen to 98 per cent. A United Kingdom-based study reported that all five failures to implant a device had occurred in the operators first 12 patients (Walker et al 2000d). Walker also noted that the mean implantation time decreased for the second set of 24 patients compared to the first, to 90 minutes from 120 minutes. In two case series studies in which preliminary data were published ahead of a more comprehensive report (Gras et al 1998, Reuter et al 2000), implantation success in the initial publication was lower than subsequent results in the later publication (84 % and 88 % in Gras et al (1998) and Gras et al (2002b) and 83 per cent and 87 per cent in Reuter et al (2000) and Reuter et al (2002).

The average time for implantation generally has been infrequently reported in previous studies. The mean duration for the procedure was noted to be 129 minutes to 139 minutes in one study (De Martino et al 2005) that included 83 patients while a study by Ellery et al (2005) that included 96 participants also recorded a mean duration for the procedure of 112 minutes for successful implantations. The Czech study by Kautzner et al (2004) similarly noted that mean procedure time was 116 minutes for patients who were successfully implanted during the final phase of the study. Walker (2000) in a small study of 54 patients reported that the mean total procedure time for all the patients was 116 minutes (range: 40 to 225 minutes). Mean procedure time was recorded as 124 minutes in another small study (Pires et al 2005) that involved just 10 participants. However, the average time required for implantation in the unsuccessful compared to the successful cases has not usually been stated in any of these studies. Results from the large COMPANION trial suggest that the median duration of the procedure was 164 minutes (2.7 hours). Consistently, the MIRACLE study reported that among the 528 patients who underwent successful implantation, the median duration of the procedure was also 2.7 hours (range 0.9 to 7.3 hours). No data were presented about the time taken for the procedure when it was not successful.

### Reasons for failure to implant a device

Detailed descriptions of the reason(s) patients could not be implanted with a CRT device are relatively infrequently reported by previous authors. Four recently published studies, including one study based in Australia, provide some details. O'Donnell et al (2005a) identified that six out of 40 Australian patients could not be implanted because of coronary sinus occlusion in two attempted procedures, an inability to obtain a stable lateral position in one and an unacceptable capture threshold in a further three. In another study, that

included 96 participants, one patient was not able to be implanted because the coronary sinus could not be identified (Ellery et al 2005). By contrast, 11 (13%) patients were unable to receive a device for this reason in the study by Mair et al (2005). Results from the study by Schuchert et al (2004) indicate that four patients were unable to undergo successful catheterisation of their coronary sinuses and an additional two failed implantation because the lead in the coronary sinus tributary was considered to be too unstable. Finally, four patients were documented to have failed implantation (Ammann et al 2004) due to non-specific technical difficulties (one patient), the inability to find an adequate pacing site (one patient) and a failure of left ventricular capture (two patients).

**Table 19 Implantation success**

| Study | n | Implantation success rate (%) |
|---|---|---|
| (Bristow et al 2004) | 617 | 87 |
| (Abraham et al 2002) | 571 | 92 |
| (Cleland et al 2005b) | 409 | 95 |
| (Cazeau et al 2001) | 67 | 75 |
| (Rossillo et al 2004) | 244 | 96 |
| (Ricci et al 2000) | 219 | 89 |
| (Mortensen et al 2004) | 198 | 95 |
| (Gasparini et al 2003e) | 159 | 99 |
| (Ermis et al 2004) | 158 | 80 |
| (Purerfellner et al 2000) | 150 | 83 |
| (Kautzner et al 2004) | 142 | 87 |
| (Lecoq et al 2005) | 139 | 88 |
| (Leclercq et al 2004) | 117 | 88 |
| (Gras et al 2002a) | 117 | 88 |
| (Hansky et al 2002) | 116 | 99 |
| (Alonso et al 2001) | 116 | 88 |
| (Reuter et al 2000) | 102 | 87 |
| (Schuchert et al 2004) | 102 | 94 |
| (Mascioli et al 2002b) | 96 | 99 |
| (Ellery et al 2005) | 93 | 89 |
| (Bax et al 2004) | 85 | 100 |
| (De Martino et al 2005) | 83 | 98 |
| (Mair et al 2005) | 79 | 89 |
| (De Cock et al 2004) | 77 | 95 |
| (Pitzalis et al 2005) | 65 | 97 |
| (Ollitrault et al 2003) | 62 | 61 |
| (Koos et al 2004) | 57 | 98 |
| (Penicka et al 2004) | 55 | 96 |
| (Walker et al 2000d) | 54 | 91 |
| (Achilli et al 2003) | 52 | 94 |
| (Daubert et al 1998) | 47 | 75 |
| (al-Khadra 2003) | 47 | 100 |
| (Ammann et al 2004) | 47 | 91 |
| (Bordachar et al 2004b) | 41 | 100 |
| (O'Donnell et al 2005b) | 40 | 88 |
| (Sawhney et al 2004) | 40 | 100 |
| (Chan et al 2003b) | 35 | 97 |
| (Bordachar et al 2004a) | 33 | 100 |
| (Etienne et al 2001) | 30 | 71 |
| (Yu et al 2003a) | 30 | 100 |
| (Teo et al 2003) | 29 | 100 |
| (Butter et al 2003) | 27 | 96 |
| (Yu et al 2002) | 25 | 100 |

**Table 19 Implantation success (continued)**

| Study | n | Implantation success rate (%) |
|---|---|---|
| (De Cock et al 2005) | 25 | 96 |
| (Bax et al 2003b) | 22 | 100 |
| (Sciagra et al 2004) | 20 | 100 |
| (Braunschweig et al 2000) | 16 | 100 |
| (De Martino et al 2004) | 16 | 94 |
| (Sayad et al 2003) | 15 | 100 |
| (Knaapen et al 2004) | 14 | 100 |
| (Kerwin et al 2000) | 13 | 100 |
| (Baker et al 2004) | 11 | 100 |
| (Kanhai et al 2004) | 1 | 100 |
| (Geske et al 2005) | 1 | 100 |

### Mortality at implantation

Fatalities at implantation appear to be rare. Five deaths (0.8%) were judged to be related to implantation in the COMPANION trial (Bristow et al 2004), the largest of the trials and involving 617 patients. Two deaths among the 571 (0.4%) participants were noted in the MIRACLE study. The deaths in the MIRACLE study were attributed to progressive hypotension in relation to one patient who died on the day of implantation, and asystole with associated neurological impairment in another patient who died one month later. One death clearly related to implantation was reported in the CARE-HF study (Cleland et al 2005b). This fatality was attributed to progressive heart failure which was aggravated by early lead displacement.

One patient's death was judged to be related to sepsis associated with the insertion of a device in the study by Mair et al (2005) that described the results from implanting 86 subjects. One death, a few hours after implantation due to cerebral bleeding, was also reported in a small study involving just 55 participants (Penicka et al 2004).

Data about mortality during follow-up from both randomised and non-randomised studies are presented under the Survival heading in the Effectiveness section of this report.

### Specific perioperative implantation problems (excluding implantation failure)

Twenty-four studies (see Table 20) provided information about the occurrence of specific problems at the time of implantation but not including the failure to implant a device. The results from the large COMPANION study indicated that 10 per cent of all participants sustained a moderate-severe adverse event during implantation (Bristow et al 2004). However, this study only reported detailed information about the incidence of three complications – CS dissection, perforation and cardiac tamponade. In addition, the large CARE-HF trial did not clearly discriminate between perioperative and postoperative problems. A common problem across many studies was a coronary sinus dissection rate of less than 1 per cent to 12 per cent (median 4.5%) that was reported in 15 studies. Arrhythmia induction was another relatively frequent complication of implantation. Eight studies, including the CARE-HF, COMPANION and MIRACLE trials, consistently recorded a 1 per cent to 2 per cent perforation rate, resulting in a

haemopericardium. Several other complications, including phrenic nerve stimulation, worsening of heart failure, coronary sinus thrombus, sensing problems, haematoma, were infrequently documented among the studies.

The studies by Kerwin et al (2000), Bax et al (2003b), Sciagra et al (2004), Sayad et al (2003), Izutani et al (2002), Chan et al (2003b), Butter et al (2003), Knaapen et al (2004), Kanhai et al (2004), Bax et al (2004), Dixon et al (2004), Ermis et al (2004), Santomauro et al (2004) all made some general statement that there were no complications during implantation.

**Coronary sinus dissection or perforation**

The occurrence of coronary sinus dissection or perforation in the COMPANION study was 0.3 per cent and 1.1 per cent respectively among the 617 patients who received a device (Bristow et al 2004). An additional 0.5 per cent developed cardiac tamponade (Bristow et al 2004). Some 2 per cent of participants were documented to have a coronary sinus dissection in the CARE-HF trial and another 2 per cent were observed to have a perforation around the time of implantation (Cleland et al 2005b). The MIRACLE trial noted that 23 (4%) patients sustained a coronary sinus dissection and 12 (2%) patients had a cardiac vein or coronary sinus perforation during implantation of the device. Of these, three patients required intravenous catecholamines or pericardiocentesis, or both, for a presumed or confirmed diagnosis of haemopericardium but all recovered without sequelae. Though a coronary sinus dissection is unlikely to have any clinical sequelae, a coronary sinus perforation is a serious and potentially fatal complication due to the development of a haemopericardium. A haemopericardium can cause cardiac tamponade and may often require an operation or a procedure to provide drainage. The results from the InSync study (Ricci et al 2000, Zardini et al 2000, Porciani et al 2000) were consistent with those reported in the MIRACLE trial. The InSync trial also reported that 10 (5%) of patients sustained a coronary sinus dissection and four (2%) exhibited a pericardial effusion. Two patients experienced cardiac tamponade and required either cardiocentesis or cardiac surgery. Five other studies also reported that approximately 5 to 6 per cent of patients sustained a coronary dissection at the time of implantation (Hansky et al 2002, Purerfellner et al 2000, Barbieri et al 2004, Mair et al 2005, De Martino et al 2005). Another relatively large case series by de Cock et al (1999) observed a 6.8 per cent rate of coronary sinus dissection while specifically employing angiographic methods to detect the complication. Similarly, the study by De Martino et al (2004), which reported that four patients (12%) were associated with coronary sinus dissection also examined a new method of catherisation and was more readily able to recognise cases of dissection, even though they may not have otherwise been clinically evident. By contrast, the results from three studies indicated that only one or two cases (1-3%) of coronary dissection occurred in each study (Alonso et al 2001, Koos et al 2004, De Cock et al 2004). Consistent results were obtained by the eight studies that reported the occurrence of perforation during implantation (De Cock et al 2004, Ellery et al 2005, Kautzner et al 2004, Cleland et al 2005b, Bristow et al 2004, Ricci et al 2000, Abraham et al 2002, de Cock et al 2004). Uniformly 1 to 2 per cent of patients in these eight studies sustained a perforation and some degree of haemopericardium. Although no study reported any fatalities associated with a coronary sinus perforation, it is a potentially fatal complication which could result in some mortality, especially if the results from a large number of patients were considered.

**Cardiac arrhythmia**

In the MIRACLE study, two patients (0.4%) were not randomised because they experienced complete heart block and required permanent pacing. One patient (0.2%)

developed asystole and required cardiopulmonary resuscitation, did not recover neurologically, and died one month later. Five relatively large studies of more than 45 participants reported a 1 to 3 per cent (median 3%) arrhythmia induction rate. Cardiac arrhythmia occurred in six (3%) of the patients in the Insync study (Ricci et al 2000, Zardini et al 2000, Porciani et al 2000). Three patients with asystole and three with ventricular fibrillation were noted in these studies and the patients required treatment with medication, temporary pacing or external defibrillation. Three other studies also observed that 2 to 3 per cent of patients experienced an episode of cardiac arrhythmia during implantation (Hansky et al 2002, Purerfellner et al 2000, Kautzner et al 2004). Res et al (2005) observed the occurrence of three cases of arrhythmia during implantation. AV block occurred in two patients during active fixation at the outflow tract while ventricular fibrillation was induced in another patient when the AP lead was advanced toward the apex. The episode of ventricular fibrillation was successfully terminated with DC shock. One relatively small case series involving 29 patients (Medina-Ravell et al 2003) and a single case report (Van Erven et al 2004) described considerably higher frequencies of arrhythmia, at 14 per cent and 100 per cent respectively). The study by Medina-Ravell et al (2003) was specifically designed to examine the occurrence of pacing site-dependent changes in repolarsiation and its potential role in the development of torsades des pointes.

**Phrenic nerve stimulation**

The study by Hansky (2002) reported that 16 (14%) patients exhibited some phrenic nerve stimulation during implantation. In most cases of intra-implantation left phrenic nerve stimulation, the problem could be overcome by simply repositioning the leads in the same vein. Another study by Kautzner et al (2004) documented that phrenic nerve stimulation was associated with only 3 per cent of implantations. None of the other studies described any cases of phrenic nerve stimulation during implantation.

**Coronary sinus thrombus**

Hansky (2002) stated that three patients (3%) experienced a coronary sinus thrombus at implantation. After the third case of thrombosis, patients were routinely heparinised and no further cases occurred in the series. No other study reported the presence of this complication at implantation using the transvenous route.

**Worsening of heart failure**

The CARE-HF trial documented the case of a patient whose heart failure deteriorated in association with the implantation of a CRT device, specifically in relation to the early dislodgement of a lead (Cleland et al 2005b). The small study by Teo et al (2003) also reported a single case where a patient experienced some deterioration of heart failure in relation to implantation. The patient in the smaller study recovered after a period of inotropic support.

**Sensing problem**

A single case report described the development at implantation of far-field sensing of the left atrial activity, which resulted in ventricular inhibition (Oguz et al 2002a). The problem was successfully resolved by decreasing ventricular sensitivity.

Two studies reported the significant rise in the acute sensing threshold for a patient at implantation (De Cock et al 2004, Bordachar et al 2004b).

**Haematoma**

Two studies reported the same frequency (2%) of haematoma occurrence at implantation (al-Khadra 2003, Mortensen et al 2004). The results from two recent studies (Kautzner et al 2004, Pires et al 2005) indicate that the haematoma incidence rate may be somewhat higher (5-10%). The development of a soft tissue haematoma is unlikely to be a serious problem. It is possible that the occurrence of this problem is under-reported in the studies – many authors may not have chosen to report relatively minor problems or they may have identified them as a later, post-operative problem, rather than a perioperative complication.

**Lead dislodgement or dislocation**

Three recent studies (Bordachar et al 2004a, Ellery et al 2005, Kautzner et al 2004) have reported the occurrence of lead dislodgement or dislocation at the time of implantation (results not listed in Table 20). The three studies have consistently documented that 2 to 3 per cent of implantations may be associated with lead dislodgement.

**Table 20 Specific implantation problems excluding failure to implant**

| Study | n | CS (and atrial) dissection n (%)[1] | Perforation (haemo-pericardium)/ cardiac tamponade n (%)[1] | Arrhythmia induction n (%)[1] | CS thrombus n (%)[1] | LPN stim-ulation n (%)[1] | Haema-toma n (%) | Sensing problem n (%) |
|---|---|---|---|---|---|---|---|---|
| (Bristow et al 2004) | 617 | 2 (<1) | 10 (2) | | | | | |
| (Abraham et al 2002) | 571 | 23 (4) | 12 (2) | 2 (<1) | | | | |
| (Cleland et al 2005b) | 409 | 10 (2) | 6 (2) | | | | | |
| (Ricci et al 2000) | 219 | 10 (5) | 4 (2) | 6 (3) | | | | |
| (Mortensen et al 2004) | 189 | | | | | | 3 (2) | |
| (Kautzner et al 2004) | 138 | 6 (4) | 2 (1) | 4 (3) | | 4 (3) | 7 (5) | |
| (Hansky et al 2002) | 116 | 6 (5) | | 3 (3) | 3 (3) | 16 (14) | | |
| (Alonso et al 2001) | 116 | 2 (2) | | | | | | |
| (de Cock et al 2004) | 103 | 7 (7) | 1 (1) | | | | | |
| (Ellery et al 2005) | 96 | | 1 (1) | | | | | |
| (Mair et al 2005) | 86 | 4 (5) | | | | | | |
| (De Martino et al 2005) | 83 | 4 (5) | | | | | | |
| (Koos et al 2004) | 81 | 1 (1) | | | | | | |
| (De Cock et al 2004) | 77 | 2 (3) | 1 (1) | | | | | 1 (1) |
| (Purerfellner et al 2000) | 47 | 3 (6) | | 1(2) | | | | |
| (al-Khadra 2003) | 47 | | | | | | 1 (2) | |
| (Bordachar et al 2004b) | 41 | | | | | | | 1 (2) |
| (Res et al 2005) | 40 | | | 2 (5) | | | | |
| (De Martino et al 2004) | 34 | 4 (12) | | | | | | |
| (Medina-Ravell et al 2003) | 29 | | | 4 (14) | | | | |
| (Barbieri et al 2004) | 18 | 1 (6) | | | | | | |
| (Pires et al 2005) | 10 | | | | | | 1 (10) | |
| (Van Erven et al 2004) | 1 | | | 1 (100) | | | | |
| (Oguz et al 2002a) | 1 | | | | | | | 1 (100) |

(%)[1] refers to percentage of participants in the trial rounded up to the nearest whole number, Note: Results from Teo et al (2003) not listed in table.

## Postoperative events

Thirty studies provided information about postoperative adverse events during follow-up (see Table 21). There were 2,813 patients (range: 1 to 524) included in the studies that

were conducted over variable periods of mean follow-up (range: <1 to 29 months). Overall, rates of postoperative events reported in the studies ranged from 2 to 100 per cent and at least in part reflected the variation in the length of follow-up and the influence of including highly-selected, and often small, patient groups. Studies conducted over a short period of follow-up generally recorded lower overall rates of adverse events eg, 4 per cent over three months (Purerfellner et al 2000) compared with 28 per cent during 15 months of follow-up (Alonso et al 2001)).

There was more consistency in the overall rate of complications recorded among the three randomised trials and the large cohort studies with more than 100 patients that provided these results. The results from these studies suggest that the overall rate of postoperative events is 2 per cent to 24 per cent with a median of about 10 per cent.

Four authors non-specifically reported that there were no postoperative events (Yu et al 2003a, Chan et al 2003b, al-Khadra 2003, Santomauro et al 2004).

**Lead dislodgement**

Lead dislodgement was the most frequently reported adverse event postoperatively. Twenty-one studies (see Table 21) with more than 15 participants reported the postoperative frequency of lead dislodgement with rates varying from 1 per cent to 15 per cent (median 7 per cent). The MIRACLE trial reported a lead dislodgement rate of 6 per cent over a follow-up period of six months (Abraham et al 2002). The CARE-HF trial also consistently reported a lead dislodgement rate of 6 per cent, even though the mean follow-up period was considerably longer at 29 months. The results from 12 other studies with more than 50 participants were inconsistent (Cazeau et al 1996, Purerfellner et al 2000, Ricci et al 2000, Hansky et al 2002, Alonso et al 2001, Gras et al 2002b, Reuter et al 2002, Mortensen et al 2004, Ollitrault et al 2003, Mair et al 2005, De Cock et al 2004, Koos et al 2004). One registry study reported that only one dislodgement occurred among 150 patients over an uncertain period of follow-up (Purerfellner et al 2000), while the MUSTIC trial described eight dislodgements (12% ) over an average follow-up period of seven months (Cazeau et al 1996). The series with the highest percentage (15%) of lead dislodgements could have related to the longer follow-up period included in this study, where the oldest replaced lead had been in position for 41 months (Alonso et al 2001). However, another study (Ollitrault et al 2003) with a similar period of follow-up only recorded a lead dislodgement rate of 3 per cent. Three more recent large studies documented lead dislodgement rates of 5 per cent to 9 per cent. The two studies (Koos et al 2004, Mair et al 2005) with the longer periods of follow up (12 to16 months) were associated with slightly more episodes of lead dislodgement (8-9%).

One small study (Kasravi et al 2005) reported a 50 per cent lead dislodgement rate over a 17-month follow-up period. However, this study was based on a small group of 14 patients who were specifically selected because they required lead extraction as a result of various complications. All the leads in this study were able to be successfully reimplanted.

**Sepsis**

Infection rates of 1 per cent to 4 per cent (median 1%) were consistently reported in nine studies (see Table 21). Sepsis associated with the pacemaker site may often require explantation although repeat implantation may occur at a later stage. In the MIRACLE study seven (1%) patients reported a pacemaker-related infection that required explantation, and four patients subsequently had the device re-implanted. In the CARE-

HF trial 1 per cent of participants were complicated by sepsis (Cleland et al 2005b). Four other large case series with more than 50 patients also reported that 1 per cent of patients developed infection that required explantation (Ricci et al 2000, Hansky et al 2002, Gras et al 2002b, Mair et al 2005). Two other large case series indicated that infection occurred in 2 per cent to 3 per cent of patients (Ollitrault et al 2003, Alonso et al 2001). A small South American series reported that 4 per cent of patients developed sepsis (Galvao et al 2002).

A tenth study (Kasravi et al 2005) also reported infection rate data and indicated that the rate of sepsis among participants was 50 per cent. However, this study was based on a small group of 14 participants who were selected because they required lead extraction after they had developed a complication.

**Pocket stimulation/phrenic nerve stimulation**

Abnormal pacing stimulation of either the pocket site or the left phrenic nerve was reported by 16 studies with a frequency of 1 per cent to 6 per cent (median 3%) (see Table 21). Two per cent of patients in the CARE-HF trial developed pocket or phrenic nerve stimulation over 29 months of follow-up (Cleland et al 2005b). Nine out of 12 large case series studies, involving more than 50 patients, have described relatively low rates (1-3%) of pocket or phrenic nerve stimulation (Ricci et al 2000, Purerfellner et al 2000, Alonso et al 2001, Gras et al 2002b, Ollitrault et al 2003, Penicka et al 2004, Mortensen et al 2004, Mair et al 2005, Koos et al 2004). Another three large studies have presented slightly higher rates (5-6%) of pocket or phrenic nerve stimulation among their participants (Ellery et al 2005, De Cock et al 2004, Schuchert et al 2004). Among all studies, in most cases, relocation of a lead successfully resolved the problem. In two small studies, single cases of pocket-related problems were reported (Braunschweig et al 2000, Galvao et al 2002). The study by Mortensen et al (2004) reported problems with the stimulator among three patients in addition to two cases of phrenic nerve stimulation.

**Elevated pacing threshold**

Elevated pacing thresholds occurred in eight studies with a frequency ranging from 2 per cent to 15 per cent (median 5%) (see Table 21). Alonso et al (2001) reported that 15 (15%) patients required re-operation due to rising pacing thresholds. The threshold increases were linked to dislocation of the lead or a connector defect (Alonso et al 2001). The small and selected patient series reported by Kasravi et al (2005) described the occurrence of two cases (14% of the sample) of exit block. The other seven studies noted that an elevated pacing threshold occurred in between 2 per cent and 9 per cent of patients (Galvao et al 2002, Purerfellner et al 2000, Ollitrault et al 2003, Daubert et al 1998, Ellery et al 2005, Mair et al 2005, Koos et al 2004).

**Arrhythmia**

Results from the CARE-HF trial indicate that the rate of atrial arrhythmia or ectopy was more common in the cardiac resynchronisation group compared to the medical therapy group, with 64 patients were affected compared to 41, p=0.02.

Three small case series studies specifically examined the postoperative frequency of arrhythmia as a complication as opposed to a mode of death (see section below), (see Table 21). One small study (Medina-Ravell et al 2003) with a short period of follow-up examined pacing site-dependent changes in QT interval, JT interval and transmural dispersion of repolarisation and their potential role in the development of torsades de pointes. Among the four cases of R on T ventricular extra-systoles, one patient developed incessant torsade des pointes. Another single case report (Akiyama et al 2002) documented the development of symptomatic arrhythmia that was considered to be generated by the pacemaker. The report described the case of a patient who was admitted six months after implantation because the premature ventricular response algorithm was activated after capture of the LV sensed ventricular events falling in the ventricular refractory period, reflecting the transeptal wavefront propagation from LV to RV. This then caused extension of the postventricular atrial refractory period starting from the VR, preventing the proper sensing of the subsequent P wave. Even after shortening the postventricular atrial refractory period down to the programmed value, the postponement of the atrial refractory period due to first degree AV block of the cycles without ventricular tracking regularly prevented sensing of the subsequent P wave during sinus tachycardia. Sinus cycles without P wave tracking were completely eliminated by turning off the premature ventricular complex response. The authors cautioned that 'when using a biventricular pacing system with a "Y" adapted left lead, it is advisable to program a shorter postventricular atrial refractory period or to program the premature ventricular complex algorithm off'. In another small study, ventricular fibrillation and/or flutter was induced in three out of seven patients. However, CRT reduced the inducibility of sustained monomorphic ventricular tachycardia from eight out of nine to one out of seven patients (60% reduction, p<0.05) (Zagrodzky et al 2001).

All of these three studies were based on small numbers and often included highly selected and/or unevenly matched patient groups. In addition, it is unclear how clinically significant some of the findings from the study by Medina-Ravell et al (2003) may actually be. By contrast with the findings from the small studies, the frequency of clinically significant arrhythmia noted in two large cases series with more than 100 patients were both very low at less than 1 per cent (Ricci et al 2000, Purerfellner et al 2000). The electrophysiologic effects of CRT remain poorly understood.

**Other complications**

Other serious postoperative events were infrequently documented. Single case reports of a pericardial effusion (Ollitrault et al 2003) and a pulmonary embolism (Sbragia et al 2003) have been described. The results from the study by Mair et al (2005) document the presence of two cases with either a pleural or cardiac effusion among the 86 participants (Mair et al 2005). Both effusions required treatment but no other information is provided about the aetiology or outcome of these two complications (Mair et al 2005).

Other studies have documented the incidence of less serious postoperative complications, such as the infrequent occurrence of one to three cases of wound haematoma in four studies (Mortensen et al 2004, Koos et al 2004, Res et al 2005, Schuchert et al 2004) and a single case of a persistent coronary sinus dissection (de Cock et al 2004).

One study has described a single episode of device dislocation and connector dysfunction that required replacement of the system (Koos et al 2004). No study has reported the need for re-intervention due to battery depletion. No studies reported air embolism, perforation of the great vessels or myocardium, and pneumothorax – all potential complications of pacemaker insertion.

**Table 21 Postoperative events**

| Study | n | Follow-up (months)[1] | Lead dislodgement n (%)[2] | Pulmonary embolism n (%)[2] | Sepsis n (%)[2] | Pocket problem stimulation/ LPN stimulation n (%)[2] | EPT n (%)[2] | Arrhythmia n (%)[2] |
|---|---|---|---|---|---|---|---|---|
| (Abraham et al 2002) | 524 | 6 | 30 (6) | | 7 (1) | | | |
| (Cleland et al 2005b) | 409 | 29 | 24 (6) | | 3 (1) | 8 (2) | | |
| (Cazeau et al 2001) | 67 | 7 | 8 (12) | | | | | |
| (Linde et al 2002b) | 48 | 6 | | | | 1(2) | | |
| (Ricci et al 2000) | 189 | 10.4 | 14 (7) | | 2 (1) | 4 (2) | | 1 (<1) |
| (Mortensen et al 2004) | 189 | 3.5 | 12 (6) | | | 5 (3) | | |
| (Purerfellner et al 2000) | 150<br>44 | ?<br>3 | 1 (1)<br>1 (2) | | | 2 (1)<br>1 (2) | <br>2 (5) | <br>1 (<1) |
| (Hansky et al 2002) | 116 | <1? | 5 (4) | 1 (1) | 1 (1) | | | |
| (Gras et al 2002a) | 103 | 12 | 10 (10) | | 1 (1) | 2 (2) | | |
| (Alonso et al 2001) | 102 | 15 | 15 (15) | | 3 (3) | 3 (3) | 15 (15) | |
| (Reuter et al 2000) | 102 | 12 | 4 (4) | | | | | |
| (Schuchert et al 2004) | 102 | 24 | | | | 6 (6) | | |
| (Ellery et al 2005) | 96 | 12 | | | | 6 (6) | 3 (3) | |
| (Mair et al 2005) | 86 | 16 | 7 (8) | 2 (2) | 1 (1) | 3 (3) | 3 (3) | |
| (De Cock et al 2004) | 77 | 6 | 4 (5) | | | 4 (5) | | |
| (Ollitrault et al 2003) | 62 | 15 | 2 (3) | | 1 (2) | 1 (2) | 1 (2) | |
| (Koos et al 2004) | 56 | 12 | 5 (9) | | | 1 (2) | 5 (9) | |
| (Penicka et al 2004) | 55 | 6 | | | | 1 (2) | | |
| (Walker et al 2000b) | 49 | 3 | 5 (10) | | | | | |
| (Res et al 2005) | 40 | 7 | 1 (3) | | | | | |
| (Daubert et al 1998) | 35 | 10.2 | 1 (3) | | | | 1 (3) | |
| (Teo et al 2003) | 29 | 1-28 | 2 (7) | | | | | |

**Table 21 Postoperative events (continued)**

| Study | n | Follow- up (months)[1] | Lead dislodgement n (%)[2] | Pulmonary embolism n (%)[2] | Sepsis n (%)[2] | Pocket problem stimulation/ LPN stimulation n (%)[2] | EPT n (%)[2] | Arrhythmia n (%)[2] |
|---|---|---|---|---|---|---|---|---|
| (Medina-Ravell et al 2003) | 29 | 0.5 | | | | | | 4 (14) |
| (Galvao 2002) | 28 | 5 | 1 (4) | | 1 (4) | 1 (4) | 2 (7) | |
| (Braunschweig et al 2000) | 16 | 9.7 | 2 (13) | | | 1 (6) | | |
| (Touiza et al 2001) | 15 | 6 | 1 (1) | | 1 (1) | | | |
| (Kasravi et al 2005) | 14 | 17 | 7 (50) | | 7 (50) | | | 2 (14) |
| (Zagrodzky et al 2001) | 7 | ? | | | | | | 3 (43) |
| (Sbragia et al 2003) | 1 | ? | | 1 (100) | | | | |
| (Akiyama et al 2002) | 1 | 6 | | | | | | 1 (100) |

[1]Mean follow-up is provided wherever possible. (%)[2] refers to percentage of participants in the trial rounded up to the nearest whole number

### Survival described in non-randomised studies

Although survival is a key effectiveness outcome (see Survival in Effectiveness Section), additional survival information was provided in 50 non-randomised studies and is presented in Table 22. Mortality at implantation was rare and most deaths during follow-up were attributed to the underlying disease rather than to the procedure. The non-randomised studies reported on survival during follow-up periods that varied from one to 25 months (see Table 22). Overall mortality rates were relatively high with nine studies (Gras et al 2002, Leclerq et al 2002a, Leclerq et al 2002b, Daubert 1998, Touiza 2001, Etienne 2001, Ohkusu 2003, Capasso et al 2005, Ammann et al 2004) exhibiting fatality rates between 20 and 40 per cent. These results reflected the underlying often poor prognosis for patients with severe heart failure. One study (Kanhai et al 2004), with a single participant who died during follow-up, presented a 100 per cent fatality rate. The mortality rate among the other studies ranged from 0 per cent to 40 per cent. Among all 50 studies, the mean mortality rate was 14 per cent and the median was 10 per cent. The mortality rate varied in relation to the length of follow-up and the characteristics of study participants. Predictably, one of the studies with a longer follow-up period of 15.4 months exhibited the highest mortality rate (40%) (Leclercq et al 2000a). This was arrived at after excluding the study with only one participant. By contrast, a 2 per cent mortality rate was reported after only three months follow-up (Walker et al 2000d). Among the 24 studies with a follow-up duration of at least 12 months, the mean and median mortality rates were 14 per cent and 13 per cent compared to 11 per cent and 9 per cent for the 23 studies with a follow-up period of less than 12 months. Two studies were of unknown duration and one study included just one participant.

For the 10 studies with greater than half of all participants in NYHA class IV at the start of the study – 18 studies did not clearly provide this information – the mortality rate ranged from 4 per cent to 40 per cent, with a median of 20 per cent. The relatively low mortality rate (7%) observed in the large InSync series may relate to the high proportion (73 per cent) of NYHA class II and III patients with less severe disease included in that study (Ricci et al 2000). Similarly, the low mortality rate exhibited in the large study by Gasparini et al (2003e) may also reflect a relatively healthier patient sample as indicated by a high proportion (80%) of patients with NYHA class III heart failure and a comparatively high mean LVEF among the group (29%).

Progressive heart failure and sudden cardiac death were the main causes of death in most of the studies. In total, 760 deaths were reported in all the studies and causes were stated for 425 (56%) of these deaths. Among the 39 studies and 425 deaths that provided data, 210 deaths (50%) were due to progressive heart failure, 138 (32%) from either an arrhythmia or sudden death, and other causes accounted for 77 (18%) deaths. Progressive heart failure was the main single cause of death in 21 of 39 studies that provided this information. Underlining the poor prognosis of people with severe heart failure, studies with the highest proportion of people in NYHA class IV often had the highest proportions of deaths related to progressive heart failure (Gaita et al 2000, Leclercq et al 2000a, Daubert et al 1998, Touiza et al 2001, Etienne et al 2001, Oguz et al 2002b). An exception was one study with 56 per cent in NYHA class IV that recorded only three deaths due to progressive heart failure (Galvao et al 2002). Sudden cardiac death was the most common cause of death in 10 studies (Gras et al 2002b, Reuter et al 2002, Walker et al 2000d, Galvao et al 2002, Mascioli et al 2002b, Penicka et al 2004, Achilli et al 2003, De Cock et al 2004, De Cock et al 2005, Kanhai et al 2004). These findings are consistent with other research that has documented that progressive heart failure and sudden cardiac death are the most frequent causes of death among patients with heart failure (Cleland et al 2002, Khand et al 2000). They are also consistent with other trial results that indicate that patients with NYHA class IV heart failure are more likely to die from progressive heart failure, whereas those patients with milder disease are more likely to have a fatal arrhythmia or sudden cardiac death (MERIT-HF Triallists Group 1999, CONSENSUS Trial Study Group 1987, Pitt et al 1999).

**Table 22 Survival data described in non-randomised studies**

| Study | Sample implanted | Follow-up period | Number of deaths | Cause of death | | |
|---|---|---|---|---|---|---|
| Author, date | n | (months) | n (%)[3] | Progressive heart failure | Arrhythmia | Other |
| (Linde et al 2002b) | 48 | 12 | 5 (10) | 2 | 2 | 1 |
| (Rossillo et al 2004) | 233 | 18 | 39 (17) | ns | ns | ns |
| (Mortensen et al 2004) | 198 | 4 | 8 (4) | 3 | 2 | 3 |
| (Ricci et al 2000) | 190 | 10.4 | 13 (7) | 6 | 5 | 2 |
| (Ermis et al 2004) | 158 | 18 | 34 (22) | ns | ns | ns |
| (Gasparini et al 2003e) | 158 | 11 | 14 (9) | ns | ns | ns |
| (Lecoq et al 2005) | 139 | 6 | 6 (4) | 4 | 1 | 1 |
| (Gras et al 2002b) (Leclercq et al 2004) | 103 | 12 | 21 (20) | 7 | 10 | 4 |
| (Reuter et al 2000) | 102 | 12 | 11 (11) | 5 | 6 | 0 |
| (Ellery et al 2005) | 96 | 12 | 2 (2) | 2 | 0 | 0 |
| (Gaita et al 2000) | 96 | 9.4 | 13 (14) | 11 | 1 | 1 |
| (Mair et al 2005) | 86 | 16 | 9 (10) | ns | ns | ns |
| (Mascioli et al 2002b) | 95 | 22 | 15 (16) | 5 | 7 | 3 |
| (Bax et al 2004) | 85 | 12 | 7 (8) | 6 | 0 | 1 |
| (Koos et al 2004) | 81 | 12 | 7 (9) | ns | ns | ns |
| (De Cock et al 2004) | 77 | 6 | 3 (4) | 1 | 2 | 0 |
| (Molhoek et al 2004c) | 74 | 14 | 9 (12) | 6 | 1 | 2 |
| (Ollitrault et al 2003) | 62 | 15 | 8 (13) | ns | ns | ns |
| (Molhoek et al 2004a) | 60 | 25 | 3 (5) | 3 | 0 | 0 |
| (Pitzalis et al 2005) | 60 | 14 | 4 (7) | 4 | 0 | 0 |
| (Yu et al 2004a) | 58 | 3 | 4 (7) | ns | ns | ns |
| (Penicka et al 2004) | 53 | 6 | 3 (6) | 0 | 2 | 1 |
| (Achilli et al 2003) | 52 | 18 | 10 (19) | 4 | 5 | 1 |
| (Lunati et al 2002) | 52 | 11.6 | 5 (10) | 3 | 1 | 1 |
| (O'Donnell et al 2005a) | 50 | 12 | 1 (2) | 1 | 0 | 0 |
| (Leclercq et al 2000a) | 50 | 15.4 | 20 (40) | 11 | 6 | 3 |
| (Walker et al 2000b) | 49 | 3 | 1 (2) | 0 | 1 | 0 |
| (Ammann et al 2004) | 43 | 12 | 12 (28) | 5 | 6 | 1 |
| (O'Donnell et al 2005b) | 40 | 9 | 1 (3) | ns | ns | ns |
| (Leclercq et al 2000b) | 37 | 13.5 | 9 (24) | ns | ns | ns |
| (Daubert et al 1998) | 35 | 10.2 | 10 (29) | 5 | 4 | 1 |
| (Toussaint et al 2003) | 34 | 20 | 3 (9) | 1 | 0 | 2 |
| (Touiza et al 2001) | 33 | 6 | 7 (21) | 6 | 1 | 0 |
| (Etienne et al 2001) | 30 | 6 | 7 (23) | 6 | 1 | 0 |
| (Teo et al 2003) | 29 | ns | 3 (10) | 2 | 1 | 0 |
| (Galvao 2002) | 28 | 5 | 3 (11) | 0 | 2 | 1 |
| (Dixon et al 2004) | 27 | 12 | 1 (4) | 0 | 0 | 1 |
| (Alonso et al 1999) | 26 | 12 | 4 (15) | ns | ns | ns |
| (Yu et al 2002) | 25 | ns | 1 (4) | 1 | 0 | 0 |

Notes: Mean follow-up period stated where available, ns = not specified, (%)[3] refers to percentage of participants in the trial rounded up to the nearest whole number

**Table 22 Survival data described in non-randomised studies (continued)**

| Study | Sample implanted | Follow-up period | Number of deaths | Cause of death | Study | Sample implanted |
|---|---|---|---|---|---|---|
| (De Cock et al 2005) | 24 | 13 | 3 (13) | 1 | 2 | 0 |
| (Sciagra et al 2004) | 20 | 3 | 1 (5) | 1 | 0 | 0 |
| (Barbieri et al 2004) | 18 | 6 | 2 (11) | ns | ns | ns |
| (Braunschweig et al 2000) | 16 | 9.7 | 2 (13) | 1 | 0 | 1 |
| (Knaapen et al 2004) | 16 | 3 | 2 (12) | 1 | 1 | 0 |
| (Oguz et al 2002b) | 16 | 7.6 | 3 (19) | 3 | 0 | 0 |
| (Capasso et al 2005) | 15 | 12 | 3 (20) | 3 | 0 | 0 |
| (Tsurugaya et al 2004) | 10 | 1 | 1 (10) | 1 | 0 | 0 |
| (Izutani et al 2002) | 8 | 9.1 | 0 (0) | 0 | 0 | 0 |
| (Ohkusu et al 2003) | 5 | 7.8 | 2 (40) | ns | ns | ns |
| (Kanhai et al 2004) | 1 | 1 | 1 (100) | 0 | 1 | 0 |

Notes: Mean follow-up period stated where available, ns = not specified, (%)[3] refers to percentage of participants in the trial rounded up to the nearest whole number

### Hospitalisation data described in non-randomised studies

The impact of CRT on hospitalisation is a key outcome considered in the effectiveness section (see Hospitalisation). However, data about hospitalisation rates have also been described in non-randomised studies. Five non-randomised studies have presented results that describe the effect of CRT on hospitalisation rates for all causes (Table 23). The before-and-after data presented by Gasparini et al (2003e) indicated that the pre-implantation hospitalisation rate was 21 or 24 per 100 patient years (95% CI: 19-22 and 22-26 per 100 patient years) in relation to patients who were judged to be either with or without coronary artery disease. The post-implantation hospitalisation rate dropped to 2 to 3 per 100 patient years (95 % CI: 1.1-3.3 and 1.8-4.5 per 100 patient years). Comparing hospitalisation rates and lengths of hospital stay one year before and one year after implantation (Mascioli et al 2002b) also reported generally similar reductions. Hospitalisation rates were reduced by 78 per cent and hospital stay reduced by 84 per cent one year after implantation (Mascioli et al 2002b). The results from the before–and-after study by O'Donnell et al (2005b) provide some rare information about the impact of CRT on hospitalisation rates among Australian patients. Although the study included only a relatively small sample and a short, six-months period of follow-up, it still described a large reduction in the number of inpatient days after implantation compared with the corresponding period prior to insertion of the device, at 1,163 versus 17 days. Another relatively large study (Koos et al 2004) with 81 participants documented a smaller relative reduction in the number of hospitalisation days after treatment. However, the absolute number of inpatient days was also very small at 12 days before implantation compared with eight days after insertion, and the reduction was still statistically significant. Finally, one small Italian study (Barbieri et al 2004) included only 18 patients and a six-month comparison period, and although both the frequency of hospitalisation and the number of inpatient days were reduced after implantation, from 1.5 hospitalisation before implantation compared with 0 after and 8 inpatient days prior to insertion and zero after implantation, neither of these results were statistically significant. It is likely, however, that this study lacked statistical power to evaluate these outcomes.

Four non-randomised studies have documented the frequency and duration of hospitalisation related to heart failure among participants during follow-up (Table 23). Molhoek et al (2004c) analysed changes in average hospitalisation rates before and after implantation in relation to patients with either ischaemic or idiopathic cardiomyopathy. Hospitalisation rates decreased from an average of 3.9 days per year before implantation to 0.5 days per year ($p<0.05$) among patients with ischaemic cardiomyopathy and from 3.8 days per year to 0.6 days per year ($p<0.05$) among people with idiopathic disease (Molhoek et al 2004c). An identical result was reported in Molheok et al (2004a), which was also published in the same year. It is possible that the two publications have presented information from the same patient group. The results from the MUSTIC trial were published in a subsequent study that described follow-up over 12 months and included an additional six-month period when randomisation was not preserved (Linde et al 2002b). Linde et al (2002b) reported 22 hospitalisations in the group receiving non-biventricular pacing compared to 11 in the group receiving CRT, or 0.14 hospitalisations per month for the non-CRT group compared to 0.02 per month for the treatment group. In this study an intention-to-treat analysis was employed but randomisation was not preserved after six months of follow-up. Finally, a small Swiss study described a marked reduction in the number of hospitalisations for heart failure among 43 patients during 12 months' follow-up with hospitalisations decreasing from 18 down to one, $p<0.0001$.

Two relatively small non-randomised studies have presented data about the effect of CRT on hospitalisations for heart failure as well, as those related to other conditions (Table 23). Braunschweig et al (2000) examined both the frequency and duration of the various reasons for hospitalisation among 16 participants during follow-up. This before-and-after study described a large and statistically significant reduction in the number of in-patient days related to the provision of CRT (Braunschweig et al 2000). Hospitalisation days for all causes decreased from 253 during the period before implantation down to 45 in the same period after the procedure ($p<0.01$). Inpatient treatment for heart failure was also significantly reduced to 183 days compared to 39 days ($p<0.01$). A similarly large reduction in the number of hospitalisation days 12 months after implantation compared with 12 months prior to the provision of CRT was reported in another small study of 27 participants based in Ireland (Dixon et al 2004).

Although the 11 before-and-after studies have all used an uncontrolled design and sometimes included a relatively small number of patients, their results are broadly consistent with those obtained in the randomised trials. In addition, the results from Gasparini et al (2003e) and Molhoek et al (2004c) suggest that the benefits of CRT in relation to hospitalisation may be equally shared by people with either an ischaemic or an idiopathic origin for their severe heart failure.

**Table 23 Hospitalisation data in non-randomised studies**

| Study | Sample | Mean follow-up period | Hospitalisation for all causes |
|---|---|---|---|
| **Non-randomised trials reporting hospitalisation rates for all causes** | | | |
| (Gasparini et al 2003e) | 158 | 11.2 months | Pre-implantation hospitalisation rate was 21 or 24 per 100 patient years (95% CI: 19-22 and 22-26 per 100 patient years) in relation to patients who were judged to be either with or without coronary artery disease. The post-implantation hospitalisation rate dropped to between 2 and 3 per 100 patient years (95 % CI: 1.1-3.3 and 1.8-4.5 per 100 patient years). |
| (Mascioli et al 2002b) | 96 | 22 months | Hospitalisation rates were reduced by 78% and hospital stay decreased by 84% one year before implantation compared with one year after implantation. |
| (Koos et al 2004) | 81 | 12 months | Hospitalisation days were fewer after implantation compared to before implantation, 8 vs 12 days, p<0.01 |
| (O'Donnell et al 2005b) | 40 | 9 months | Hospitalisation days were lower during the 9-month period after implantation compared to 9 months before implantation (1,163 vs 17 days) excluding implantation days. |
| (Barbieri et al 2004) | 18 | 6 months | Number of hospitalisations 6 months before implantation = 1.5 compared with 0 during 6 months after implantation (p=0.08).<br>Number of inpatient days 6 months before implantation = 8 compared with 0 during 6 months after implantation (p=0.06). |
| **Non-randomised trials reporting cardiovascular or heart failure hospitalisation rates** | | | |
| (Molhoek et al 2004c) | 74 | 14 months | Hospitalisation rates decreased from an average of 3.9 +/-4.8 days per year before implantation to 0.5 +/-1.9 days per year (p<0.05) among patients (n=34) with ischaemic cardiomyopathy and from 3.8 +/- 5.1 days per year to 0.6 +/-1.5 days per year (p<0.05) among people (n=40) with idiopathic disease.<br>The number of annual hospitalisations per patient decreased from 0.8 +/- 1.2 before to 0.1 +/- 0.5 after implantation for patients with ischaemic cardiomyopathy (p<0.05) and decreased from 0.7+/-1 before to 0.2 +/- 0.3 after implantations for patients with idiopathic cardiomyopathy (p<0.05). |
| (Molhoek et al 2004a) | 60 | 25 months | Annual hospitalisations per patient dropped from 0.8 before implantation to 0.2 after implantation. |
| (Linde et al 2002b)<br>MUSTIC | 48 | 12 months | 22 hospitalisations in the control group compared to 11 in the CRT plus OPT group ( 0.14/month hospitalisations for the control group compared to 0.02/month for the treatment group) |
| (Ammann et al 2004) | 43 | 12 months | Hospitalisations for heart failure were reduced from 18 during 12 months prior to implantation to 1 in same period after, p<0.0001). |
| **Non-randomised trials reporting cardiovascular/heart failure and all-cause hospitalisation rates** | | | |
| (Dixon et al 2004) | 27 | 12 months | Days of hospitalisation for all causes over 12 months prior to implantation compared to 12 months after implantation decreased from 483 to 140 (p<0.001). Days of hospitalisation for heart failure decreased from 472 to 9 (p<0.001). |
| (Braunschweig et al 2000) | 16 | 9.7 months | Total hospitalisations: 253 vs 45 days, p<0.01<br>Heart failure hospitalisations: 183 vs 39 days, p<0.01. |

### Other issues

#### Scarcity of any Australian data

No studies that have provided information about the nature and frequency of perioperative or postoperative complications were conducted in Australia. Aside from one study that presented some information about the success of implantation (O'Donnell et al 2005b), local data about the safety of the procedure have not been published.

#### Lack of information about the safety of specific systems

Data about the types of pacemaker and lead systems, the site of implantation and the methods of pacing have not been described in all the studies. With the rare exceptions of Hansky et al (2002), Ellery et al (2005) and Kautzner et al (2004), most studies have not described the frequency and type of adverse events in relation to the types of equipment used.

Similarly, aside from the studies by Rossillo et al (2004) and Res et al (2005), safety data have not usually been related to specific sites of implantation or methods of pacing.

#### Learning curve

Several studies observed that a learning curve effect was evident with undertaking the procedure. The time required to undertake the procedure, the success of implantation and the frequency of adverse events were noted to improve in association with more operator and treatment centre experience with the procedure (Purerfellner et al 2000, Walker et al 2000b, Alonso et al 2001, Lecoq et al 2005, Kautzner et al 2004).

#### Long-term complication rates

Longer term follow-up data over periods exceeding 12 months about the safety of the procedure have been presented as the results from one large clinical trial with 29 months' follow-up (CARE-HF) and several non-randomised studies. The rates of common postoperative complications were consistent with the results obtained from the MIRACLE trial, which included only a six-month follow-up period. The rates of the most frequently reported complications, lead dislodgement and sepsis, were the same, at 6 per cent and 1 per cent respectively in both studies. To date, published results from the CARE-HF study have not documented the occurrence of any new serious postoperative events that were not reported in the MIRACLE trial.

## Summary

The procedure is associated with an acceptable safety profile, and fatalities related to CRT either at implantation (0.2-0.8 % in randomised trials) or during follow-up are rare. Most deaths after implantation have usually been attributed to the underlying disease. The implantation success rate is generally high at approximately 90 per cent, especially in recent studies. Complications at implantation are relatively uncommon and usually not associated with severe clinical sequelae, although about 1 to 2 per cent of patients may sustain a potentially fatal coronary sinus perforation. Postoperatively, approximately 7 per cent of patients developed a complication during the six months of follow-up in the MIRACLE study. The most common complication was lead dislodgement that

impinged on the effectiveness of the device and often required a further procedure to restore the patency of the intervention.

In the MIRACLE study, the largest study reporting follow-up data among the 92 per cent of patients who were successfully implanted with a CRT device, approximately 6 per cent of patients sustained a complication at implantation and a further 7 per cent experienced an adverse event during six months of follow-up.

Long-term follow-up data over periods greater than 12 months about the safety of the procedure have been presented as the results from CARE-HF, a large clinical trial with 29 months' follow-up, and several non-randomised studies. The results from these studies, with the possible exception of those related to atrial arrhythmia and ectopy, do not suggest that either the nature or frequency of postoperative complications markedly change over longer periods of follow-up. The rates of common postoperative complications, such as lead dislodgement, sepsis and pocket stimulation, were consistent with the results obtained from the MIRACLE trial, which had a considerably shorter duration of follow-up.

A learning curve appears to exist for treatment centres and operators so the time required undertaking the procedure, the success of implantation and the frequency of adverse events all appear to improve in association with experience.

In conclusion, CRT appears to have an acceptable safety profile compared to the condition being treated, and in relation to other treatments that are currently routinely provided.

## Is it effective?

Four randomised trials – CARE-HF, COMPANION, MUSTIC and MIRACLE – have considered the effect of CRT on a range of outcomes.

### Comparison of the baseline characteristics of the RCT participants

The participants in the four randomised trials were broadly similar at baseline (see Table 24). The largest trials – COMPANION and CARE-HF – included participants with the oldest mean age (65-67 years) although differences were small. The MUSTIC and CATE-HF trials included most males (73-75% versus 67-69% in the other two trials). MUSTIC participants were exclusively NYHA class III participants. Fewer participants in the COMPANION study compared to the other three studies were NYHA Class III (82-87% versus 90-94%). Fewer patients in MUSTIC and CARE-HF had an ischaemic origin for their cardiomyopathy (37% and 36-40% compared to 50-58% in MIRACLE and COMPANION). There were largely small differences in several physiological and electrocardiographical measurements (eg, mean QRS interval 176 ms in MUSTIC versus 165-167 ms in MIRACLE, 160 ms in CARE-HF and 158-60 ms in COMPANION). The baseline mean distance walked in six minutes was lower in the COMPANION trial (244 and 274 metres) compared to MUSTIC (320 metres) and MIRACLE (291 and 305 metres). Most participants in the four trials were treated with angiotensin-converting enzyme inhibitors/angiotensin-receptor antagonists, however, there were marked differences in the proportion of patients receiving some other pharmacological treatments. A higher proportion of participants in the CARE-HF, COMPANION and MIRACLE studies received beta-blockers compared with MUSTIC (70-55% versus 28%).

This suggests that participants in the CARE-HF and COMPANION studies were comparatively well-treated groups with relatively high rates of beta-blockage protection. Compared to MUSTIC and CARE-HF, a higher proportion of participants in the MIRACLE study received treatment with digitalis (78-79% versus 40-48%). The drug treatments provided in the COMPANION study were not fully reported. Although diuretic and digoxin treatments were permitted in the COMPANION trial, the proportions of patients who received these medications were not stated. The proportion of patients receiving amiodarone in CARE-HF, COMPANION and MIRACLE, or spironolactone in MIRACLE, were also not clearly described. The use of medication in the trials broadly paralleled the recommendations from recent national guidelines (National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand 2002).

Detailed comparative information about the study participants in the two trials is provided in Table 24. It should be noted that the table excludes information about the treatment group in the COMPANION study who also received treatment with a defibrillator.

**Table 24 Comparison of effectiveness studies**

| | (Cazeau et al 2001) MUSTIC | (Abraham et al 2002) MIRACLE | | (Bristow et al 2004) COMPANION* | | (Cleland et al 2005) CARE-HF | |
|---|---|---|---|---|---|---|---|
| | Both groups | Control group | CRT group | Control group | CRT group | Control group | CRT group |
| Number | 67 | 225 | 228 | 308 | 617 | 404 | 409 |
| Demographics | | | | | | | |
| Mean age [yr] (SD) | 63 (10) | 65 (11.2) | 64 (10.7) | 67 (ns) | 65 (ns) | 66 (ns) | 67 (ns) |
| Gender [male %] | 75 | 68 | 68 | 69 | 67 | 73 | 74 |
| White race [%] | ns | 91 | 90 | ns | ns | ns | ns |
| Heart failure characteristics | | | | | | | |
| NYHA class III [%] | 100 | 91 | 90 | 82 | 87 | 93 | 94 |
| Ischaemia [%] | 37 | 58 | 50 | 59 | 54 | 36 | 40 |
| Score on Minnesota Living with Heart Failure Questionnaire (SD) | ns | 59 (21) | 59 (20) | ns | ns | ns | ns |
| Mean measurements | | | | | | | |
| LVEF [%] (SD) | 22 (8) | 21.6 (6.2) | 21.8 (6.3) | 23 (ns) | 22 (ns) | 25 (ns) | 25 (ns) |
| LVEDD [mm] (SD) | 73 (10) | 69 (10) | 70 (10) | 68 (ns) | 67 (ns) | ns | ns |
| Mitral regurgitant area [$cm^{2}$] (SD) | 7.4 (6.8) | 7.2 (4.9) | 7.6 (6.4) | ns | ns | ns | ns |
| ECG measurements | | | | | | | |
| Heart rate [beats/min] (SD) | 75 (13) | 75 (13) | 73 (13) | 72 (ns) | 72 (ns) | 70 | 69 |
| Duration of QRS interval [ms] (SD) | 176 (19) | 165 (20) | 167 (21) | 158 (ns) | 160 (ns) | 160 (ns) | 160 (ns) |
| LBBB [%] | 87 | ns | ns | 70 | 69 | ns | ns |
| PR interval [ms] (SD) | 215 (43) | ns | ns | ns | ns | ns | ns |
| Physiological measures | | | | | | | |
| Distance walked in 6 minutes [m] (SD) | 320 (97) | 291 (101) | 305 (85) | 244 (ns) | 274 (ns) | ns | ns |
| Total exercise time [sec] (SD) | ns | 462 (217) | 484 (209) | ns | ns | ns | ns |
| Peak oxygen consumption [ml/kg/min] (SD) | 13.6 (3.8) | 13.7 (3.8) | 14.0 (3.5) | ns | ns | ns | ns |
| Systolic blood pressure [mm Hg] (SD) | 117 (14) | 115 (18) | 114 (18) | 112 (ns) | 110 (ns) | 110 (ns) | 110 (ns) |
| Diastolic blood pressure [mm Hg] (SD) | 74 (9) | 68 (10) | 69 (10) | 64 (ns) | 68 (ns) | 70 (ns) | 70 (ns) |
| Weight [kg] (SD) | 79 (19) | ns | ns | ns | ns | ns | ns |
| Drug treatments | | | | | | | |
| Receiving digitalis [%] | 48 | 79 | 78 | ns | ns | 45 | 40 |
| Diuretics [%] | 94 | 93 | 94 | ns | ns | 44 | 43 |
| ACE inhibitors or angiotensin-receptor antagonists [%] | 96 | 90 | 93 | 89 | 89 | 95 | 95 |
| Beta-blockers [%] | 28 | 55 | 62 | 66 | 68 | 74 | 70 |
| Spironolactone [%] | 22 | ns | ns | 55 | 53 | 59 | 54 |
| Amiodarone [%] | 31 | ns | ns | ns | ns | ns | ns |

* defibrillator group left out

### Primary and secondary outcomes

Compared with the control group, CRT was associated with improvements in all primary outcomes in the four trials. In CARE-HF, the study with the longest duration of follow-up, the primary endpoint was a composite of death from any cause or an unplanned hospitalisation for a major cardiovascular event. Secondary endpoints were death from any cause; death from any cause or unplanned hospitalisation with heart failure; and quality of life and NYHA status at 90 days. The study results indicate that CRT in addition to OPT was associated with a significant reduction in the hazard ratio for the primary endpoint. Furthermore the rate of all-cause mortality was significantly reduced in the CRT plus OPT group. Other improvements in the remaining secondary outcomes were also associated with the intervention group. Quality of life and NYHA status were significantly higher in the CRT plus OPT group compared to the control at 90 days follow-up. Death from any cause and unplanned hospitalisation with worsening heart failure were significantly reduced among members of the CRT plus OPT group compared to controls, and the rate of unplanned hospitalisation with worsening heart failure was also significantly lower in the group that received pacing therapy in addition to OPT. The results from the sub-group analyses suggested that the benefits of pacing therapy were similar among patients with either an ischaemic or non-ischaemic origin for their cardiomyopathy; patients younger or older than 66.4 years; and females compared with males. In COMPANION, the largest study, the primary outcome was a composite examining death or hospitalisation from any cause at 12 months (Bristow et al 2004). The secondary endpoints were death from any cause, death or hospitalisation due to cardiovascular causes, death or hospitalisation due to heart failure and adverse events. The trial was stopped early when the study steering committee indicated that the pacemaker group and the pacemaker-defibrillator group had crossed a primary or secondary endpoint. The study results suggest that the addition of CRT to optimal pharmacological treatment resulted in a significant lowering of the hazard ratio for the primary endpoint and some secondary endpoints. Among the sub-group results, the use of CRT appeared to most benefit patients with NYHA IV and it led to a progressive lowering of the primary endpoint hazard ratio with increasing QRS interval. Similarly, the use of resynchronisation therapy in combination with beta-blockers or sprinoloactone apparently reduced the risk further than the combination of the therapy and any other agents (Bristow et al 2004). In the MIRACLE study differences in favour of the CRT plus OPT group were apparent from one month after treatment and the magnitude of improvement was maintained throughout the entire study period (Abraham et al 2002). Furthermore, the magnitude of effect on the endpoints was not changed by the use of beta-blockers, the cause of heart failure (ischaemic versus non-ischaemic), the configuration of the QRS complex (left or right bundle branch block), or the baseline duration of the QRS interval.

### Survival

Survival as a separate outcome measure was assessed as a secondary outcome in all four randomised trials. In the CARE-HF study at the end of a mean period of 29 months follow-up, the all-cause mortality rate was 20 per cent in the cardiac resynchronisation group compared to 30 per cent in the group receiving medical therapy only (hazard ratio = 0.64, 95% CI: 0.48-0.85, $p<0.002$) (Cleland et al 2005b). The principal cause of death was cardiovascular in 167 (83%) patients. The cause of death was attributed to worsening heart failure in 56 (47%) of the 120 patient who died in the control group and in 33 (40%) of the 82 deaths in the group receiving resynchronisation plus medical therapy. The mode of death was classified as sudden in 38 (32%) of the 120 patients who died in

the control group and 29 (35%) of the 82 patients who died in the CRT plus OPT group. The one-year and two-year mortality rates in the medical therapy only group were 12.6 and 25.1 per cent compared with 9.7 and 18 per cent, respectively in the medical therapy plus CRT group (Cleland et al 2005b). In the COMPANION study the 12-month rate of death from any cause was reported as 19 per cent among the control group and 15 per cent among the pacemaker group (Bristow et al 2004)(see Table 25). These rates equate to approximately 59 and 93 fatalities in the two groups respectively. The implantation of a pacemaker was associated with a statistically non-significant reduction in the risk of death from any cause (hazard ratio = 0.76, 95% CI: 0.58-1.01, p=0.059, adjusted p=0.06) (Bristow et al 2004). Twenty-eight deaths (6% of participants) were recorded in the MIRACLE trial. Mortality was 27 per cent lower in the active treatment group, where 12 deaths occurred compared to 16 in the control group over a six-month period (hazard ratio: 0.73, 0.34-1.54) (Abraham et al 2002).

The mortality rate (7%) in the MUSTIC trial was similar over nearly the same period of follow-up as the MIRACLE study (Cazeau et al 2001). One death occurred before randomisation and one occurred in the active treatment group, compared to two among the control group.

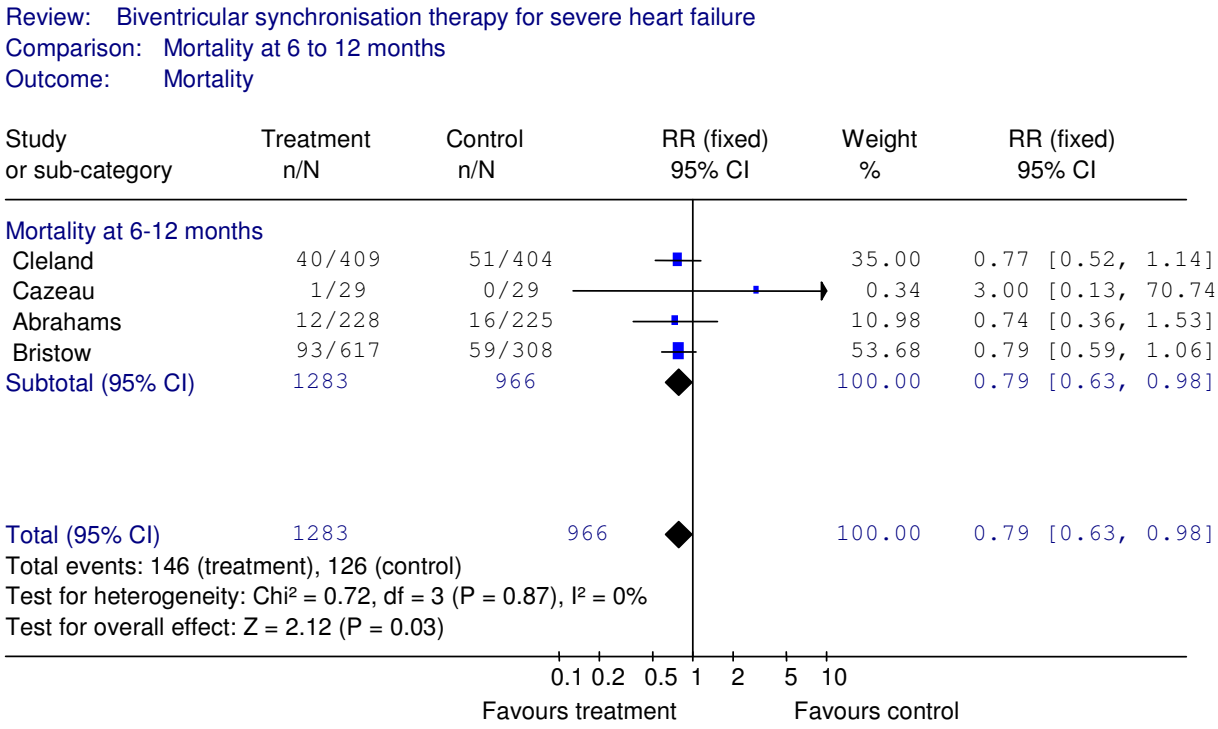
The COMPANION study was designed with a composite primary endpoint that included both hospitalisation and mortality. Although death from any cause was included as a secondary endpoint, the study was stopped before the event rate was able to provide a statistically significant difference between the study groups if one existed. Both the MIRACLE and MUSTIC studies clearly lacked statistical power related to their small sample size and were unable to assess reliably the effect of the intervention on mortality.

Detailed results from the COMPANION study in relation to the timing and the cause of death among participants are not yet available. In particular, the number of deaths that occurred at three or six months follow-up have not been accurately reported yet to assist with the valid comparison of data from the three studies. Neither the MIRACLE nor MUSTIC trials clearly specified the cause of death among the fatalities.

**Meta-analysis of survival data from randomised trials**

A forest plot including the survival data provided in the four main randomised trials assessing the effectiveness of CRT in relation to mortality at 6-12 months follow up is provided in Figure 2. The forest plot illustrates that CRT is associated with a 21 per cent reduction in the relative risk of mortality, and the reduction is statistically significant. There is a 95 per cent probability that CRT plus OPT may reduce the risk of mortality by as much as 37 per cent or as little as 2 per cent. This result is not associated with significant statistical heterogeneity and a fixed-effect model is presented. However, it should be noted that the mortality data was obtained from trials with varying lengths of follow-up. Furthermore, only 12-month mortality data is provided from the CARE-HF, trial even though the study also reported mortality data from longer periods of follow-up, up to a mean period of 29 months.

**Figure 2 Forest plot of mortality for CRT between 6 and 12 months**




## Long-term survival

The results from the CARE-HF trial provide unique information about the effectiveness of CRT in addition to OPT over an extended period of follow-up (mean duration of 29 months). The mortality rate in the OPT group was 12.6 per cent at one year and 25.1 per cent at two years (Cleland et al 2005b). By comparison, 9.7 per cent of the CRT group in the trial had died after one year and 18 per cent were dead after two years of follow-up. From these results and the information presented in the Kaplan-Meier survival curves in the study report (Cleland et al 2005b) it appears that the relative benefits of CRT over OPT become increasingly more pronounced after about 300 days of follow-up post implantation.

**Table 25 Survival**

| Study | Study patients | Follow-up period | Total number of deaths | Cause of death | | |
|---|---|---|---|---|---|---|
| Author, date | n | (months) | n (%)[3] | Progressive heart failure | Arrhythmia | Other |
| **Randomised trials** | | | | | | |
| (Cleland et al 2005b) | 813 | 29.4 | 202 (25) | 89 | 67 | 46 |
| (Bristow et al 2004) | 925 | 12 | 170 (18) | ns | ns | ns |
| (Abraham et al 2002) | 453 | 6 | 28 (6) | ns | ns | ns |
| (Cazeau et al 2001) | 59 | 7 | 4 (7) | ns | ns | ns |
| **Randomised trial not assessing mortality as an outcome** | | | | | | |
| (Sawhney et al 2004) | 40 | 3 | 1 (3) | ns | ns | ns |

Notes: Mean follow-up period stated where available, ns = not specified, (%)[3] refers to percentage of participants in the trial rounded up to the nearest whole number

### Hospitalisations

Fourteen studies provided information concerning comparative hospitalisation rates (see Table 26). The study with the longest follow-up period, CARE-HF, separately reported unplanned hospitalisation data related to cardiovascular events and worsening heart failure, but did not report all-cause hospitalisation rates (Cleland et al 2005b). In the CARE-HF trial the addition of CRT to OPT was associated with a significant reduction in the rate of unplanned hospitalisation for any cardiovascular event compared to OPT alone (184 events in the control group compared to 125, hazard ratio = 0.61, 95% CI: 0.49-0.77, $p<0.001$). Similarly, the CRT plus OPT group recorded a significantly lower rate of unplanned hospitalisation with worsening heart failure by the end of the study (133 in the control group and 72 in the CRT plus OPT group, hazard ratio = 0.48, 95% CI: 0.36-0.64, $p<0.001$). The results from the CARE-HF study suggest that absolute risk reduction for hospitalisation related to a cardiovascular event is about 15 per cent (95% CI: 8-22). From this estimate it can be calculated that about seven patients (95% CI: 5-13) would need to be implanted with a CRT device in order to prevent one hospitalisation for a cardiovascular event over 29 months. Similarly, the absolute risk reduction for hospitalisation related to worsening heart failure is also about 15 per cent (95% CI: 9-21). Therefore, about seven patients (95% CI: 5-11) would also need to be implanted with a CRT device in order to prevent one hospitalisation for worsening heart failure over 29 months. The results from the first period of the MUSTIC study also describe a significant reduction in the number of hospitalisations associated with the active pacing group compared to the inactive control group (3 versus 9 hospitalisations, $p<0.05$). The large COMPANION study only reported hospitalisation data as part of a composite outcome that also included death. Composite data from the COMPANION trial have not been presented in Table 26.

In the MIRACLE trial (Abraham et al 2002), pacing was associated with a significantly lower frequency of hospitalisation ($p=0.02$). Fifty hospitalisations for heart failure were recorded among 34 control patients, for a total of 363 inpatient days. This was compared to 25 hospitalisations for heart failure among 18 patients in the CRT plus OPT group, for a total of 83 inpatient days. Hospitalisations for lead-related problems were lower in

the CRT group (11 compared with nine). However, a similar number of hospitalisations not related to either heart failure or lead problems were recorded for both study groups (37 in the CRT plus OPT group versus 33 in the control group). The results from the MIRACLE study indicate that CRT plus OPT was associated with a statistically significant 51 per cent reduction in the relative risk and an 11 per cent reduction in the absolute risk of hospitalisation (Abraham et al 2002). The reduction in the absolute risk of hospitalisation in this trial suggests that only nine patients would need to be treated over six months in order to prevent one additional episode of hospitalisation for heart failure (Abraham et al 2002).

**Table 26 Hospitalisations**

| Study | Sample | Mean follow-up period | Hospitalisation for all causes |
|---|---|---|---|
| **Randomised trials reporting hospitalisation rates for heart failure and other causes** | | | |
| (Abraham et al 2002)<br>MIRACLE | 453 | 6 months | 75 admissions for 52 patients for a total of 446 days<br>34 control patients had 50 hospitalisations for heart failure and 363 days in hospital (mean days hospitalised = 10.7 +/- 11.6 days)<br>18 CRT plus OPT patients had 25 hospitalisations for heart failure and 83 days in hospital (mean days hospitalised = 4.5 +/- 4.2 days).<br>Hospitalisations for lead related problems were 11 and 3 in the CRT and control groups respectively.<br>Similar number of hospitalisations not related to heart failure or leads: 37 and 33 in CRT and controls groups. |
| **Randomised trials reporting cardiovascular or heart failure hospitalisation rates** | | | |
| (Cleland et al 2005b)<br>CARE-HF | 813 | 29 months | Hospitalisations for cardiovascular events were lower in CRT group: 184 vs 125 (hazard ratio = 0.61, 95% CI: 0.49-0.77, p<0.001).<br>Hospitalisations for worsening heart failure were lower in CRT group: 133 vs 72, (hazard ratio: 0.48, 95% CI: 0.36-0.64, p<0.001). |
| (Cazeau et al 2001)<br>MUSTIC | 67 | 3 months | During first period there were 3 hospitalisations for heart failure among patients in active group vs 9 in inactive group (p<0.05). |

## Quality of life

Quality of life in all four trials, as measured by the Minnesota Living with Heart Failure Questionnaire, significantly improved for people who received CRT and medical treatment compared to those who were provided with only medical treatment. In the CARE-HF trial (Cleland et al 2005b) the mean score on the Minnesota Questionnaire after 90 days of follow-up for members of the medical therapy only group was 40 (+/- SD 22) compared with 31 (+/-22) for members of the CRT plus medical treatment group (hazard ratio= -10, 95% CI: -8 - -12, p<0.001). The mean change among members of the control group in the score on the Minnesota Questionnaire recorded after six months follow-up in the COMPANION trial was reduced by 12 (+/-SD 23) compared to a reduction of 25 (+/-26) (p<0.001) among participants in the pacemaker arm (Bristow et al 2004). Median Minnesota Questionnaire scores were reduced by 18 points in the intervention group compared to nine in the control group in the MIRACLE study

(p=0.001). Similarly, in the MUSTIC trial the mean score for the resynchronisation and medical treatment group was 29.6 compared to 43.2 in the group that received only medical treatment (p<0.001) (Cazeau et al 2001). It is notable that the results from both trials are almost identical, even though the MIRACLE study involved a double-blind design, whereas the COMPANION study only blinded assessors.

Consistent with the improved quality of life results recorded by the specialised Minnesota Questionnaire, participants in the CRT group of the CARE-HF trial (Cleland et al 2005b) were also associated with a higher measure of general quality of life as assessed by the EuroQoL instrument after the same three-month period of follow-up. The EuroQoL EQ-5D score for the medical therapy alone group was 0.63 (+/- 0.29) compared to 0.70 (+/-0.28) for members of the CRT plus medical therapy group (hazard ratio = 0.08, 95% CI: 0.04 – 0.12, p<0.001).

**NYHA class**

In relation to the results from the CARE-HF trial (Cleland et al 2005b), after just 90 days of follow-up mean NYHA class was significantly lower among members of the CRT plus OPT group compared to medical therapy alone (2.1 +/-1.0 compared with 2.7+/-0.9, hazard ratio= 0.6, 95% CI: 0.4-0.7, p<0.001). At 18 months follow-up, 105 of the patients in the cardiac resynchronisation group were in NYHA class I, 150 were in NYHA class II, and 80 were in NYHA class II or IV. The respective values for the medical therapy alone group were 39, 112 and 152 (Cleland et al 2005b). Likewise, some 38 per cent of participants improved in NYHA class symptoms among the control group while 61 per cent of the members of the pacemaker CRT group improved in the COMPANION study (p<0.001) (Bristow et al 2004). Compared to the control group, patients assigned to CRT had an improvement in mean NYHA functional class in the MIRACLE study (p<0.001) (Abraham et al 2002). Some 143 (68%) patients improved by one or more functional classes in the CRT group compared to 74 (38%) in the control group. Within the CRT plus OPT group, 64 patients (30%) exhibited no change in NYHA class and four (2%) worsened, whereas 115 patients (59%) did not change their NYHA class and seven (4%) worsened in the OPT-alone control group.

The MUSTIC study did not report data on change in NYHA functional group.

**Six-minute walk test**

Members of the control group in the COMPANION study increased their mean distance walked in six minutes by only one metre (+/- 93 SD) compared to an average improvement of 40 metres (+/- 96) among the participants in the pacemaker CRT group (p<0.001) (Bristow et al 2004). In the MIRACLE trial patients receiving CRT increased their distance walked in six minutes by a median of 39 metres (95% CI: 26-54) compared to the control group who improved their median distance by 10 metres (95% CI: 0-25 metres)(p=0.005) (Abraham et al 2002). In the MUSTIC trial, the mean distance increased to 399.2 metres (+/– 100.5) during active pacing compared to 325.7 metres (+/- 134.4) with inactive pacing (p<0.001) (Cazeau et al 2001).

The CARE-HF study did not report data on change in the six-minute walk.

**Peak oxygen consumption**

In the MIRACLE study, median peak oxygen consumption increased among the CRT group by 1.1ml/kg/min (95% CI: 0.6-1.7) compared to 0.2 ml/kg/min (95% CI: -0.2 – 0.8) for the control group (p<0.009) (Abraham et al 2002). In the MUSTIC trial mean

peak oxygen uptake increased to 16.2 (+/- 4.7) ml/kg/min during active pacing compared to 15 (+/- 4.9)mg/kg/min during inactive pacing (p=0.029) (Cazeau et al 2001).

The CARE-HF and COMPANION studies did not report data on change in peak oxygen consumption.

**Total exercise time**

The CRT group in the MIRACLE study increased median total exercise time by 81 seconds (95% CI: 62 – 119) compared to the 19 seconds (95% CI: -1-47) median improvement for the control groups (p=0.001) (Abraham et al 2002). Total exercise time was not assessed in the CARE-HF, COMPANION or MUSTIC studies.

**Patients' preference**

At the end of the crossover phase in the MUSTIC trial, 41 (85%) patients indicated they preferred the period corresponding to the active pacing mode (p<0.001), two patients (4%) preferred the period corresponding to the inactive-pacing mode and five (10%) had no preference (Cazeau et al 2001). Patient preference was not assessed in the CARE-HF, COMPANION and MIRACLE studies.

**Patients' view of progress**

In the MIRACLE study, 166 (79%) people in the CRT group reported that they had slightly, moderately or markedly improved, compared with 110 (57%) people in the control group (Abraham et al 2002). By contrast, 34 (17%) people in the control group considered that they had deteriorated compared to only eight (3%) in the CRT plus OPT group. Twenty-six (12%) and 51 (26%) people in the CRT plus OPT and control groups respectively reported that there was no change in their clinical progress. Overall, there was a significant difference between the results from the two study groups (p<0.001). The CARE-HF, COMPANION and the MUSTIC trials did not report patient assessments of their progress.

### Long-term (greater than six months) follow-up

Data from the CARE-HF trial provides information about the effectiveness of CRT therapy in addition to OPT after periods of follow-up greater than six months, in relation to the primary outcome – combined death and unplanned hospitalisation for a cardiovascular event – and some secondary outcomes – death from any cause, composite death from any cause and unplanned hospitalisation for worsening heart failure. The mean duration of follow-up in the CARE-HF trial was 29.4 months and the range was 18 to 44.7 months. Changes in NYHA class and quality of life were only assessed at 90 days' follow-up.

The COMPANION trial reported results at 12 months follow-up in relation to its primary outcome – death or hospitalisation from any cause – and secondary outcomes – death from all causes, death or hospitalisations from cardiovascular causes, death or hospitalisation due to heart failure (Bristow et al 2004). Data about changes in patient quality of life and intermediate outcomes – six-minute walk and NYHA class – were only presented up to six months of follow-up (Bristow et al 2004).

Neither the MIRACLE or MUSTIC trials assessed the long-term, post six-month, effectiveness of resynchronisation therapy. However, Linde, in a subsequent publication described the long-term outcomes for the participants in the MUSTIC trial over a further

six months (Linde et al 2002b). Of 48 patients, 41 elected to receive active treatment at the end of the initial six-month follow-up and all the remaining patients were subsequently programmed to receive CRT during the following three months. The results, reported on an intention–to-treat basis, indicate that the benefits recorded in the earlier MUSTIC report were maintained at 12-month follow-up. Walking distance was 20 per cent higher in the active treatment group (348 +/- 98 metres versus 418 +/- 112 metres, p=0.0001), Minnesota Questionnaire scores were reduced by 36 per cent (47 +/- 23 versus 30 +/- 22, p=0.0001), and peak oxygen uptake was increased by 11 per cent (14.9 +/- 4.7 versus 16.6 +/- 3.6mg/kg/min, p>0.05).

**Summary of effectiveness**

Tables 27 and 28 summarise main effectiveness results from the CARE-HF, COMPANION, MIRACLE and MUSTIC trials. CARE-HF, the trial with the longest follow-up duration, documented significant reductions in various combined endpoints, including deaths/hospitalisations for cardiovascular events, cardiovascular deaths/hospitalisations, and deaths/hospitalisations for heart failure. Hospitalisations related to either cardiovascular events or heart failure were also significantly reduced. The study results indicate that there was a statistically significant 36 per cent reduction in all-cause mortality by the end of the 29-month follow-up period (hazard ratio = 0.64, 95% CI: 0.48-0.85, p<0.001). This result suggests that there is a 95 per cent probability that the risk of mortality may be reduced by as much as 52 per cent or as little as 15 per cent over 29 months. From the study results, the absolute risk reduction associated with the addition of CRT to OPT can be estimated to be about 10 per cent (95% CI: 4-16) and therefore about 10 patients would need to be treated with a device in order to prevent one death from any cause over a 29-month period. From the confidence interval, it can be estimated that the likely number of patients that would need to be implanted with a device in order to prevent one death over a period of 29 months is between six and 25 patients.

The large COMPANION study recorded significant reductions in various composite endpoints, including all-cause mortality/hospitalisation, mortality/hospitalisation due to cardiovascular causes, and mortality/hospitalisation due to heart failure. The published results from the study suggest there was a 24 per cent reduction in the hazard ratio of death from any cause associated with pacemaker CRT which was not statistically significant (OR=0.76, 95% CI: 0.58-1.01, p=0.06). Neither the MIRACLE nor the MUSTIC trials were suitably powered to assess the effect of CRT on survival.

The results from a meta-analysis that included 6 to 12 month mortality data from the four randomised controlled trials indicated that CRT was also associated with a reduction of 21 per cent in the relative risk of mortality, and this result was statistically significant (RR=0.79, 95% CI: 0.63-0.98). This estimate indicates that there is 95 per cent probability that the therapy may reduce the mortality risk by as much as 37 per cent or as little as 2 per cent during up to one year of follow-up. The results from the meta-analysis indicate that CRT plus OPT is associated with a statistically non-significant absolute risk reduction of three per cent (95% CI: -0.06-0.01). From this result it can be estimated that the number needed to treat (NNT) over 12 months in order to prevent one additional death is 33 patients. From the confidence interval, it can be inferred with 95 per cent probability that the NNT may be as low as 16 or zero (that is, for every 100 patients the treatment may actually be associated with no reduction in the absolute number of deaths over 12-month follow-up).

The results from the CARE-HF study suggest that absolute risk reduction for hospitalisation related to a cardiovascular event is 15 per cent (95% CI: 8-22). From this estimate it can be calculated that about seven patients (95% CI: 5-13) would need to be implanted with a CRT device in order to prevent one hospitalisation for a cardiovascular event over 29 months. Similarly, the absolute risk reduction for hospitalisation related to worsening heart failure is also 15 per cent (95% CI: 9-21). Therefore, about seven patients (95% CI: 5-7) would also need to be implanted with a CRT device in order to prevent one hospitalisation for worsening heart failure over 29 months. Both the MIRACLE and MUSTIC trials reported significant reductions in the frequency of heart failure related hospitalisations among members of the CRT plus OPT group. Separate data related to hospitalisations were not currently available from the COMPANION trial.

The four studies consistently reported significant improvements in relation to the quality of life and functional state associated with the intervention group, whether assessed by patients, professionals or objective measures. The benefits for the CRT plus OPT group were incremental over the placebo effect associated with improvements in these outcomes among the control group. Detailed comparisons between study results are limited because of the use of different measures and varying methods. The available data suggests that benefits are sustained and possibly even increased over longer periods of follow-up, of 12 months and more, however, more data is needed before reliable conclusions can be made about the very long-term, post two-year, effectiveness of the intervention. It was concluded that there is an improvement in survival up to 29 months mean follow-up but very long-term data are absent.

**Table 27 Summary of clinical results from trials addressing the effectiveness of CRT**

| | (Cazeau et al 2001) MUSTIC | | Abraham et al (2002) MIRACLE | | (Bristow et al 2004) COMPANION | | (Cleland et al 2005b) CARE-HF | |
|---|---|---|---|---|---|---|---|---|
| n | 58 | | 571 | | 925 | | 813 | |
| Study type | Crossover | | RCT | | RCT | | RCT | |
| | Active | Inactive | Pacing | Control | Pacing | Control | Pacing | Control |
| *Primary outcomes in the trials* | | | | | *Secondary outcomes in the trials* | | | |
| NYHA class | ns | ns | 68 | 38*** | 61 | 38*** | 2.1 | 2.7*** |
| | | | % improving 1 or more classes at 6 mths | | % improvement in symptoms at 6 mths | | Mean class at 3 months | |
| Minnesota Questionnaire | 30 | 43*** | -18 | -9*** | -25 | -12*** | 31 | 40*** |
| | Mean comparison | | Median decrease | | % increase in QoL | | Mean comparison at 90 days | |
| 6 minute walk | 399 | 326*** | +39 | +10** | 40 | 1*** | ns | ns |
| | Mean comparison, metres | | Median increase, metres | | Increase in metres | | | |
| *Primary outcomes in the trial* | | | | | | | | |
| Composite deaths and hospitalisation from all causes | ns | ns | ns | ns | Hazard ratio = 0.81** 95% CI: 0.69-0.96 | | ns | ns |
| Composite deaths and hospitalisation for cardio-vascular events | ns | ns | ns | ns | ns | ns | Hazard ratio = 0.63 *** 95% CI: 0.51-0.77 | |
| Unplanned hospitalisation for a cardiovascular event | ns | ns | ns | ns | ns | ns | Hazard ratio = 0.61*** 95% CI:0.49-0.77 | |
| *Secondary outcomes in the trials* | | | | | | | | |
| Survival (no of deaths all causes) | 1 | 2 | 12 | 16 | ?59 | ?93 | 82 | 120*** |
| | | | | | | | Hazard ratio = 0.64*** 0.48-0.85 | |
| Composite cardiovascular deaths and hospitalisation | ns | ns | ns | ns | Hazard ratio = 0.75** 95% CI: 0.63-0.90 | | 159 | 224*** |
| | | | | | | | Hazard ratio = 0.63*** 95% CI: 0.51-0.77 | |
| Hospitalisations (frequency related to heart failure) | 11 | 22 | 25 | 50* | ns | ns | 72 | 133*** |
| | | | | | | | Hazard ratio = 0.48*** 95% CI: 0.36-0.64 | |
| Composite deaths and hospitalis-ations related to heart failure | ns | ns | ns | ns | Hazard ratio = 0.66** 95% CI: 0.53-0.87 | | 118 | 191*** |
| | | | | | | | Hazard ratio = 0.54*** 95% CI: 0.43-0.68 | |

Key: * = p < or = 0.05, ** = p < or = 0.01, *** = p < or = 0.001

**Table 28 Summary of exercise test results from trials addressing the effectiveness of CRT**

| | (Cazeau et al 2001) MUSTIC | | (Abraham et al.,2002) MIRACLE | | (Bristow et al 2004) COMPANION | | (Cleland et al 2005b) CARE-HF | |
|---|---|---|---|---|---|---|---|---|
| | Active | In-active | Pacing | Control | Pacing | Control | Pacing | Control |
| | Primary outcome in the trials | | | | Secondary outcome in the trials | | | |
| Six-minute walk | 399 | 326*** | +39 | +10** | 40 | 1*** | ns | ns |
| | Mean comparison, metres | | Median increase, metres | | Increase in metres | | | |
| | Secondary outcomes in the trials | | | | | | | |
| Peak oxygen consumption | 16 | 15* | +1.1 | +0.2** | ns | ns | ns | ns |
| | Mean comparison ml/kg/min | | Median increase ml/kg/min | | | | | |
| Treadmill time (sec) | ns | ns | +81 | +19*** | ns | ns | ns | ns |

Key:
* p < or = 0.05,
** p < or = 0.01
*** p < or = 0.001

## Conclusion

In conclusion, there is reliable evidence that CRT can effectively improve exercise capacity and quality of life over a relatively short period of follow-up, from three to six months.

CRT has been associated with lower all-cause mortality rates at six and 12 months' follow-up, but the results from individual trials were not statistically significant. Combining the results from separate trials in a meta-analysis indicates that CRT effectively reduces mortality up to one year of follow-up. Furthermore the results from one trial suggest that CRT is also effective at improving survival over longer periods of follow-up, of up to 29 months. Other results from four randomised trials confirm that CRT effectively reduces combined mortality and hospitalisation rates in relation to all-causes, cardiovascular causes and heart failure at both 12 and 29 months' follow-up. In addition, the intervention also effectively reduces the frequency of hospitalisation related to cardiovascular events and heart failure over short and longer periods of follow-up of six to 29 months. However, there is still insufficient information to fully ascertain the effect of CRT on short-term and long-term hospitalisation rates for all causes, and not just those associated with cardiovascular or heart failure related problems.

## What are the economic considerations?

The purpose of this section is to provide an economic appraisal of adding CRT to optimal pharmacological treatment of heart failure. The economic analysis was based mainly on the CARE-HF study, with some data derived from the MIRACLE study, as these studies provided data on mortality, hospitalisation, and quality of life which allowed for the most accurate cost and outcome estimates to be derived. Australian cost data were derived from public and private hospital AR-DRG cost data. The cost of the CRT device and equipment was based on current market prices quoted at the time of this review. It is not known what proportion of patients would likely receive CRT from the public or private sector. For this reason, all results are presented separately using public and private hospital data. There are four parts to the economic analysis:

- The assumptions and derivation of variable values are outlined.
- A decision analysis is used to determine the incremental cost-effectiveness of adding CRT to optimal pharmacological treatment.
- Sensitivity analysis is used to determine how much uncertainty there may be around the conclusion of the decision analysis.
- A total cost assessment is carried out to determine what the total cost implications of each treatment strategy would be for the Australian health system.

The basis for the main conclusions of this section is a decision analysis conducted on CRT together with pharmacological treatment, compared with using optimal pharmacological treatment only. A general guide to decision analysis and the interpretation of results is included as an appendix to this report. The outcomes of interest are the number of days of hospitalisation, life years saved, quality-adjusted life years saved, and the total cost per patient. These outcomes and all other variables are estimated for periods from two years following the beginning of treatment to patients' lifetimes, where the latter is based on projection.

The number of days of hospitalisation includes all days in hospital required to receive CRT treatment, ie, implantation of the device; all days in hospital as a result of heart failure during the first six months of treatment; and, all days in hospital resulting from a need for further surgery that is directly related to the treatment ie, replacing the device, etc. However, it may be more useful to consider only the difference in hospitalisation for major cardiovascular events, which is what the treatment is intended to reduce, and for this reason both total hospitalisation and hospitalisation for major cardiovascular events are presented.

Total cost per patient includes all hospital and drug costs relating to the treatment. These costs are included in the analysis whether they are incurred by the patient – including through the patient's private health insurance – the federal government, or the state government. With the exception of the cost of pharmaceuticals, all included costs would normally be incurred in a hospital setting.

The specific costs included in the analysis are:

- All device and equipment costs associated with implantation of the device, or any subsequent surgery to re-position the device, replace the device, reconnect leads, or replace batteries.
- All hospital costs including overhead costs, staff costs, operating room costs, etc.
- All pharmaceutical costs.

In order to conduct a complete economic assessment of CRT, a large amount of information pertaining to probabilities and the components of outcome variables was required. This involved making certain assumptions where data were unavailable or inappropriate for this context. The following section details how these variables were derived.

## Economic assumptions and derivation of variable values

### Optimal Pharmacological Treatment

In order to derive the cost of optimal pharmacological treatment a typical treatment plan was developed and the associated costs were derived for a 12-month period. This is shown in Table 29 below.

**Table 29 Estimated cost of optimal pharmacological treatment**

*All drug types, probabilities, and doses are based on expert opinion. Drug prices are dispensed prices listed in the Schedule of Pharmaceutical Benefits (effective April 1, 2005).*

| Drug type | Probability | Average daily dose | Dispensed price/ max quantity | Expected 12-month cost [a,b] |
|---|---|---|---|---|
| ACE inhibitors (Ramipil) | 0.90 | 5 mg | $20.73 / 30 x 5mg | $253*0.90=$228 |
| Loop diuretics (Frusemide)[c] | 0.85 | 80 mg | $7.81 / 100 x 40mg | $57*0.85=$48 |
| | 0.15 | 56mg | | $3*0.15=$6 |
| Beta blockers (Carvedilol) | 0.90 | 25 mg | $109.34/ 60 x 25mg | $600*0.90=$540 |
| | Lower dose | 6.25mg | $71.68 / 60 x 6.25mg | $437*0.90=$393 |
| | Higher dose | 50mg | $109.34 / 60 x 25mg | $1201*0.90=$1,081 |
| Digoxin | 0.60 | 125 mg | $8.46 / 200 x 62.5mg | $31*0.60=$19 |
| Spironolac-tone | 0.70 | 25mg | $12.71 /100 x 25mg | $47*0.70=$33 |
| Calcium channel blockers (Amlodipine) | 0.10 | 5mg | $25.07 / 30 x 5mg | $306*0.10=$31 |
| | Higher dose | 10mg | $39.12 / 30 x 10mg | $477*0.10=$48 |
| All receptor antagonists (Irbesartan) | 0.10 | 150mg | $27.33 /30 x 150mg | $333*0.10=$33 |
| Other vasodilators (Isosorbide mononitrate) | 0.05 | 120mg | $24.89 /30 x 120mg | $304*0.05=$15 |
| Total | | | | $953<br>low dose: $806<br>high dose: $1,511 |

[a] Costs are estimates only as patients may choose to purchase drugs in different formats, which would cause costs to vary slightly. Estimates are based on dosages of tablets being as close as possible to the daily dosage and on minimum listed prices.

[b] cost for 365 days * probability

[c] 10 – 15% of patients may take Frusemide intermittently. Accordingly Frusemide dose is adjusted to 70% (56mg) for 15% of patients to account for 70% intermittent dose for these patients.

The total 12-month cost of optimal pharmacological treatment is estimated to be $953. Sensitivity arising from the possibility of higher or lower doses, particularly for Carvedilol, suggests that the total cost could be as low as $806 or as high as $1,511. Although the cost of optimal pharmacological treatment is not an incremental cost initially, it will add to incremental cost over the longer term as patients in the CRT group expect to survive longer than patients in the OPT group, implying increased costs for pharmacological treatment.

### Implantation of the CRT device

In approximately 85 per cent of cases, the device can be implanted successfully on the first attempt (CARE-HF study). A second attempt at implantation is expected to have a 68 per cent success rate (CARE-HF study). These yield an overall success rate amongst eligible

patients of 95 per cent. The following assumptions are made in deriving costs and outcome data associated with successful implantation of the device:

- The average length of stay for implantation of the device in Australia is likely to be the same as for implantation of a standard cardiac pacemaker (National Hospital Cost Data Collection Cost Weights for AR-DRG Version 4.1 2000-01, AR-DRG F12Z) (4.57 days in public hospitals and 4.17 days in private hospitals). This is very close to the mean 4.5 days of hospitalisation for implantation reported in the CARE-HF study.

- The intensity of hospital care, and therefore the cost per day, is the same for patients having been implanted with the device as for patients implanted with the above cardiac pacemaker.

- From the information provided by the MSAC applicant, the incremental time spent in a cardiac catheterisation suite for implantation of the device is assumed to be 105 minutes over the time requirement for implantation of a cardiac pacemaker.

- From the information provided by the MSAC applicant, the cost of 105 minutes of time in excess of the time required for cardiac pacemaker implantation in the operating theatre is approximately $409.26.

- The specific model of standard cardiac pacemaker or CRT device does not affect the time requirements for implantation of the device.

- The costs of a CRT device and of associated equipment are accurately reflected by market prices quoted at the time of this review: The generator costs approximately $5,900 in public hospitals and $12,500 in private hospitals; the LV lead costs approximately $2,100 in public hospitals and $4,500 in private hospitals; and, the RV leads (of which two are required) cost approximately $550 each in public hospitals and $1,000 each in private hospitals.

- The cost of a cardiac pacemaker can be approximated by the prosthesis cost from AR-DRG F12Z, implantation of a cardiac pacemaker, at $2,708 in public hospitals and $12,109 in private hospitals).

- A failed attempt at implantation results in the same costs as a successful attempt, minus the cost of the generator and the leads.

The cost of implanting a cardiac pacemaker is used as the basis from which to derive the cost of implanting the CRT device. The average cost per admission for implantation of a standard cardiac pacemaker (AR-DRG F12Z) is $9,934 in public hospitals and $16,453 in private hospitals. From this, the cost of the pacemaker device at $2,708 in public hospitals and $12,109 in private hospitals, approximated by the prosthesis costs listed for AR-DRG F12Z, is subtracted to derive the non-device hospital cost of implantation. This is $7,226 for public hospitals. For private hospitals, the result of this calculation, $4,344, needs to be added to the relevant Medicare Benefits Schedule fees. No MBS items currently exist for procedures involving CRT. For this reason, the estimates in this analysis are based on the existing MBS items that approximate the likely Medicare costs of implantation of a CRT device (see Table 3 for full descriptions). These are assumed to be:

- Item number 38218 for insertion, removal, or replacement of cardiac pacemaker ($216.75);

- Item number 61109 for fluoroscopy in an angiography suite in conjunction with a surgical procedure ($258.90); and,

- A combination of item number 38284 ($710.50) and item number 38278 ($541.95), for insertion, removal or replacement of dual-chamber and single-chamber permanent electrodes, respectively.

It is further assumed that these procedures would be carried out by a single operator and that the Medicare Benefits rules applying to multiple procedures would also apply in this context, resulting in a cost of $1,139. Adding this to the private hospital cost derived from AR-DRG data produces an estimated non-device cost of implantation in a private hospital of $5,483. In order to reflect the increased time requirement for implanting a CRT device over what is required to implant a cardiac pacemaker, these costs are adjusted to account for the additional time in the operating theatre needed for implantation of the CRT device. Implantation of a standard cardiac pacemaker is said to require 45 minutes in the cardiac catheterisation suite whereas implantation of a typical CRT device is said to require 150 minutes – an additional time requirement of 105 minutes, according to information provided by the MSAC applicant. This additional time is valued at $409.26.

Therefore the total non-device cost of implantation of the CRT device is estimated to be $7,635 in public hospitals and $5,892 in private hospitals. Table 30 below shows the calculation of these additional costs in the operating room. This calculation assumes that the only incremental costs to using additional time in the cardiac catheterisation suite are labour costs, as all non-labour costs are fixed. Although this may not be accurate, any incremental non-labour costs that are not fixed are probably small, relative to labour costs.

**Table 30 Incremental cost of implanting a CRT device over a cardiac pacemaker**

*All information in this table is based on that provided by the MSAC applicant*

| Labour used | Hourly rate[1] | Labour cost for implantation of a cardiac pacemaker (45 minutes)[2] | Incremental labour cost for implantation of the CRT device (additional 105 minutes)[3] |
|---|---|---|---|
| Cardiologist | $92.64 | $69.48 | $162.12 |
| Registrar | $73.32 | $54.99 | $128.31 |
| Radiographer casual | $24.31 | $18.23 | $42.54 |
| Scrub nurse casual | $24.12 | $18.09 | $42.21 |
| Circulating nurse casual | $19.47 | $14.60 | $34.07 |
| Total | $233.86 | $175.40 | $409.26 |

[1] Hourly rates are based on teaching hospital human resources department rates and data from the Department of Productivity and Labour Relations' Wageline service.

[2] 45 minutes required for implantation of a cardiac pacemaker is based on time requirements for the CONTAK TR.

[3] Additional time of 105 minutes is based on 45 minutes required for implantation of a cardiac pacemaker and 150 minutes required for implantation of the CRT device.

Taking the total non-device cost of implanting the CRT device, which is $7,635 in public hospitals and $5,892 in private hospitals, and dividing this by the 4.57 day length of stay in public hospitals and 4.17 day length of stay in private hospitals generates the average non-device cost per day for a patient admitted for implantation of the CRT device at $1,671 in public hospitals and $1,413 in private hospitals. These costs allow the final estimates to be tested for sensitivity to the assumptions regarding length of stay.

To derive the total procedural cost of successfully implanting the CRT device, the cost of the device (approximately $5,900 in public hospitals and $12,500 in private hospitals) as well as the cost of the LV lead (approximately $2,100 in public hospitals and $4,500 in private hospitals) and the cost of the RA/RV leads – approximately $550 each in public hospitals and $1000 each in private hospitals – are added to the derived total non-device cost of implantation – $7,635 in public hospitals and $5,892 in private hospitals. The result of this calculation is $16,735 for public hospitals and $24,892 for private hospitals.

As shown in Table 31 below, the successful implantation of the CRT device, therefore, implies an average total cost of $16,735 for public hospitals and $24,892 for private hospitals and an average length of stay of 4.57 days in public hospitals at a non-device cost of $1,671 per day and an average length of stay of 4.17 days at a non-device cost of $1,413 in private hospitals.

Assuming that unsuccessful implantation results in only device costs not being incurred, an unsuccessful attempt at implantation of the CRT device implies an average total cost of $7,635 in public hospitals and $5,892 in private hospitals.

**Table 31 Summary of costs for implantation of the CRT device***

| Cost components | Public hospital ($) | Private hospital ($) |
|---|---|---|
| Device/equipment cost | 9,100 | 19,000 |
| Non-device hospital cost of implantation of cardiac pacemaker [a] | 7,226 | 5,483 |
| Additional hospital cost for implantation of a CRT device [b] | 409 | 409 |
| Total non-device hospital cost | 7,635 | 5,892 |
| Average length of stay [c] | 4.57 | 4.17 |
| Implied non-device cost per day of hospitalisation (including time in operating theatre) | 1,671 | 1,413 |
| Total cost of successful implantation (public hospital) | 16,735 | 24,892 |
| Total cost of unsuccessful implantation (public hospital) | 7,635 | 5,892 |

* Small discrepancies may occur in this table due to round-off error.

[a] AR-DRG F12Z National Hospital Cost Data Collection. Cost weights for AR-DRG Version 4.2, 2002-2003, public/private sector, estimated. Private hospital costs are supplemented by relevant Medicare Benefits Schedule fees.

[b] Applicant's MSAC submission.

[c] AR-DRG F12Z: National Hospital Cost Data Collection. Cost weights for AR-DRG Version 4. 2, 2002-2003, public/private sector, estimated. Private hospital costs are supplemented by relevant Medicare Benefits Schedule fees.

### Hospitalisation for a major cardiovascular event

During the course of treatment, some patients will be admitted to hospital for a major cardiovascular event. The probability of admission and the average length of stay are related to the effectiveness of the treatment the patient was receiving prior to being hospitalised. The following assumptions are made in deriving costs and outcome data

associated with hospitalisation for a major cardiovascular event during the course of treatment:

- The cost per day of hospitalisation for a major cardiovascular event can be approximated by deriving cost per day from AR-DRG F62A (Average cost per heart failure with shock and complications: National Hospital Cost Data Collection Cost Weights for AR-DRG Version 4.2, 2002-2003, Estimated: AR-DRG F62A).

- Over approximately 29.4 months, patients undergoing CRT are expected to face a 54 per cent probability of hospitalisation for a major cardiovascular event – based on 222 hospitalisations among 409 patients in the CARE-HF study – and patients on optimal pharmacological treatment are expected to face a 95 per cent probability of hospitalisation for a major cardiovascular event, based on 384 hospitalisations among 404 patients in the CARE-HF study.

- Estimates of the number of days of hospitalisation are based on the duration and probability of hospitalisation for a major cardiovascular event from the results of the MIRACLE study and the CARE-HF study.

The average cost per admission for heart failure (AR-DRG F62A) is $7,629, with an average length of stay of 11.23 days in public hospitals. This implies an average cost per day of hospitalisation of $679. Using average cost per heart failure with shock but without complications (AR-DRG F62B) results in an average cost per day of $650, which is only about $29 less than with complications, so the amount implied by the assumption of complications is fairly insignificant. In private hospitals, the average cost per admission for heart failure (AR-DRG F62A) is $7,330, with an average length of stay of 14.96 days. This implies an average cost per day of hospitalisation of $490. Using average cost per heart failure with shock but without complications (AR-DRG F62B) results in an average cost per day of $449, which is only about $41 less than with complications, so again the amount implied by the assumption of complications is fairly insignificant.

According to a personal communication from the main author of the MIRACLE study, the mean length of stay of patients on CRT is estimated to be 4.50 days. This implies an estimated cost per hospitalisation of $3,056 for public hospitals and $2,205 for private hospitals.

Also, according to a personal communication from the main author of the MIRACLE study, the mean length of stay for patients on optimal pharmacological treatment only is estimated to be 10.7 days. This implies an estimated cost per hospitalisation of $7,265 for public hospitals and $5,243 for private hospitals.

The estimated costs of hospitalisation for a major cardiovascular event are summarized in Table 32.

**Table 32 Estimated cost of hospitalisation for heart failure**

| Treatment | Cost component | Public hospital | Private hospital |
|---|---|---|---|
| CRT+ drugs | Mean length of stay for heart failure* | 4.50 days | 4.50 days |
| | Mean cost per day of hospitalisation for heart failure** | $679 | $490 |
| | Estimated cost per hospitalisation for heart failure | $3,056 | $2,205 |
| Drugs only | Mean length of stay for heart failure* | 10.70 days | 10.70 days |
| | Mean cost per day of hospitalisation for heart failure** | $679 | $490 |
| | Estimated cost per hospitalisation for heart failure | $7,265 | $5,243 |

* MIRACLE study.

** Derived from the total average cost of AR-DRG F62A ($7,629 in public hospitals and $7,330 in private hospitals) and the average length of stay for AR-DRG F62A (11.23 days in public hospitals and 14.96 days in private hospitals) – National Hospital Cost Data Collection Cost Weights for AR-DRG Version 4.2 Round 7 (2002-2003), Public Sector/Private Sector, Estimated.

According to expert opinion, the difference in cost between public and private hospitals may be due in part to a difference in case-mix, with most very sick heart failure patients admitted to public hospitals.

### Additional surgery on patients undergoing CRT

According to the expert opinion of the MSAC Advisory Panel, of the patients who are successfully implanted with a CRT device, approximately 8 per cent will require additional surgery for device-related problems, translating into 15 per cent of hospitalisations for a major cardiovascular event amongst CRT patients, within two years. This surgery may include re-positioning the device, reconnecting leads, replacing the device, or removing the device. In order to account for the cost of these procedures as well as the days of hospitalisation implied, three assumptions are made.

First, it is assumed that the average length of stay for replacement, removal, re-positioning, or reconnecting a lead on the device is included in the average length of stay of hospitalisations for heart failure. Because a patient must first experience a problem and be admitted to hospital before having unexpected surgery, it is assumed that admissions which result in this type of surgery are classified as admissions for heart failure, therefore, the length of stay of these admissions would be included in the calculation of mean duration of hospitalisation for heart failure. It follows, therefore, that there would be no incremental days of hospitalisation to those that are already accounted for. However, the estimated cost of hospitalisation for a major cardiovascular event in this report is based on AR-DRG data (AR-DRG F62A) that does not include surgery. Therefore, the operating room and device costs of these additional procedures are incremental to those costs already accounted for as costs of hospitalisation for heart failure.

The second assumption in accounting for the cost of removing, replacing, re-positioning, or reconnecting a lead on the device is that the cardiac catheterisation suite room costs of these procedures can be approximated by some portion of the operating room costs for implantation or replacement of a cardiac pacemaker (AR-DRG F12Z and AR-DRG F17Z) and the incremental time cost of implantation of the CRT device, at $409.26 (see section titled 'Successful implantation of the CRT device'), and that these costs include the cost of fluoroscopy, which would be approximately equal to fluoroscopy costs for these operations on CRT patients:

- The cardiac catheterisation suite cost of removal of the device in public hospitals is approximated by the AR-DRG operating room cost of implantation of a standard cardiac pacemaker, $1,262;

- The cardiac catheterisation suite cost of removal of the device in private hospitals is approximated by the AR-DRG operating room cost of implantation of a standard cardiac pacemaker, $773, plus the relevant Medicare fees, amounting to $1,139 (as derived in the 'Implantation of the CRT device' section) for a total of $1,912.

- The cardiac catheterisation suite cost of replacement of the device in public hospitals is approximated by the AR-DRG operating room cost of replacement of a cardiac pacemaker, $1,262, added to the incremental time cost of implantation of the device, $409.26. These costs total $1,671.

- The cardiac catheterisation suite cost of replacement of the device in private hospitals is approximated by the AR-DRG operating room cost of replacement of a cardiac pacemaker, $554, added to the incremental time cost of implantation of the device, $409.26, plus the relevant Medicare fees, amounting to $1,139 (as derived in the 'Implantation of the CRT device' section) for a total of $2,102.

- The public hospital cardiac catheterisation suite cost of repositioning the device is approximately 50 per cent of the operating room cost of implantation of a cardiac pacemaker ($631).

- The private hospital cardiac catheterisation suite cost of repositioning the is approximately 50 per cent of the operating room cost of implantation of a cardiac pacemaker ($387) plus the relevant Medicare fees, amounting to $1,139 (as derived in the 'Implantation of the CRT device' section).

- The public hospital cardiac catheterisation suite cost of reconnecting a lead on the device is approximately 50 per cent of the operating room cost of implantation of a cardiac pacemaker ($631).

- The private hospital cardiac catheterisation suite cost of reconnecting a lead on the device is approximately 50 per cent of the operating room cost of implantation of a cardiac pacemaker ($387) plus the relevant Medicare fees, amounting to $1,139 (as derived in the 'Implantation of the CRT device' section).

- The device and equipment costs, which are also incremental to the cost of hospitalization for heart failure, apply only in the case of replacement. In public hospitals, the cost would be $9,100 and in private hospitals the cost would be $19,000.

Third, it is assumed that patients undergoing additional surgery will do so in the following proportions:

- 10 per cent will require removal of the device.

- 10 per cent will require replacement of the device.

- 40 per cent will require repositioning the device.
- 40 per cent will require reconnecting a lead on the device.

The average incremental cost of additional surgery for device-related problems is, therefore, $1,748 in public hospitals and $3,521 in private hospitals. These values are calculated in Table 33.

**Table 33 Expected operating room and device cost of additional surgery***

| Procedure | Cost component | Public hospital | Private hospital |
|---|---|---|---|
| Removal of the device | | | |
| | Cardiac catheterisation suite cost [a] | $1,262 | $773 |
| | Device cost | n/a | n/a |
| | Medicare cost | n/a | $1,139 |
| | Total operating room and device cost | $1,262 | $1,912 |
| | Conditional probability of removal of device | 0.10 | 0.10 |
| | Expected cardiac catheterisation suite and device cost conditional on needing surgery | $126 | $191 |
| Replacement of the device | | | |
| | Cardiac catheterisation suite cost [b] | $1,671 | $554 |
| | Additional cardiac catheterisation suite cost | $409.26 | $409.26 |
| | Device cost [c] | $9,100 | $19,000 |
| | Medicare cost | n/a | $1,139 |
| | Total operating room and device cost | $11,180 | $21,102 |
| | Conditional probability of replacement of device | 0.10 | 0.10 |
| | Expected cardiac catheterisation suite and device cost conditional on needing surgery | $1,118 | $2,110 |
| Reposition the device | | | |
| | Cardiac catheterisation suite cost of implantation of cardiac pacemaker | $1,262 | $773 |
| | Adjustment factor | 0.50 | 0.50 |
| | Medicare cost | n/a | $1,139 |
| | Conditional probability of repositioning device | 0.40 | 0.40 |
| | Expected cardiac catheterisation suite and device cost conditional on needing surgery | $252 | $610 |
| Reconnect a lead | | | |
| | Cardiac catheterisation suite cost of implantation of cardiac pacemaker | $1,262 | $773 |
| | Adjustment factor | 0.50 | 0.50 |
| | Medicare cost | n/a | $1,139 |
| | Conditional probability of re-connecting a lead on the device | 0.40 | 0.40 |
| | Expected cardiac catheterisation suite and device cost conditional on needing surgery | $252 | $610 |
| Weighted average cost of additional surgery | | $1,748 | $3,521 |

* Small discrepancies may occur in this table due to round-off error

In addition to device-related problems, all patients who are successfully implanted with the CRT device will require generator replacement every five years. The cost of generator replacement includes the cost of the generator itself at approximately $5,900 in public hospitals and $12,500 in private hospitals, as well as the cost of replacing it. The latter is approximated by the cost of replacing a cardiac pacemaker, minus the cost of the pacemaker device, which is $4,952 (derived from DRG data) in public hospitals and $3,793 in private hospitals ($2,654 derived from DRG data plus $1,139 in Medicare costs as derived in the 'Implantation of the CRT device' section. The expected length of stay for generator replacement is 2.78 days in public hospitals and 2.41 days in private hospitals (AR-DRG F17Z, pacemaker replacement).

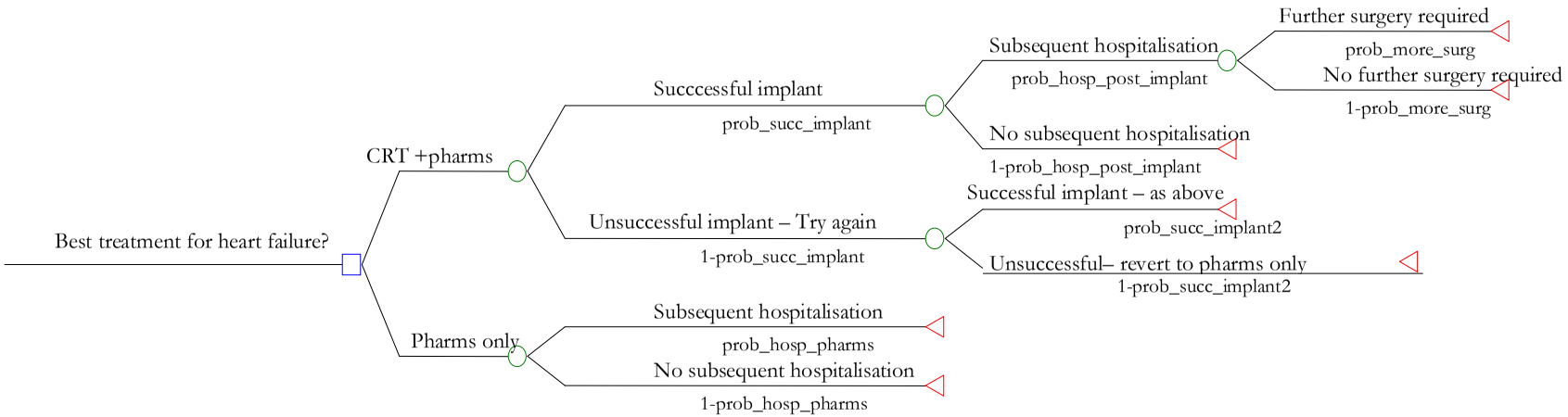



**Figure 3 Decision-tree model for CRT + OPT compared to OPT alone**

**Table 34 Data included in base case, decision analysis**

| Branch name | Probability value (upper / lower sensitivity) | Cost value (upper / lower sensitivity) | Hospital days value (upper / lower sensitivity) |
|---|---|---|---|
| **CRT + pharms** | 1.00 | $2,335 (drug cost over 29.4 months, mean follow-up in CARE-HF study) | 0 |
| Successful implant | 0.85 Based on CARE-HF study | $16,735 (public hospital), $24,892 (private hospital)<br>Based on AR-DRG F12Z and expert opinion | 4.57 in public hospitals, 4.17 in private hospitals (3.00 / 4.57) Based on AR-DRG F12Z and expert opinion |
| Unsuccessful implant – try again | 0.15 Based on CARE-HF study | $7,635 (public hospital), $5,243 (private hospital)<br>Based on AR-DRG F12Z and expert opinion | 4.57 in public hospitals, 4.17 in private hospitals (3.00 / 4.57) Based on AR-DRG F12Z and expert opinion |
| Successful implant – as above (second attempt is successful, patient proceeds in the same way as those in whom implantation was successful on the first attempt) | 0.68 Based on CARE-HF study | $16,735 (public hospital), $24,892 (private hospital)<br>Based on AR-DRG F12Z and expert opinion | 4.57 in public hospitals, 4.17 in private hospitals (3.00 / 4.57) Based on AR-DRG F12Z and expert opinion |
| Unsuccessful – revert to pharms only as below (second attempt is unsuccessful, patient receives optimal pharmacological treatment) | 0.32 Based on CARE-HF study | $7,635 (public hospital), $5,243 (private hospital)<br>Based on AR-DRG F12Z and expert opinion | 4.57 in public hospitals, 4.17 in private hospitals (3.00 / 4.57) Based on AR-DRG F12Z and expert opinion |
| Subsequent hospitalisation | 0.54 Based on CARE-HF study | $3,056 (public hospital), $2,205 (private hospital) (b) | 4.50 (0.30 – 8.7) Based on MIRACLE study |
| No subsequent hospitalisation | 0.46 Based on CARE-HF study | $0.00 | 0 |
| Further surgery required | 0.15 Based on expert opinion that 6-10% of successful implantations would require further surgery | $1,748 (public hospital), $3,521 (private hospital) | 0 - assumed to be included in hospital days for heart failure |
| No further surgery required | 0.86 Based on expert opinion as above | $0.00 | 0 |
| **Pharms only** | 1.00 | $2,335 (drug cost over 29.4 months, mean follow-up in CARE-HF study) | 0 |
| Subsequent hospitalisation | 0.95 Based on CARE-HF study | $7,265 (public hospital), $5,243 (private hospital) (b) | 10.70 (0 - 22.3) Based on MIRACLE study |
| No subsequent hospitalisation | 0.05 Based on CARE-HF study | $0.00 | 0 |

(a) sensitivity tested by varying cost components: cost per day of hospitalisation, probability of successful implantation

(b) sensitivity tested by varying duration of hospitalisation

Several patient outcomes are considered in the economic and decision analysis:

- Total number of hospital days over 29.4 months (the mean follow-up period in the CARE-HF study), five years, 10 years, and patients' lifetimes. Hospitalisation for implantation, hospitalisation for a major cardiovascular event, and hospitalisation for battery replacement or other device-related procedures, based on DRG data, expert opinion, the MIRACLE study, and the CARE-HF study.

- The total number of hospital days, excluding hospitalisation for implantation, over 29.4 months, five years, ten years, and patients' lifetimes.

- Life years saved over a period of two years, based on figures derived from the CARE-HF study and projected to 29.4 months, five years, 10 years, and lifetime; and.

- Quality-adjusted life years saved over a period of two years, 29.4 months, five years, 10 years, and lifetime, based on mortality data and NYHA class derived from the CARE-HF study and utilities of NYHA classes derived from Nichol et al. (2004).

## Decision analysis

The previous section outlined the assumptions and derivations of variable values that are relevant to the question of cost and cost-effectiveness. In this section, these variables are applied to a decision tree (a basic guide to decision analysis is provide at the end of this section) to show how the different probabilities, costs, hospitalisation days, mortality, and quality of life measures contribute to the expected outcomes over a period of approximately 29.4 months, the mean follow-up time in the CARE-HF study.

As shown in the decision trees, implantation of the CRT device is expected to fail in some cases. In these cases, a second attempt at implantation may be made. If the second attempt is also unsuccessful, the patient receives only pharmacological treatment. After the beginning of treatment, either by optimal pharmacological treatment or pharmacological treatment with CRT, patients face a probability of hospitalisation for a major cardiovascular event. This probability is lower for patients in the CRT group than for those in the optimal pharmacological treatment group. The duration of hospitalisation is also shorter for patients in the CRT group than for patients in the pharmacological treatment group.

Finally, patients on CRT who have been hospitalised for a major cardiovascular event face a further probability that additional surgery will be required to correct any problems that may have arisen with the device. Over the longer term, these patients will also require a change of generator approximately every five years.

### Expected cost per patient

In public hospitals, the expected total, discounted at 5 per cent per annum, cost of a decision to use optimal pharmacological treatment is $7,358 over a period of approximately 29.4 months. When CRT is added to optimal pharmacological treatment, the expected total cost of the decision increases to $21,132 – an increase of $13,774. In private hospitals, the expected total cost of a decision to use optimal pharmacological

treatment is $5,827. When CRT is added to optimal pharmacological treatment, the expected total cost of the decision increases to $28,247 – an increase of $22,419. Device costs account for most of the difference which is approximately $8,281 in public hospitals and $17,290 in private hospitals when costs and probabilities are taken into account. The relatively higher cost of hospitalisation for implantation, especially where implantation is attempted a second time, accounts for the remainder of the difference in expected cost (see section titled 'Successful implantation of the CRT device'). These costs are shown in Table 35 below.

**Table 35 Cost and incremental cost per patient***

| | Optimal pharmacological treatment | Optimal pharmacological treatment with CRT |
|---|---|---|
| **Public hospital** | | |
| Cost ($) | 7,358 | 21,132 |
| Incremental cost ($) | | 13,774 |
| **Private hospital** | | |
| Cost ($) | 5,827 | 28,247 |
| Incremental cost ($) | | 22,419 |
| * Costs are discounted at 5 per cent per annum | | |

### Expected number of days of hospitalisation

When expected outcomes are calculated for a decision to use either form of treatment for heart failure, it is revealed that a decision to use optimal pharmacological treatment alone results in a higher number of days of hospitalisation than optimal pharmacological treatment combined with CRT.

For public hospitals, the expected number of days of hospitalisation is 10.17 for a patient on optimal pharmacological treatment alone and 7.77 days for a patient who also receives CRT. This results in a decrease in hospital days of 2.39 days over the first 29.4 months when CRT is added to optimal pharmacological treatment. For private hospitals, the expected number of days of hospitalisation is 10.17 for a patient on optimal pharmacological treatment alone and 7.31 days for a patient who also receives CRT, resulting in a decrease in hospital days of 2.86 days over the first 29.4 months when CRT is added to optimal pharmacological treatment.

The estimates described above include the days of hospitalisation for implantation of the device. Excluding these, and considering only days of hospitalisation for a major cardiovascular event or for unplanned device-related surgery, the total number of days hospitalisation for patients on CRT is 2.52 in both public and private hospitals. This implies a reduction in hospitalisation days of 7.65 days over 29.4 months relative to patients on optimal pharmacological treatment alone.

These estimates are shown in Table 36 below.

**Table 36 Total hospital days and hospital days not including implantation**

| | Optimal Pharmacological Treatment | Optimal Pharmacological Treatment with CRT |
|---|---|---|
| **Public hospital** | | |
| Total days | 10.17 | 7.77 |
| Incremental days | 2.39 | |
| Days not including implantation | 10.17 | 2.52 |
| Incremental days | 7.65 | |
| **Private hospital** | | |
| Total days | 10.17 | 7.31 |
| Incremental days | 2.86 | |
| Days not including implantation | 10.17 | 2.52 |
| Incremental days | 7.65 | |

### Life years saved and quality-adjusted life years (QALYs) saved

Estimates of life years saved were derived from the CARE-HF study mortality figures, which were provided for the first and second years of the study. These allow life years saved to be estimated at the two-year point. Based on these figures, CRT combined with optimal pharmacological treatment is expected to result in 0.07 incremental life years saved per patient at two years after implantation of the device, discounted at 5 per cent per annum.

Projecting the mortality figures forward to five years, based on the conservative assumption that the mortality rates observed over the first two years would remain constant, thus implying survival curves remain parallel for the two patient groups (see Appendix H for projection methodology), results in 0.33 incremental life years saved as a result of combining CRT with optimal pharmacological therapy, discounted at 5 per cent per annum). Projecting the mortality figures to the 10-year point results in 0.79 incremental life years saved as a result of combining CRT with optimal pharmacological therapy, discounted at 5 per cent per annum). Projecting the mortality figures further forward, in order to generate lifetime estimates of life years saved, results in 1.52 incremental life years saved per patient, discounted at 5 per cent per annum, as a result of combining CRT with optimal pharmacological therapy. These results are presented in Table 37 below.

In addition to mortality data, the CARE-HF study also provided the NYHA class for the two groups of patients after 90 days follow-up. Based on the assumption that the quality of life improvement, as measured by NYHA class, resulting from treatment would occur within 90 days and not be reversed or further improved subsequently, this information was combined with the life years saved estimates. Utilities for NYHA classes from Nichol et al 2004 (see Table 37 below for a summary of utilities) were used in order to generate estimated of QALYs saved. These results are conservative in that they do not assume that patients would experience further improvement in NYHA class beyond the 90-day point. The results are presented in Table 37 below.

**Table 37 Utilities used to derive QALY results (based on Nichol et al. 2004)**

| NYHA Class | Utility (+/- SD) |
|---|---|
| NYHA Class II | 0.82+/-0.16 |
| NYHA Class III | 0.72+/-0.21 |
| NYHA Class IV | 0.58+/-0.25 |

**Table 38 Incremental life years saved and quality-adjusted life years saved when CRT is added to optimal pharmacological treatment**

| | **Incremental life years saved** (discounted at 5 per cent per annum) | **Incremental QALYs saved** (based on patients remaining at the NYHA class observed at 90 days, discounted at 5 per cent per annum) |
|---|---|---|
| At two years based on data derived from the CARE-HF study | 0.07 | 0.16 |
| At 29.4 months (the mean follow-up of the CARE-HF study) based on CARE-HF two-year mortality projected forward to match cost data | 0.10 | 0.20 |
| At five years, based on projecting the two-year mortality data forward | 0.33 | 0.46 |
| At 10 years, based on projecting the two-year mortality data forward | 0.79 | 0.91 |
| Lifetime, based on projecting the mortality data forward | 1.52 | 1.54 |

### Cost-effectiveness: Reduction in hospitalisation

When expected cost per patient is combined with the expected number of days of hospitalisation in order to determine a measure of cost-effectiveness in terms of cost per hospital day avoided and considering only hospitalisation post-implantation for major cardiovascular events or device-related problems, the increased cost of CRT and reduction in hospitalisation result in a cost-effectiveness ratio of $1,801 per hospital day avoided in public hospitals. The equivalent ratio for private hospitals is $2,931 per hospital day avoided. These results are summarised in Table 39 below.

**Table 39 Cost-effectiveness: Cost per hospital day avoided***

| | Optimal pharmacological treatment | | CRT + optimal pharmacological treatment | |
|---|---|---|---|---|
| | Public hospital | Private hospital | Public hospital | Private hospital |
| Expected total cost per patient | $7,358 | $5,827 | $21,132 | $28,247 |
| Expected number of days hospitalisation (excluding implantation) | 10.17 | 10.17 | 2.52 | |
| Incremental cost | | | $13,774 | $22,419 |
| Incremental effectiveness | | | 7.65 | |
| (reduction in hospital days, excluding implantation) | | | | |
| Incremental cost-effectiveness | | | $1,801 | $2,931 |
| (Cost per hospital day avoided, excluding hospital days for implantation) | | | | |

*Due to round-off error, small discrepancies may appear in this table.

### Cost-effectiveness: Incremental cost per life year saved and incremental cost per quality-adjusted life year saved

In order to combine expected cost per patient with the expected number of life years saved and with the expected number of QALYs saved, it was necessary to project mortality figures forward by approximately six months to reconcile the time difference in the reporting of mortality, at two years, and the reporting of hospitalisation, at 29.4 months, in the CARE-HF study. Calculating incremental cost per life year saved or incremental cost per QALY saved indicates that using CRT in addition to optimal pharmacological treatment results in an increase in life years and in QALYs at the expense of a higher expected cost per patient. Specifically, the incremental costs are $133,244 per life year saved or $68,588 per QALY saved at the 29.4-month point, based on public hospital cost data. These estimates would be $216,865per life year saved and $111,633 per QALY saved if private hospital cost data is used.

Cost-effectiveness improves significantly if the mortality data is projected forward and with costs also projected forward, assuming patients in both groups continue to experience the same hospitalisation rate annually for major cardiovascular events and that the CRT device requires a battery change every five years. This eventually results in an expected incremental lifetime cost of $18,872 based on public hospital cost data and $33,640 based on private hospital cost data when CRT is added to optimal pharmacological treatment. The corresponding incremental cost per life year saved is $12,426 or $21,151, and the corresponding incremental cost per QALY saved is $12,257or $21,850 for public and private hospitals, respectively. The significant improvement in the cost-effectiveness ratio is attributable to the substantial number of life-years saved when mortality data is projected forward, and to the cumulative effect of the higher hospitalisation costs for patients on optimal pharmacological treatment only. These results, as well as results for projections to five and 10 years, are summarised in Table 40 below.

**Table 40 Cost-effectiveness: Cost per life year saved and cost per quality-adjusted life year saved**

| | Incremental cost per life year saved ($) | | Incremental cost per QALY saved ($) | |
|---|---|---|---|---|
| | Public hospital | Private hospital | Public hospital | Private hospital |
| At 29.4 months* | 133,244 | 216,865 | 68,588 | 111,633 |
| At five years** | 35,436 | 63,861 | 25,362 | 45,706 |
| At 10 years** | 18,713 | 34,302 | 16,350 | 29,971 |
| Lifetime** | 12,426 | 21,151 | 12,257 | 21,850 |

* Costs based on results of CARE-HF and MIRACLE studies, mortality data derived from CARE-HF study projected forward the minimum amount of six months in order to allow compatibility with costs. Discounting at 5 per cent per annum.

** Costs and mortality based on projection of shorter term data derived from the CARE-HF and MIRACLE studies. Discounting at 5 per cent per annum.

### Sensitivity analysis

Sensitivity analysis on the results presented above showed that the conclusions are robust to statistically reasonable changes in key parameters. That is, over a patient's lifetime, a decision to use CRT in addition to optimal pharmacological treatment appears to be a cost-effective way of increasing the number of life years and quality-adjusted life years saved. The sensitivity analysis involved:

- Estimating results based on discounting costs only, not life years;
- Varying the probability of successful implantation on the first attempt to 99 per cent from 85 per cent;
- Reducing the duration of hospitalisation for implantation of the CRT device from 4.57 days to 3.00 days (suggested by the MSAC Advisory Panel);
- Reducing the cost of the generator and leads to the lower end of the range provided by the applicant (details shown in Table 41 below);
- Increasing the cost of the generator and leads to the higher end of the range provided by the applicant (details shown in Table 41 below).

**Table 41 Device and equipment costs***

| | Item | Public hospital cost ($) | Private hospital cost ($) |
|---|---|---|---|
| **Base Case** | Generator | 5,900 | 12,500 |
| | LV lead | 2,100 | 4,500 |
| | RA/RV lead (each, 2 required) | 550 | 1,000 |
| | **Total device/equipment cost** | **9,100** | **19,000** |
| **Lower estimates** | Generator | 5,600 | 9,000 |
| | LV lead | 1,900 | 3,000 |
| | RA/RV lead (each, 2 required) | 500 | 800 |
| | **Total device/equipment cost** | **8,500** | **13,600** |
| **Higher estimates** | Generator | 6,200 | 16,000 |
| | LV lead | 2,300 | 6,000 |
| | RA/RV lead (each, 2 required) | 600 | 1,200 |
| | **Total device/equipment cost** | **9,700** | **24,400** |

* Market prices quoted at the time of this review.

- Increasing the duration of hospitalisation for a major cardiovascular event for CRT patients from 4.50 days to 8.7 days, which is the higher value of the 95 per cent confidence interval suggested by the main author of the MIRACLE study in a personal communication;

- Reducing the duration of hospitalisation for a major cardiovascular event for CRT patients from 4.50 days to 0.30 days, which is the lower value of the 95 per cent confidence interval suggested by the main author of the MIRACLE study in a personal communication;

- Reducing the duration of hospitalisation for heart failure for patients on optimal pharmacological treatment alone from 10.70 days to 0 days, which is the lower value of the 95 per cent confidence interval suggested by the main author of the MIRACLE study in a personal communication;

- Varying the cost of optimal pharmacological treatment to reflect the possibility of lower and higher doses of certain drugs. A range of $806 to $1,511 was included (see Table 22); and,

- Reducing the cost per day of hospitalisation for implantation of the device to the same as would be expected for heart failure, that is to $679 per day in public hospitals and $490 in private hospitals (see section titled 'Hospitalisation for heart failure'). This implies a lower intensity of hospital care for CRT patients during hospitalisation for implantation of the device than was assumed in the base case.

The results of the sensitivity analysis on incremental cost per patient, number of hospital days avoided, incremental cost per life year saved, and incremental cost per quality-adjusted life year saved are presented in Tables 42, 43, and 44 below.

**Table 42 Incremental cost per patient and hospital days avoided over approximately 29.4 months, by adding CRT to optimal pharmacological treatment, based on public hospital data**

| Assumption variation | Incremental cost per patient ($) | Hospital days avoided | |
|---|---|---|---|
| | | Total | Excluding days for implantation |
| **Base case** | **13,774** | **2.39** | **7.65** |
| Life years not discounted | 13,561 | 2.39 | 7.65 |
| Increased probability of successful implantation | 12,922 | 3.11 | 7.73 |
| Shorter hospitalisation for implantation | 10,920 | 4.20 | 7.65 |
| Increased cost of generator and leads | 14,346 | 2.39 | 7.65 |
| Reduced cost of generator and leads | 13,203 | 2.39 | 7.65 |
| Longer hospitalisation for major cardiovascular event for CRT patients | 15,004 | 0.40 | 5.30 |
| Shorter hospitalisation for major cardiovascular event for CRT patients | 12,545 | 4.74 | 10.0 |
| Shorter hospitalisation for major cardiovascular event for OPT patients | 18,995 | -7.77 | -2.52 |
| Lower drug cost | 13,759 | 2.39 | 7.65 |
| Higher drug cost | 13,832 | 2.39 | 7.65 |
| Reduced cost per day of hospitalisation for implantation | 9,850 | 2.39 | 7.65 |

**Table 43 Incremental cost per patient and hospital days avoided over approximately 29.4 months, by adding CRT to optimal pharmacological treatment, based on private hospital data**

| Assumption variation | Incremental cost per patient ($) | Hospital days avoided | |
|---|---|---|---|
| | | Total | Excluding days for implantation |
| **Base case** | **22,419** | **2.85** | **7.65** |
| Life years not discounted | 22,267 | 2.85 | 7.65 |
| Increased probability of successful implantation | 22,316 | 3.52 | 7.73 |
| Shorter hospitalisation for implantation | 21,017 | 4.20 | 7.65 |
| Increased cost of generator and leads | 27,560 | 2.85 | 7.65 |
| Reduced cost of generator and leads | 12,899 | 2.85 | 7.65 |
| Longer hospitalisation for major cardiovascular event for CRT patients | 23,307 | 0.50 | 5.30 |
| Shorter hospitalisation for major cardiovascular event for CRT patients | 21,532 | 5.20 | 10.00 |
| Shorter hospitalisation for major cardiovascular event for OPT patients | 26,186 | -7.31 | -2.52 |
| Lower drug cost | 22,404 | 2.85 | 7.65 |
| Higher drug cost | 22,477 | 2.85 | 7.65 |
| Reduced cost per day of hospitalisation for implantation | 19,772 | 2.85 | 7.65 |

**Table 44 Incremental cost per life year saved and incremental cost per quality-adjusted life year (QALY) saved by adding CRT to optimal pharmacological treatment over lifetime projection**

| Assumption variation | Incremental cost per life year saved ($) | | Incremental cost per QALY saved ($) | |
|---|---|---|---|---|
| | Public hospital | Private hospital | Public hospital | Private hospital |
| **Base case** | **12,426** | **22,151** | **12,257** | **21,850** |
| Life years not discounted | 8,449 | 15,116 | 8,803 | 15,749 |
| Increased probability of successful implantation | 11,857 | 22,299 | 11,696 | 21,997 |
| Shorter hospitalisation for implantation | 10,546 | 21,228 | 10,403 | 20,939 |
| Increased cost of generator and leads | 12,970 | 27,488 | 12,793 | 27,115 |
| Reduced cost of generator and leads | 11,883 | 13,930 | 11,721 | 13,741 |
| Longer hospitalisation for major cardiovascular event for CRT patients | 15,057 | 24,049 | 14,852 | 23,723 |
| Shorter hospitalisation for major cardiovascular event for CRT patients | 9,795 | 20,252 | 9,662 | 19,977 |
| Shorter hospitalisation for major cardiovascular event for OPT patients | 21,399 | 28,626 | 21,108 | 28,237 |
| Lower drug cost | 12,279 | 22,004 | 12,112 | 21,705 |
| Higher drug cost | 12,984 | 22,709 | 12,808 | 22,400 |
| Reduced cost per day of hospitalisation for implantation | 9,842 | 20,408 | 9,708 | 20,131 |

As shown in Table 43 above, none of the variations introduced to the model resulted in an unfavourable cost-effectiveness ratio for a decision to add CRT to optimal pharmacological treatment when costs and mortality are projected to patients' lifetimes. However, the ratio shows some sensitivity to changes in the assumptions of the model. In particular, if the cost of the device and equipment is at the high end of the range of market prices facing private hospitals or if the duration of hospitalisation for a major cardiovascular event in a patient on optimal pharmacological treatment is at the lower end of the 95 per cent confidence interval (0 days), the cost-effectiveness ratio increases substantially.

## Total cost estimates

It is estimated that there are currently approximately 3,860 patients (see clinical need section) who would be theoretically eligible for CRT in Australia. However, the number of new patients per year would likely be about 10 per cent of the 3,860 figure – about 386 patients, based on expert opinion. Of these 386 patients, some would choose not to receive CRT and others may be excluded due to co-morbidities. There exists no data that would provide a realistic estimate of the number who would actually receive CRT. For this reason, ongoing total annual cost estimates are generated using 25 per cent, 50 per cent, and 75 per cent of the 386 figure, based on expert opinion of the MSAC Advisory Panel).

The costs included in the analysis are the same as those included in the decision analysis. That is, they include all hospital, device, and drug costs whether these are financed by the Federal Government, State Governments, insurance companies or by the patient directly. However, because the data pertaining to probabilities of events is drawn principally from the CARE-HF study, which was based on an approximately 29.4 month follow-up, the estimates of annual cost here are based on the assumption that, apart from implantation costs, the costs of both types of treatment are evenly spread over the 29.4 months.

**Table 45 Estimated ongoing total annual cost based on annual cohorts of 386 newly eligible patients***

| | Optimal Pharmacological Treatment | | CRT+Optimal Pharmacological Treatment | |
|---|---|---|---|---|
| | Public hospital | Private hospital | Public hospital | Private hospital |
| Cohort size | 386 | 386 | 386 | 386 |
| Drug costs | 6,508 | 6,508 | 9,115 | 9,115 |
| Implantation costs | n/a | n/a | 17,444 | 24,865 |
| Cost of hospitalisation for major cardiovascular events | 19,239 | 13,884 | 7,425 | 5,359 |
| Cost of surgery for device related-problems | n/a | n/a | 135 | 272 |
| Cost of generator change | n/a | n/a | 14,737 | 22,126 |
| **Total ongoing annual cost based on annual cohorts of 386 eligible patients** | **9,938,342** | **7,871,312** | **18,858,416** | **23,830,482** |
| **Incremental annual cost** | | | **8,920,074** | **15,959,170** |
| Total annual cost with 75% uptake of CRT<br>(based on annual cohorts of approximately 290 patients) with 25% of eligible patients on OPT alone | | | 14,143,812 (CRT patients)+ 2,484,586 (OPT patients) =16,628,398 | 17,872,862 (CRT patients) + 1,967,828 (OPT patients) =19,840,690 |
| **Incremental annual cost over 100% of patients on OPT alone** | | | **8,757,086** | **11,969,378** |
| **Total annual cost with 50% uptake of CRT**<br>(based on annual cohort of approximately 193 patients per year) with 50% of eligible patients on OPT alone | | | 9,429,208 (CRT patients)+ 4,969,171 (OPT patients) =14,398,379 | 11,915,241 (CRT patients)+ 3,935,656 (OPT patients) =15,850,897 |
| **Incremental annual cost over 100% of patients on OPT alone** | | | **4,460,037** | **7,979,585** |
| **Total annual cost with 25% uptake of CRT**<br>(based on annual cohorts of approximately 97 patients per year) with 75% of eligible patients on OPT alone | | | 4,714,604 (CRT patients)+ 7,453,757 (OPT patients) =12,168,361 | 5,957,621 (CRT patients)+ 5,903,484 (OPT patients) =11,861,105 |
| **Incremental annual cost over 100% of patients on OPT alone** | | | **2,230,019** | **3,989,793** |

* Costs represent not only the first-year costs of each newly eligible annual cohort of patients but also the same year costs of previous cohorts of patients who survive and are incurring the longer term costs of treatment.

N.B.: Small discrepancies may occur in this table due to rounding off.

As shown in Table 44, the total annual cost of a decision to use optimal pharmacological treatment alone for the relevant 380 patients is expected to be between $7,871,312 and $9,938,342, depending on the proportion of patients who receive treatment in public or private hospitals. The total annual cost of a decision to use CRT in addition to optimal pharmacological treatment for ongoing annual cohorts of 380 patients is expected to be between $18,858,416 and $23,830,482, depending on the proportion of patients who receive treatment in public or private hospitals. This results in an annual incremental cost of up to $15,959,170. But because uptake of CRT is unlikely to be 100 per cent, there is considerable uncertainty surrounding the actual annual incremental costs, over providing optimal pharmacological treatment alone to all patients, which are likely to be in the range of $2,230,019 to $11,969,378.

However, the initial total annual costs of offering CRT in addition to optimal pharmacological treatment, could be significantly higher than the ongoing annual costs estimated in Table 44.

According to expert opinion of the MSAC Advisory Panel, initial take-up and capacity is likely to be in the range of 200, 500, 1,000, or 1,500 patients due to the existing 3,860 theoretically eligible patients who may demand this treatment from a health system. This range of patient numbers suggests incremental costs in the first year could be as low as $3,142,890 or as high as $35,695,875.

# Discussion

## The safety of CRT

CRT can be successfully implanted in approximately 90 per cent of patients. The safety profile of CRT appears acceptable. Complications at implantation are uncommon and infrequently associated with serious clinical sequelae. Fatalities are rare and occur at only approximately 0.4 per cent of implantations, usually related to the development of an arrhythmia. In addition, approximately 1 per cent to 2 per cent of patients may sustain a potentially lethal coronary sinus perforation. Postoperative adverse events occur among approximately 12 per cent of patients followed over 29 months. Lead dislodgement is the most common postoperative complication and approximately 6 per cent of patients during follow-up will need to have a dislodged lead replaced. Infection may require system removal in about 1 per cent of patients. The incidence of complications increases over the length of follow-up and is reduced with more operator experience with the procedure as well as technical improvements in the device. Serious postoperative complications such as arrhythmia have infrequently been reported during follow-up whilst others like pulmonary embolism also appear to be rare.

## The effectiveness of CRT

Four generally well designed, multi-centre, randomised controlled trials have consistently reported similar favourable benefits from CRT in relation to patient quality of life and a number of surrogate endpoints measuring exercise performance and functional ability (Bristow et al 2004, Abraham et al 2002, Cazeau et al 2001, Cleland et al 2005b). All primary and secondary endpoints in the three trials – quality of life, exercise capacity, composite death and hospitalisation rates, all-cause mortality, hospitalisation rates after implantation, NYHA class change – were associated with favourable results. Only the CARE-HF trial had statistical power to reliably assess the impact of CRT on mortality. The results from the CARE-HF study confirm that CRT reliably reduces mortality over long periods, at a mean duration of 29 months of follow-up. The study results indicate that there was a statistically significant 36 per cent reduction in all-cause mortality by the end of the 29 month follow-up period (hazard ratio = 0.64, 95% CI: 0.48-0.85, $p<0.001$). This result suggests that there is a 95 per cent probability that the risk of mortality may be reduced by as much as 52 per cent or as little as 15 per cent over 29 months. From the study results, the absolute risk reduction associated with the addition of CRT to OPT can be estimated to be about 10 per cent (95 per cent CI: 4-16) and therefore about 10 patients would need to be treated with a device in order to prevent one death from any cause over a 29-month period. From the confidence interval it can be estimated that the likely number of patients that would need to be implanted with a device in order to prevent one death over a period of 29 months is between six and 25 patients.

The primary outcome in the COMPANION trial was a composite that combined both mortality and hospitalisation rates, and the study was stopped early when this outcome was achieved for the CRT and the combined CRT and implantable defibrillator study groups. Although mortality, separated from hospitalisation, for the CRT-alone treatment group in the COMPANION study appears to be lower in the treatment group

compared with the control group, this result was marginally not statistically significant (Bristow et al 2004). The results from the MIRACLE and MUSTIC trials lacked sufficient statistical power to reliably assess this issue at between six and 12 months' follow-up. In a meta-analysis that combined the mortality data at six to 12 months follow-up from the four studies – CARE-HF, COMPANION, MIRACLE, MUSTIC – CRT was associated with a 21 per cent reduction in the relative risk of mortality and a 3 per cent reduction in the absolute risk of death. The results from the meta-analysis suggest that 33 people would need to be treated over 12 months with CRT to avoid one additional death. Although there is a 95 per cent probability that the number needed to treat may be as low as 17, it is also possible that the treatment could be associated with no effect.

In the CARE-HF trial the addition of CRT to OPT was associated with a significant reduction in the rate of unplanned hospitalisation for any cardiovascular event compared with OPT alone (184 events in the control group compared with 125, hazard ratio = 0.61, 95% CI: 0.49-0.77, $p<0.001$). Similarly, the CRT plus OPT group recorded a significantly lower rate of unplanned hospitalisation with worsening heart failure by the end of the study (133 in the control group and 72 in the treatment group, hazard ratio = 0.48, 95% CI: 0.36-0.64, $p<0.001$). The results from the CARE-HF study suggest that absolute risk reduction for hospitalisation related to a cardiovascular event is 15 per cent (95% CI: 8-22). From this estimate it can be calculated that about seven patients (95% CI: 5-13) would need to be implanted with a CRT device in order to prevent one hospitalisation for a cardiovascular event over 29 months. Similarly, the absolute risk reduction for hospitalisation related to worsening heart failure is also 15 per cent (95% CI: 9-21). Therefore, about seven patients (95% CI: 5-11) would also need to be implanted with a CRT device in order to prevent one hospitalisation for worsening heart failure over 29 months. Separate hospitalisation data has not yet been published from the COMPANION study. However, the results from the MIRACLE study indicate that CRT plus OPT was associated with a statistically significant 51 per cent reduction in the relative risk and an 11 per cent reduction in the absolute risk of hospitalisation (Abraham et al 2002). The reduction in the absolute risk of hospitalisation in this trial suggests that only nine patients would need to be treated over six months in order to prevent one additional episode of hospitalisation for heart failure (Abraham et al 2002).

The advisory panel considered that the benefits from CRT plus OPT were clinically significant in appropriately selected patients in relation to short-term survival and quality of life. Furthermore, the panel considered that there was also a clear improvement in survival at 12 months' follow-up and the long-term effectiveness of CRT plus OPT over 29 months has been established. Finally, in addition to significant improvements in Minnesota Living with Heart Failure Questionnaire results, the panel recognised that patients in the main trials frequently improved in NYHA class, most often from class III to II. This was considered to represent a significant change in quality of life for the participants.

## Cost-effectiveness of CRT

Currently available evidence suggests that CRT reduces the total number of days of hospitalisation relative to optimal pharmacological treatment alone due to a substantial reduction in hospitalisation for major cardiovascular events. Over approximately 29.4 months – the mean follow-up time in the CARE-HF study – CRT is associated with an

incremental cost of $13,774 per patient in public hospitals and $22,419 per patient in private hospitals. The associated reduction in post-implantation hospitalisation for major cardiovascular events, including those associated with device-related problems, is 7.65 days in both public and private hospitals. In terms of cost-effectiveness, this implies an incremental cost per hospital day avoided of $1,801 per hospital day avoided, based on public hospital costs, and $2,931 per hospital day avoided, based on private hospital costs.

Mortality data at two years of follow-up and data on quality of life allowed the estimation of incremental cost per life year saved and incremental cost per quality-adjusted life year saved. Over a patient's lifetime, CRT is expected to be associated with an increase of 1.52 discounted or 2.74 undiscounted life years and 1.54 discounted or 2.63 undiscounted quality-adjusted life years. The expected lifetime incremental cost per life year saved and per quality-adjusted life year (QALY) saved were estimated to be $12,426 and $12,257 based on public hospital data, and $21,151 and $21,850 based on private hospital data. These estimates are based on conservative projections, which do not allow for changes in mortality rates beyond two years or changes in quality of life beyond 90 days. Longer term data on these variables are not currently available.

Sensitivity analysis showed that the conclusion of the analysis is robust to plausible variations in key parameters of the model. That is, the conclusion that adding CRT to optimal pharmacological treatment is expected to be associated with a favourable incremental cost-effectiveness ratio is robust. However, the ratio is sensitive to these variations, suggesting that an incremental cost-effectiveness ratio in the range of up to $29,000 per life year saved, or per QALY saved, is plausible.

The total incremental annual cost of adding CRT to optimal pharmacological treatment was estimated under various assumptions regarding initial and long-term take-up. Long-term incremental annual costs are expected to be between $2,230,019 and $11,969,378 based on between 97 and 290 new patients annually. However, short-term incremental annual costs could be as high as $35,695,875 if a large number of existing eligible patients, say approximately 1,500 demand, and receive, CRT.

## Applicability of the evidence

Currently available evidence suggests that CRT is not a stand-alone treatment for heart failure but an adjunct to optimal pharmacological therapy. Optimal pharmacological treatment should be employed and various drugs such as ACE inhibitors and beta-blockers titrated up to maximally tolerated doses according to current guidelines before CRT is used.

There are unlikely to be any major biological or cultural differences between patient populations in the United States and Australia that would prevent the results from the largest and most robust trials – CARE-HF, COMPANION and MIRACLE studies – being relevant to the Australian setting. The generally consistent results obtained from the two Australian studies (O'Donnell et al 2005a, O'Donnell et al 2005b), when compared with the findings from other non-randomised studies conducted in United States or European settings, also underpin this assumption. However, the results from the trials can only be directly generalised to Australian patients with the same clinical parameters as the inclusion criteria for the study. These parameters include patients with moderate to severe heart failure (NYHA class III or IV), left ventricular ejection fraction

below 35 per cent, left ventricular end-diastolic dimension of 55 mm or more, a QRS interval of 130 msec or more (120 msec or more in the COMPANION), and those who are already receiving optimal pharmacological therapy. Most studies of the effectiveness and safety of CRT, including CARE-HF, COMPANION and MIRACLE, have included a higher proportion of males and whether similar results would be achieved in patient populations composed of mainly females remains to be ascertained. It is likely that cardiac laboratories situated in major tertiary centres in Australia could successfully undertake the procedure. The results obtained by local clinicians and treatment centres may be subject to learning curve effects as experience is acquired with the procedure in Australia.

## General limitations of the data

The studies have varied in their definition of optimal pharmacological therapy and their use of various medications among study participants. Losses to follow-up were evident although there were no losses related to worsening heart failure or death. In two of the four trials, patients were randomised after successful implantation and the results from each of these trials can therefore only be generalised to patients who are able to undergo the procedure.

Apart from the three randomised trials, most of the information about the safety of CRT is largely derived from a number of non-randomised comparative studies and case reports. These studies have often not included a control group and they are inherently less able to reduce the potential for bias in their results (National Health and Medical Research Council 2000). Furthermore, caution should be exercised when making comparisons between study results. Consistent definitions of follow-up periods and methods of assessment have not been employed. Differences in the procedures, patient characteristics, the methods and definitions used to identify problems and the time periods over which the presence of complications were assessed may also exist between studies.

## Specific major limitations of the data

### Mortality

A limitation is that only one of the presented studies (CARE-HF) were sufficiently statistically powered to adequately assess the effect of CRT on mortality alone. The only other study designed to be adequately powered to potentially answer this question was the COMPANION trial (Bristow et al 2000). However this trial was stopped early in 2002 before all of the trial endpoints were achieved (Bristow et al 2004). To date, the published results from this study do not enable an adequate assessment of the effects of CRT without a defibrillator on heart failure mortality rates.

### Hospitalisation rates

Only limited data were available about the effects of CRT plus OPT on all-cause rates of hospitalisation. The CARE-HF trial presented only hospitalisation data in relation to cardiovascular events and worsening heart failure The COMPANION trial provided this data only in relation to composite endpoints that also included mortality (Bristow et al 2004).

### Long-term effects

Most of the published trial information about the longer term effects of CRT over at last 12 months were presented in the CARE-HF and COMPANION studies. However, the results in these studies are mainly presented as composite rates that combine both mortality and hospitalisation data. Two other trials – MIRACLE and MUSTIC – with an exception related to the follow-up of a relatively small number of participants who selected their own therapy after six months (Linde et al 2002b) have been limited to only six months' follow-up. The effect of CRT plus OPT on all long-term outcomes remains to be fully established.

### Placebo effect

Investigations related to the effectiveness of the implantation of a cardiac device may be subject to a significant placebo effect (Linde et al 1999, Nishimura et al 1997). The large multi-centre, double-blinded MIRACLE (Abraham et al 2002) study and the longer follow-up period associated with the MUSTIC (Linde et al 2002b) study may have avoided some of the potential for a placebo effect. However, some effect was still evident in the results from the MIRACLE trial where, although functional class improved in two-thirds of patients in the CRT plus OPT group, it also improved in one third of controls. And while quality of life increased by 63 per cent in the active treatment group, it also improved by 38 per cent among controls.

### Potentially relevant, non-appraised literature

The following potentially important issues were outside of the criteria employed for this review and have not been formally reviewed: electrophysiological and/or haemodynamic studies, the role of CRT in patients with atrial fibrillation, the role of four-chamber versus three-chamber pacing, the optimal site for LV and RV pacing, the role of isolated LV pacing alone or in comparison to CRT, the role of combined defibrillators with CRT, the optimal electrical configuration, the role of transseptal placement of the LV lead, and the exact mechanisms of haemodynamic improvement.

The role of defibrillators with or without CRT is an especially important issue not covered by this review. Patients with heart failure have an increased risk of arrhythmia and sudden cardiac death, and it is possible that CRT may offer greater survival benefit when combined with the anti-tachycardial therapies of an implantable cardioverter defibrillator.

Another important issue that has not been examined in this review is the question of whether CRT can reverse LV remodelling and whether CRT may have a preventive role in earlier stages of heart failure by avoiding the progression of LV dysfunction.

### Lack of definitions

The lack of clearly defined criteria for the various underlying aetiologies of heart failure, the absence of consistent definitions for optimal pharmacological therapy and the dearth of any universal criteria for the development of complications have all limited the ability to draw inferences from the available data. Similarly, the studies may have varied in the methods that were used to identify the presence of different problems and the time periods over which the presence of complications were assessed.

### Arrhythmogenic potential of CRT

There is still uncertainty about the effects of CRT on arrhythmia. Up to 35 per cent of patients with indications for CRT may have an inducible ventricular arrhythmia (Lam et al 2000). No study has yet adequately assessed the effect of CRT on arrhythmia induction. While some research suggests that CRT can reduce the development of tachycardia (Bocchiardo et al 2000a) and the total number of arrhythmia episodes (Walker et al 2000f, Higgins et al 2000, Zagrodzky et al 2001), experts have cautioned that a pro-arrhythmic effect is also possible (Pavia and Wilkoff 2001, Dresing and Natale 2001). Notwithstanding any possible effect on arrhythmia induction, it is possible that BST may expose patients to relatively greater levels of risk from sudden cardiac death by reducing the risk of death from progressive heart failure.

It is possible that difficult coronary sinus catheterisation may cause traumatic right bundle branch block and it may also result in transient complete heart block in patients with pre-existing left bundle branch block. This complication may be prevented by implanting the RV lead first (Gras et al 2002a).

### Other theoretically possible safety issues

Air embolism, perforation of the great vessels or myocardium, and pneumothorax are potential complications of any pacemaker insertion (Conti 2001), which have not yet been identified in any study assessing the safety of CRT.

### Potential confounding factors

The sub-group results from the CARE-HF, COMPANION and MIRACLE studies suggest that the effectiveness of the intervention was not reduced when potential confounders such as the use of beta-blockers, the cause of heart failure (ischaemic versus non-ischaemic), the configuration of the QRS complex (left or right bundle branch block), and the baseline duration of the QRS interval were considered in the analysis.

The role of several potential confounders has not yet been fully determined including:

- The aetiology of heart failure.

No randomised study has yet adequately presented results that closely examine findings in relation to the aetiology of a participant's heart failure as a primary outcome. Existing studies have included patients with a variety of aetiologies for their heart failure but the extent and direction of aetiology of heart failure as a potential confounding factor remains unclear.

- Improvements in technology.

Complication rates may have varied over the time frame of the study in relation to the use of more sophisticated technology.

- Operator and centre learning curves.

Several studies have suggested that a learning curve may exist for operators and centres where initial experience was associated with higher rates of adverse events compared to more experienced operators and centres (see, for example, Alonso et al 2001, and Walker et al 2000b).

## Other issues

### Treatment centres

Currently, provision of the treatment has largely been restricted to specialised centres in the United States and Europe. Left ventricular lead introduction requires training and pacemaker programming and follow-up that is more complicated than conventional pacemakers (Linde 2000). The procedure is also associated with the uncommon but potentially serious complication of coronary sinus perforation. It is important that centres and specialists undertaking the procedure have the skills and resources needed to identify and treat this complication.

### Effect of CRT on pharmacological treatment

A potential benefit of CRT that requires further research is whether the treatment can support systolic blood pressure among some patients and enable them to receive an increase in the dose of their medication towards those doses associated with optimal benefit (Touiza et al 2001).

### Selection of appropriate candidates for therapy

Study results indicate that not all patients respond to treatment. In view of the costs involved in pacemaker implantation and follow-up, reliable predictors of response are needed to help select the most appropriate candidates for treatment (Linde 2000). A key issue in patient selection is what criteria should be used to define the presence of ventricular dysnchronisation – electrical, mechanical or both? (Leclercq and Daubert 2000). Although a QRS width greater than 150 ms has repeatedly been found to discriminate between responders and non-responders to CRT, for any given QRS width there is considerable variation in response (Kass 2002). Not all patients with wide QRS complexes will show benefit and some with shorter QRS width may show benefit from CRT (Auricchio et al 1999b). To complicate the issue, the electrical approach to diagnosing ventricular asynchrony (QRS duration >150 msec) does not clearly correlate with the mechanical aspects of asynchrony (Reuter et al 2000) and the precise value of the correlation of QRS duration to ventricular asynchrony is not known (Gras et al 2002a). Echocardiographic parameters are being investigated in order to better describe the mechanical aspects of ventricular asynchrony, and parameters such as prolonged aortic pre-ejection delay, increased inter-ventricular delay and LV segmental post-systolic contraction are being evaluated in the CARE-HF study (see Table 38) (Cleland et al 2001b).

Finally, the effectiveness of the treatment remains to be ascertained for other patient groups not well represented in completed trials, such as those with less impaired left ventricular function, RBBB, or those patients with a conventional indication for a pacemaker (Breithardt et al 2002c).

### Comparison of results from different systems

Data about the types of pacemaker and lead systems used, the site of implantation and the methods of pacing have not been described in all the studies. With the rare exception of Hansky et al (2002), most studies have not identified the frequency and type of adverse events in relation to the types of equipment used. Similarly, safety and effectiveness data has not usually been attributed to specific sites of implantation or methods of pacing. In the United States, resynchronisation therapy devices are available from three different manufacturers (Guidant, Medtronic, St Jude Medical) (Saxon et al 2000). Some significant differences may exist – eg, leads may use either central stylet or over-the-wire designs – between different systems developed by various manufacturers (Pavia and Wilkoff 2001). To date, no published study has specifically compared the effectiveness and/or safety of devices from different manufacturers.

### Impact of new technology

Technological advances in lead and pacemaker design are rapidly occurring, rapidly making the results of trials redundant because of changes in technology. For example, the PATH CHF study was conducted with leads that were inserted via an epicardial approach and this has now been superseded by transvenous implantation. New technological developments will continue to have a major impact on the use of CRT and future developments may, for example, reduce the not insignificant rate of lead dislodgement associated with current devices. The potential benefits of programming specific, optimised interventricular delay after CRT implantation may also be achieved in the future (Saad and Wilkoff 2002).

### International recommendations

Guidelines concerning the use of CRT have been published in several other countries. In the United States, ACC/AHA/NASPE practice guidelines have advocated the use of BST for patients with medically refractory symptomatic heart failure (NYHA III or IV), idiopathic or ischaemic cardiomyopathy, prolonged QRS interval (>130 msec), LV end-diastolic diameter >55 mm and an ejection fraction <35 per cent (Gregoratos et al 2002). The recommendation was graded as Type IIa, indicating that it was considered that the balance of evidence supported the use of the therapy. The National Institute for Clinical Excellence in the United Kingdom has determined that CRT should be considered in selected patients with left ventricular systolic dysfunction (LVEF <35 per cent), drug refractory symptoms, and a QRS duration >120 ms (Anonymous 2003).

It should be noted that this MSAC review includes an economic analysis based on Australian cost data.

### Ongoing studies of the effectiveness of cardiac resynchronisation therapy

A number of ongoing RCTs studies (see Table 36) have been identified that are designed to help resolve at least some of the outstanding issues related to CRT. Studies are planned or being undertaken that will determine the effectiveness and safety of CRT with and without implantable cardiac defibrillators among patients in either sinus rhythm or atrial fibrillation. Further data expected from these trials will help evaluate whether patients with ischaemic or non-ischaemic cardiomyopathy will benefit from the implantation of a defibrillator with or without CRT (Bristow et al 2000). Most trials, with the exception of PERFECT, which is still in the planning stage, will employ selection criteria similar to those used in MIRACLE and COMPANION studies. The

Pacing for Cardiomyopathies (PACMAN) study is a multi-centre trial aiming to enrol about 326 patients with similar characteristics to MIRACLE and the COMPANION trial will assess the effectiveness of CRT with or without an ICD (Auricchio and Klein 2001) (see Table 44).

**Table 46 Ongoing or nearly completed studies**

| Study | Total intended sample size without ICDs | Follow-up: minimum period | Selection criteria | Primary outcomes | Estimated reporting date |
|---|---|---|---|---|---|
| COMPANION (Bristow et al 2000) | 1,320 | 1 year | OPT<br>18 yrs<br>NYHAIII or IV<br>QRS >120 msec<br>SR | Mortality or hospitalisation | Reported in 2004 but sub-group information expected in 2005 |
| PERFECT | 2,400 (may include ICDs – planning ongoing) | 1 year | OPT<br>NYHA any<br>QRS any<br>SR/AF | Mortality<br>Morbidity / | ? |
| Re-Le-Vent<br>(Saxon et al 2000) | 224 | 6 mths | OPT<br>? | Mortality | ? |
| VecToR | 420 | 6 mths | HYHA II-IV<br>QRS>140msec<br>EF<35%<br>LVEDD>55mm | Symptoms<br>Exercise capacity<br>QOL | ? |
| PACMAN | 228 (including ICDs) | 6 mths | NYHA III<br>EF <35%<br>QRS >150ms | Exercise capacity | 2003 |

Based on Cleland et al (2002), Trautmann et al (2002) and Saad and Wilkoff (2002)

# Conclusions

## Clinical need

Heart failure is an important cause of mortality and hospitalisation in Australia. Although current pharmacological agents can dramatically modify the natural history of heart failure, many patients remain symptomatic despite maximal medical therapy. In contrast to the positive results from clinical trials, the evidence from epidemiological studies suggests there may not have been any major improvement in the prognosis of heart failure over the last 40 years.

Approximately one-third of patients with heart failure may exhibit intraventricular conduction delay characterised by a wide QRS complex on electrocardiography. Prolonged QRS duration or ventricular dysynchrony results in decreased contractility, placing the failing heart at a significant mechanical disadvantage. This has been shown to be an independent prognostic risk factor for increased mortality. Pharmacological therapy cannot normalise intraventricular delays and is therefore unable to address the mechanical dysynchrony. The underlying rationale for CRT is to improve the sequence of electrical activation or synchronisation of the two atria, followed by the two ventricles, and thereby improve the mechanical efficiency of the heart by creating a more coordinated and efficient systolic contraction. It is estimated that in Australia, approximately 3,860 people may be potentially eligible for CRT.

## Safety

CRT is associated with an acceptable short-term safety profile. Implantation is successful in about 90 per cent of patients. Fatalities at implantation are rare (<1%) and although complications may arise in approximately 6 per cent of implantations, most are unlikely to be serious – with the exception of perforation, which occurs in 1-2 per cent of implantations. Postoperative complications occur among 7 per cent of patients over six months of follow-up and commonly involve lead problems, such as dislodgement, and infection. These require the patient to undergo a repeat procedure but are usually not life- threatening. Reliable data about the long-term safety of CRT suggests that complication rates are not markedly higher. Approximately 12 per cent of patients sustain an adverse event followed over 29 months.

## Effectiveness

There is evidence of short-term but clinically relevant improvements in exercise capacity and quality of life. There are also clear improvements in survival associated with CRT at 12 months' follow-up. Reliable long-term follow-up data also indicate that CRT significantly improves survival. Hospitalisation rates for cardiovascular events and worsening heart failure are markedly reduced by CRT up to 29 months' follow-up. These studies were largely performed in CHF patients with moderate to severe symptoms (NYHA classes III and IV) associated with moderate to severe left ventricular systolic dysfunction (LVEF $\leq$35%), sinus rhythm and evidence of ventricular dysynchrony (QRS$\geq$120ms).

## Cost-effectiveness

The economic analysis reveals that the expected number of hospital days associated with a decision to use optimal pharmacological treatment with CRT is lower than for a decision to use optimal pharmacological treatment alone, due to a substantial reduction in hospitalisation for major cardiovascular events. The analysis also revealed that adding CRT to optimal pharmacological treatment is associated with a significant number of life years saved and quality-adjusted life years saved, although this does not translate into a favourable cost-effectiveness ratio unless the mortality and cost data are projected forward to generate lifetime differences. Lifetime estimates, based on the data presented in the CARE-HF study, suggest a favourable incremental cost-effectiveness ratio of between $12,426 and $21,151 per life year saved and between $12,257 and $21,850 per QALY saved.

The results of sensitivity testing suggest that, although the cost-effectiveness ratios are sensitive to plausible variations in assumptions of the model, none of these variations would change the conclusion of a favourable cost-effectiveness ratio based on lifetime estimates.

Total annual cost estimates for the two forms of treatment suggest that adding CRT to optimal pharmacological treatment would add between $2,230,019 and $11,969,378 to total annual costs over the long term, based on between 97 and 290 new patients annually. Initial annual costs could be significantly higher due to the large existing stock of eligible patients.

**Summary of conclusions**

Clinical need for CRT has been established in relation to patients with moderate to severe heart failure (NYHA classes III and IV symptoms) associated with moderate to severe left ventricular systolic dysfunction (LVEF $\leq$35%) and evidence of ventricular dysynchrony (QRS$\geq$120ms).

CRT has an acceptable safety profile when undertaken by appropriately trained personnel at a tertiary centre in the short term following implantation, and during longer term follow-up.

There is reliable evidence that CRT can effectively improve symptoms, exercise capacity and quality of life in the short term and reduce the need for hospitalisation in the longer term, measured over up to 29 months). The data indicate that there are significant improvements in survival with CRT at both 12 months and longer term, 29 months, follow-up.

CRT appears to be cost-effective using a projected cost-utility analysis.

# Recommendation

On the strength of evidence pertaining to safety, effectiveness and cost-effectiveness, MSAC recommends that public funding should be supported for the use of cardiac resynchronisation therapy in patients who have moderate to severe chronic heart failure (NYHA class III or IV) despite optimised medical therapy and who meet all of the following criteria-sinus rhythm, a left ventricular ejection fraction of less than or equal to 35% and a QRS duration greater than or equal to 120ms

- The Minister for Health and Ageing accepted this recommendation on 28 November 2005 –

# Appendix A MSAC terms of reference and membership

The MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of the MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

| **Member** | **Expertise or Affiliation** |
|---|---|
| Dr Stephen Blamey (Chair) | general surgery |
| Associate Professor John Atherton | cardiology |
| Professor Syd Bell | pathology |
| Dr Michael Cleary | emergency medicine |
| Dr Paul Craft | clinical epidemiology and oncology |
| Dr Gerry FitzGerald | Australian Health Ministers' Advisory Council representative |
| Dr Kwun Fong | thoracic medicine |
| Dr Debra Graves | medical administrator |
| Professor Jane Hall | health economics |
| Professor John Horvath | Chief Medical Officer, Department of Health and Ageing |
| Dr Terri Jackson | health economics |
| Professor Brendon Kearney | health administration and planning |
| Associate Professor Donald Perry-Keene | endocrinology |
| Dr Ray Kirk | health research |
| Dr Michael Kitchener | nuclear medicine |
| Professor Alan Lopez | medical statistics and population health |
| Dr Ewa Piejko | general practice |
| Ms Sheila Rimmer | consumer health issues |

| | |
|---|---|
| Ms Samantha Robertson | Acting Assistant Secretary<br>Department of Health and Ageing |
| Professor Jeffrey Robinson | obstetrics and gynaecology |
| Professor Michael Solomon | colorectal surgery, clinical epidemiology |
| Professor Ken Thomson | radiology |
| Dr Douglas Travis | urology |

# Appendix B Advisory panel

### Advisory panel for MSAC application 1042 Cardiac resynchronisation therapy for heart failure.

| | |
|---|---|
| Associate Professor John Atherton (Chair from March 2005)<br>MBBS, PhD, FRACP | Member of MSAC |
| Dr John Primrose (Chair until March 2005)<br>MBBS (Hons), FRANZCR<br>Senior Medical Advisor, Department of Health and Ageing | Department of Health and Ageing |
| Dr Stephen Blamey<br>MB BS FRACS | Chair of MSAC |
| Professor Richmond Jeremy<br>MB BS PhD FRACP FAHA FESC FCSANZ | Co-opted expert |
| Mr Ivan Kayne<br>Member St Vincent's Hospital Community Advisory Committee, Melbourne | Nominee of Consumers' Health Forum of Australia |
| Associate Professor Peter MacDonald<br>MBBS, FRACP, PhD, MD<br>Senior Staff Cardiologist, Cardiopulmonary Transplant Unit, St Vincent's Hospital, Darlinghurst NSW | Nominee of Cardiac Society of Australia and New Zealand |
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## Evaluators

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## Department of Health and Ageing

| | |
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| Mr Mike McKenzie (until July 2003) | Health Technology Section |
| Ms Alex Lloyd (from July 2003) | Health Technology Section |

# Appendix C Studies included in the review

**Table 47 Studies included under safety**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Bradley et l 2003)<br><br>Location: Multiple trials<br><br>Study period: 1966-2002<br><br>Study type: Meta-analysis<br><br>Level I | Systematic review examining whether cardiac resynchronisation therapy reduces mortality from progressive heart failure. Search of MEDLINE, EMBASE, Cochrane Trials Registry, US Govt sites, Reports at Scientific Meetings, bibliographies. Searches performed in May and June 2002 of 6883 potentially relevant reports. 4 RCTs were included with 1,634 patients.<br><br>Follow up:<br>Studies were required to have follow-up of at least 3 months.<br><br>Inclusion criteria:<br>RCTs of CRT for treatment of chronic symptomatic LV dysfunction. Reported death, hospitalisation for heart failure or ventricular arrhythmias as outcomes.<br>Ventricular arrhythmia studies were restricted to ICDs.<br><br>Exclusion criteria:<br>Another report provided more complete and/or updated data.<br>Report concerned research design only.<br>Follow-up < 3 mths. | Safety results: 1,634 patients<br><br>Implantation success rate: not stated.<br><br>Perioperative: not stated.<br><br>Postoperative:<br>Death from progressive heart failure (Pacemaker trials only): OR 0.40 (0.12-1.29) – 590 patients.<br><br>Secondary outcomes:<br>All cause mortality (Pacemaker trials only): OR 0.79 (0.39-1.58).<br><br>Hospitalisation: MIRACLE study intervention patients: 275 days among 230 patients versus control patients: 664 days and 231 patients. Pooled odds of heart failure hospitalisation 0.71 (95% CI 0.53-0.96) in intervention versus control group.<br><br>Patient characteristics:<br>Trials selected: Contak CD, InSync ICD, MIRACLE, MUSTIC, mean age 63-66 years, males 70-84%, NYHA II-IV Contak and InSynch), III-IV (MIRACLE), III (MUSTIC), mean EF 21-23%, mean QRS duration 158-176 ms, 1580 of 1634 patients underwent transvenous placement of leads. | Author's conclusions:<br>'CRT reduces mortality from progressive heart failure in patients with symptomatic LV dysfunction and ventricular dyssynchrony. Also reduces heart failure hospitalisation and shows a trend towards reducing all-cause mortality.<br><br>Comments: Two independent data extractors.<br><br>Included patients with implantable cardioverter defibrillators (2 of the 4 RCTs).<br><br>Unscheduled crossover 0-6.9% in group originally receiving CRT and 3.4-8.5% in group originally receiving no CRT.<br><br>Drop-out for reasons other than death or heart transplantation: 0.4-2.7% for patients originally receiving CRT and 0.8-2.7% in group originally receiving no CRT.<br><br>Results of interest were part of two sub-analyses only.<br>All ITT analysis<br>All industry funded<br>Allocation generation not reported<br>Blinding: One trial single blind, others double blind<br>Follow-up all >80%<br>Comparison group – yes in all |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Brophy 2004)<br><br>Location: Multiple trials<br><br>Study period: Not stated<br><br>Study type: Meta-analysis<br><br>Level I | Systematic review examining potential use of cardiac resynchronisation therapy at McGill University Health Centre. Search of MEDLINE, EMBASE, Cochrane Trials Registry, Websites. 7 RCTs and 9 non-randomised trials were included.<br><br>Follow-up: Not stated.<br><br>Inclusion criteria: Not specified. | Safety results: Unspecified total number of patients<br><br>Implantation success rate: 88-92%<br><br>Perioperative:<br>0.3% rate of death related to implantation procedure (COMPANION data). Approximately 4% of patients were reported in some studies to have died after implantation and prior to randomisation without specification of causes.<br>The most common perioperative complications were listed as: lead dislodgement (5%), coronary sinus dissection (3%), perforation (2%), exit block (7%), elevated pacing threshold (3%).<br><br>Postoperative:<br>After implantation the most common complications were: arrhythmias (18%), worsening of heart failure (16%), hypotension (15%), lead dislodgement (11%), infection (1%), loss of capture (2%).<br>Mortality: (Based on MIRACLE and unpublished COMPANION results) no significant reduction in all-cause mortality at 6 months OR = 0.91, 95% CI: 0.61-1.34.<br>Re-hospitalisation: (MUSTIC and MIRACLE) significant 57% reduction in heart failure hospitalisations after 6 months OR = 0.43, 95% CI: 0.25-0.75.<br><br>Patient characteristics:<br>Not specified for the included studies. | Author's conclusions:<br>'Based on lack of mortality benefits, the marginal impact on quality of life, the lack of long-term results at this time, the presence of ongoing research designed to establish the benefits of this therapy, and the considerable opportunity costs, the author did not recommend the use of biventricular pacemakers with ICD at this time at McGill'.<br><br>Comments:<br>Methods not specified.<br><br>A limited economic analysis as a cost comparison was conducted using local data.<br><br>Included patients with implantable cardioverter defibrillators.<br><br>Blinding: One trial single blind, others double blind<br>Follow-up all >80%<br>Comparison group – yes in all |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author: (Oduneye 2003)<br><br>Location: Multiple trials<br><br>Study period: 1966-2002<br><br>Study type: Systematic review<br><br>Level I | Systematic review of randomised controlled trials to assess the effects of cardiac resynchronisation in people with heart failure. Search of MEDLINE (1966-2002), EMBASE (1980-2002), Cochrane Controlled Trials Register (1st Issue, 2003), Clinical Evidence Issue 8, Centre for Reviews and Dissemination Databases. Search terms not described. No additional searches were conducted using author names and trial acronyms. No search for reports at scientific meetings. Bibliographies of reviews articles were not searched. Search performed in January 2003.<br><br>From an unstated number of potentially relevant reports initially identified, 9 potentially relevant randomised controlled trials were considered. One RCT (the MIRACLE study) met the inclusion criteria and was evaluated.<br><br>Follow-up: 6 months.<br><br>Inclusion criteria:<br><br>RCTS of permanent pacemaker to left and right ventricles with ventricular resynchronisation versus medication or any other therapy group for treatment of chronic heart failure and no other indication for ventricular pacing. Studies were excluded if people had indications for pacing based on rhythm disturbance or if the comparator was univentricular pacing or if the intervention included an implantable cardioverter defibrillator. Reports in formats other than journal articles and non-English language studies were not included. Eligible studies reported outcomes including: death or hospitalisation for heart failure death from any cause, disability, functional outcomes, exercise tolerance, quality of life and any clinical outcome. | Safety results: (based on MIRACLE study)<br><br>Implantation success rate: 92%.<br><br>Perioperative:<br><br>Adverse events included permanent heart block requiring pacing, coronary sinus dissection (4%), perforation (2%), need to replace leads (6%), infection.<br><br>Postoperative:<br><br>Death rates similar between groups (intervention group = 5.3% versus 7.1% hazard ratio = 0.73, 95% CI = 0.34 – 1.54.<br><br>Patient characteristics:<br><br>The single included trial = MIRACLE study.<br><br>Baseline characteristics of the study participants were not described. | Author's conclusions:<br><br>'Good Evidence that cardiac resynchronisation improved symptoms after 6 months. However, in a high proportion of study participants, insertion of the device failed or adverse events occurred. Long-term effects of cardiac resynchronisation are unknown.'<br><br>Comments:<br><br>Results from only a single trial (MIRACLE study) were reported.<br><br>Blinding: One trial double blind<br><br>Follow-up all >80%<br><br>Comparison group – yes |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author: (McAlister 2004)<br><br>Location: Multiple trials<br><br>Study period: 1980-2003<br><br>Study type: Meta-analysis<br><br>Level I | MEDLINE (1980-2003), EMBASE (1980-2003), Cochrane Controlled Trials Register (2002 Vol 4), International Pharmaceutical Abstracts, Web of Science, Pubmed, HTA electronic databases, US FDA Reports. Search strategies were provided and terms included: biventricular pacing, biventricular pacemaker, resynchronisation, pacing and heart failure. Websites on clinical trials were searched. Additional information was requested from primary authors and manufacturing companies. A search for reports at scientific meetings was conducted. Bibliographies of reviews articles were searched. No restriction was made for dates of publication. Not restricted by language.<br><br>Follow-up: >2 weeks.<br><br>Inclusion criteria:<br>RCTS for efficacy and safety plus prospective cohort studies for safety.<br><br>Study duration: >2 weeks.<br><br>Outcomes:<br>All-cause mortality or heart failure hospitalisation. | Implantation success rate: not stated in relation to CRT alone<br>Perioperative: not stated in relation to CRT alone<br><br>Postoperative:<br>All-cause mortality:<br>CRT reduced all-cause mortality by 21% RR=0.70, 95% CI: 0.66-0.96. This result included all 9 trials. A sensitivity analysis was conducted using meta-regression to examine the effect of ICDs on the efficacy of resynchronisation therapy. The benefits of CRT did not appreciably differ between patients with or without an ICD (p>0.2). But the data from the COMPANION trial was preliminary and did not include data on patients with and without an ICD.<br><br>Heart failure hospitalisations:<br>Non-significant reduction among 6 trials RR=0.68, 95% CI: 0.41-1.12. Heterogeneous result p=0.01, I2 = 65%. Sensitivity analysis again indicated no significant difference between patients with or without an ICD.<br><br>Patient characteristics:<br>Baseline characteristics of the participants in the separate studies were presented and closely examined. The baseline characteristics were generally similar across studies: all trials enrolled patients with prolonged QRS and restricted LVEF < 40%. The mean age across the trials was 64 years, 74% of patients were male, 58% had ischaemic cause of heart failure, 75% had NYHA class III, 10% had NYHA class IV. However, Garrigue et al (2002) and MUSTIC AF only included patients with atrial fibrillation. MIRACLE ICD, CONTAK CD and COMPANION. Included a study group who received pacing + ICD therapy. The PATH CHF trial included patients who were only implanted with a transthoracic approach.<br>The demographic characteristics of the cohort study patients were similar to those in the trials. | Author's conclusions:<br>'In selected patients with heart failure, cardiac resynchronisation therapy improves functional and haemodynamic status, reduces heart failure hospitalisations and reduces all-cause mortality.'<br><br>Comments:<br>Included patients with implantable cardioverter defibrillators.<br>Results of interest were part of sensitivity analyses only.<br>All used ITT analyses<br>All trials were industry funded<br><br>Blinding:<br>4 trials were double blind, 3 single blind, 2 were open label.<br><br>Follow-up all >80%<br>Comparison group – yes in all trials |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Cleland et al 2005)<br><br>Location:<br>Austria, Belgium, Denmark, Finland, France, Italy, The Netherlands, Sweden, Switzerland, United Kingdom.<br>(82 European study sites)<br><br>Study period:<br>Recruitment Jan 2001 to march 2003.<br><br>Study type:<br>RCT<br><br>Level II | Randomised controlled trial comparing medical therapy alone (n=404) with medical therapy plus cardiac resynchronisation therapy (n=409) in patients with NYHA class III or IV heart failure. Randomisation stratified by NYHA class.<br>Medtronic InSynch or InSynch III devise inserted. LV lead positioned to pace the lateral or posterolateral left ventricular wall.<br><br>Follow-up:<br>Mean follow-up 29.4 months (range 18.0-44.7)<br><br>Inclusion criteria:<br>≥ 18 years<br>Heart failure for at least six weeks<br>NYHA Class III or IV despite receipt of standard pharmacologic therapy<br>LVEF ≤35% LVEDD ≥30mm<br>QRS ≥120 msec<br>Patients with QRS 120-149 msec were required to meet two of the following three additional criteria for dyssynchrony:<br>- aortic pre-ejection delay of >140 msec<br>- interventricular mechanical delay of >40 msec<br>- delayed activation of posterolateral left ventricular wall<br><br>Exclusion criteria: Major cardiovascular event in previous six weeks Conventional indications for pacemaker or ICD<br>Heart failure requiring continuous IV therapy<br>Atrial arrhythmia | Perioperative and postoperative:<br>One death from heart failure aggravated by lead dislodgement.<br>Lead displacement (24 patients, 5.9%)<br>Coronary sinus dissection (10 patients, 2.4%)<br>Pocket erosion (8 patients, 2.0%)<br>Pneumothorax (6 patients, 1.5%)<br>Device related infection (3 patients, 1.0%)<br>Implantation success rate 390/409 (95%). 349 were successful on the first attempt.<br><br>Perioperative: Median inpatient stay for implantation = 5 days (range 2-8).<br><br>Postoperative :<br>Death (CRT v. no CRT): 20% v. 30% (hazard ratio 0.64, 95% CI 0.48-0.85, P<0.002).<br>Death from any cause and unplanned hospitalisation with heart failure (CRT v. no CRT): hazard ratio 0.54, 95% CI 0.43-0.68, P<0.001.<br><br>Patient characteristics:<br>Median age: 66 years v. 67 years (no CRT v. CRT)<br>Male sex 73% v. 74% (no CRT v. CRT)<br>NYHA class IV 7% v. 6% (no CRT v. CRT)<br>Dilated cardiomyopathy 48% v. 43% (no CRT v. CRT)<br>IHD 36% v. 40% (no CRT v. CRT)<br>Median LVEF 25% v. 25% (no CRT v. CRT)<br>QRS duration 160msec v. 160msec (no CRT v. CRT)<br>ACE inhibitor or angiotension receptor blocker 95% v. 95% (no CRT v. CRT). Beta-blocker 74% v. 70% (no CRT v. CRT)<br>Spironolactone 59% v. 54% (no CRT v. CRT)<br>High dose loop diuretic 44% v. 43% (no CRT v. CRT)<br>Digoxin 45% v. 40% (no CRT v. CRT) | Comments:<br>Implantation of CRT (without ICD) was attempted in 43 patients and of CRT with ICD in 23 patients.<br>Implantation of a device was attempted in 404 of 409 assigned to the CRT group<br>Medtronic Corporation funded the trial and provided a study manager to supervise its conduct. The sponsor had no access to the database and did not participate in the study analysis or study writing.<br>Emergency heart transplantation counted as a death.<br>Study was unblinded but members of the endpoints committee were not aware of patients' treatment assignments.<br><br>Unblinded except for endpoint committee<br>Follow-up completeness: satisfactory.<br>Comparison group: randomised. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Bristow et al 2004)<br><br>Location: USA (128 centres).<br><br>Study period: Enrolment: Jan 20, 2000 – Nov 18, 2002.<br><br>Study type: RCT<br><br>Level II | RCT – 1:2:2 Optimal medical therapy: BVT without defibrillator, BVT with defibrillator. 1,520 patients were randomised.<br>Contak TR model 1241 pacemaker.<br>Blinding of assignment among steering committee, endpoints committee and sponsor. Other groups not blinded: Patients, physicians, statisticians, data management group, data safety and monitoring board.<br><br>Primary endpoints:<br>Death and hospitalisation (all cause and heart failure specific).<br><br>Follow-up:<br>Median follow-up: 11.9 mths in pharmacologic gp, 16.2 mths in the pacemaker group, 15.7 mths in the pacemaker-defibrillator gp.<br><br>Inclusion criteria:<br>NYHA Class III-IV, LV EF ≤ 35%, QRS ≥ 120 msec, PR interval > 150 msec, sinus rhythm, no clinical indication for a pacemaker or implantable defibrillator, hospitalisation for the treatment of heart failure or the equivalent in the preceding 12 mths. | Safety results: 595 patients<br><br>Implantation success rate: 541/595 (91%)<br><br>Perioperative:<br>5 deaths (0.8%) adjudicated as procedural related.<br>Moderate to severe adverse events related to the procedure: 10% in the pacemaker group including coronary venous dissection (0.3%), coronary venous perforation (1.1%) and coronary venous tamponade (0.5%).<br>Median duration of procedure: 164 minutes.<br><br>Postoperative:<br>Mortality rates 30 days after randomisation were similar in the 3 groups: 1.0% in the pacemaker group, 1.8% in the pacemaker-defibrillator group, 1.2% in the pharmacologic group (p=0.79).<br>61% of patients in the medication-only group had a moderate or severe adverse event from any cause compared with 66% of patients in the pacemaker group (p=0.15).<br><br>Patient characteristics:<br>Mean age 67 yrs, 67% male, 87% NYHA III, mean LV EF= 0.20, distance walked in 6 min 274 m, mean QRS interval 160 msec. | Authors' conclusions:<br>No specific safety conclusions.<br><br>'In selected patients, cardiac-resynchronisation therapy with a pacemaker or a pacemaker-defibrillator can improve the clinical course of chronic heart failure due to a dilated cardiomyopathy. The pacemaker is associated with a reduction in hospitalisations and symptoms and improved exercise tolerance and quality of life, and the addition of a defibrillator to cardiac resynchronisation 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.'<br><br>Comments:<br>Only 1.9% of the reported 10% incidence of moderate to severe adverse events were described.<br><br>Selected series included in a RCT<br><br>Blinding:<br>Blinding status uncertain re the ascribing of safety related outcomes<br>Follow-up completeness. >80%<br>Comparison group: yes |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Abraham et al 2002)<br><br>Location:<br>45 centres in the US and Canada.<br><br>Study period:<br>November 1998 – December 2000.<br><br>Study type:<br>Multi-site RCT (CRT pacing vs no pacing).<br><br>Level II | Primary aim was to assess therapeutic effectiveness of CRT. Safety was a secondary outcome. 571 patients with heart failure were enrolled. Withdrawals n=4 due to unstable condition. 71 implanted patients participated in three-month pilot. 453 patients randomised to control (no pacing) or pacing.<br><br>Follow-up:<br>Duration of six months.<br><br>Inclusion criteria:<br>NYHA class III or IV, LVEF< or =35%, LVEDD > or = 55mm, QRS 130ms or >, and 6-min walk 450 m or less, optimised medical treatment, no pacemaker or defibrillator, sinus rhythm, no atrial arrhthymia in last month, systolic blood pressure <170 and >80 mmHg, heart rate <140 bpm, serum creatinine <265µmol/l. | MIRACLE trial results:<br>Implantation: failure to implant 43/567 (92% successful), CS dissection n=23, CV or CS perforation n=12 (3 with presumed or confirmed haemopericardium).<br><br>Post-operative:<br>Control (n=225): Deaths n=16, other withdrawals n=8 (received transplant n=2, device complications n=1, missed 6 month f/u n=5), early programming to pacing n=10 (worsening cardiac failure n=7, bradycardia n=3), 50 hospitalisations for 34 patients for total 363 days for heart failure. Hospitalisations for lead dislodgement n=3 patients. 33 hospitalisations for non-HF or non-LV lead causes.<br>Pacing (n=228): Deaths n=12, other withdrawals n=1 (device complications n=1), 25 hospitalisations for 18 patients for total 83 days for heart failure. Hospitalisations for lead dislodgement n=11 patients. 37 hospitalisations for non-HF or non-LV lead causes.<br>All patients: LV lead dislodgement n=30 (20 requiring repositioning and 10 requiring relocation), pacemaker infection requiring explantation n=7 (4 re-implanted).<br><br>Patient characteristics:<br>Mean age (intervention group): 63.9 (10.7) years, 308/453 male, mean QRS (intervention group) = 167 (21) ms, mean LVEF (intervention group) = 21.8 (6)%, rhythm = all in SR, NYHA class III n=410 (control n=205, pacing n=205), NYHA class IV n=43 (control n=20, pacing n=23, aetiology = ischaemia 54% intervention group, 59% control group. | Authors' comment:<br>'When all possible reasons for technical failure were considered, about 8% of the 571 participating patients were unable to receive and be maintained on resynchronisation therapy for the planned duration of treatment.'<br><br>Comments:<br>Median duration of implantation among the successful = 2.7 hours (range 0.9 – 7.3 hours).<br>Groups were comparable at baseline.<br>Sample size adequate.<br>Intention-to-treat analysis.<br>Checks for contamination/crossover: 10 in control group were re-assigned.<br>Follow-up described and used objective tests.<br>No losses to follow-up related to worsening heart failure or death.<br>Double blind.<br>Parallel control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Cazeau et al 2001)<br><br>Location:<br>15 centres in six European countries.<br><br>Study period:<br>March 1998 – March 1999.<br><br>Study type:<br>Randomised, crossover study (Multisite Stimulation in Cardiomyo-pathies Trial MUSTIC).<br><br>Level II | Aim was to assess the therapeutic effectiveness and safety of CRT. 67 patients were enrolled in SR group.<br><br>Withdrawals n=3; due to unstable heart failure (n=2, 1 of whom died) and pre-existing indication for pacing (n=1). Implantation occurred 4/52 post-enrolment. 2/52 later randomised to 12/52 BiV pacing or VVI40 pacing followed by 12/52 of BiV pacing or VVI40 pacing respectively.<br><br>Follow-up: Total duration seven months.<br><br>Inclusion criteria:<br>Severe heart failure due to idiopathic or ischaemic cause, EF<35%, EDD >60mm, sinus rhythm, QRS interval>150msec, no standard indication for pacemaker, in NYHA class III for at least 1 month while receiving optimal therapy (diuretics, ACE inhibitor at max doses for >1 month), none of the following exclusion criteria: diagnosis of hypertrophic or restrictive cardiomyopathy, suspected acute myocarditis, correctable valvulopathy, an acute coronary syndrome (<3/12), coronary revascularisation in last 3/12 or scheduled, treatment-resistant hypertension, severe COAD, unable to walk, life expectancy <1 year due to non-cardiac causes, indication for pacemaker. | MUSTIC trial Results:<br>Implantation: (n=64) failure to implant LV lead n=5 (withdrawn from study), failure to reach LV lateral position n=13.<br><br>Postoperative:<br>(n=58, above 5 failed implantation + 1 death prior to pacemaker activation): lead dislodgement n=8 (successfully corrected in 5), death n=3 (1 after 26 days of active pacing, 2 in second crossover phase), uncorrectable loss of pacing efficacy n=2, severe cardiac decompensation n=4 (1 in first X-over phase (inactive pacing) and 3 in second crossover phase (1 inactive pacing with AMI, 1 inactive pacing developing AF, 1 active but with rapidly progressive AS). Hospitalisations for heart failure (in first period only) n=12 (9 inactive pacing, 3 active pacing).<br><br>Patient characteristics:<br>Average age = 63 (10) years, 50/67 male, mean QRS = 176 (19) ms, mean LVEF = 22 (8)%, rhythm = all patients in SR, NYHA class III only, aetiology = ischaemia (n=25). | Author's conclusion:<br>'The results with respect to mortality and morbidity should be interpreted with caution in this relatively small study.'<br><br>Comments:<br>Safety was a secondary outcome.<br>Follow-up fully described.<br>Intention-to-treat analysis.<br>Total mortality five of 67 patients (7.5%) but study not powered for mortality.<br>Single blind.<br>No external control group – patients were their own controls. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Walker et al 2000f)<br><br>Location:<br>England<br><br>Study period:<br>Study dates not stated.<br><br>Study type:<br>Randomised crossover trial.<br><br>Level II | Aim was to assess the effectiveness of CRT in suppressing ventricular arrythmias. 20 patients enrolled. 1 month after implantation randomised to two 3-month periods. Patients in SR compared normal SR with BiV (DDD) pacing (3 month period for each). (Patients in AF compared with control (VVIR) pacing with BiV (DDDR) pacing). Aim was top assess the effectiveness of CRT in suppressing ventricular arrhythmias by CRT.<br><br>Follow-up:<br>Duration of seven months.<br><br>Inclusion criteria:<br>Not stated. | Implantation: No complications reported by authors.<br>Postoperative: No increase in arrhythmias found with CRT pacing.<br><br>Patient characteristics:<br>Mean age = 60 (12) yrs, 15/20 male, mean QRS = 163 (22) (SR patients only), mean LVEF = not given, rhythm = SR n=12, chronic AF n=8, NYHA class III n=15, class IV n=5, aetiology = idiopathic dilated cardiomyopathy (n=10), ischaemia (n=10). | Author's conclusion:<br>'In a population of patients with heart failure, CRT significantly decreases ventricular ectopic counts compared with both sinus rhythm and right ventricular pacing.'<br><br>Comments:<br>No patients had a conventional indication for pacemaker, none had sustained ventricular tachycardia before implantation.<br>Only two patients were taking an anti-arrhythmic (amiodarone n=1, beta-blocker n=1).<br>Limited baseline comparisons of groups.<br>Selected – no criteria.<br>Single blinded trial.<br>Satisfactory follow-up.<br>Crossover control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Butter et al 2003)<br><br>Location:<br>Multiple centres in Europe<br><br>Study period:<br>Not stated<br><br>Study type:<br>Prospective case series<br><br>Level IV | Comparative testing of five different guiding catheter shapes of the EASYTRAK series on 29 consecutive patients. Four new catheters: Multipurpose Hook (MPH), Multipurpose Long (MPL), Amplatz 6 (CS-A6), Coronary Sinus Hook (CS-H), were tested in a prospective random order with reference to the standard the Multi-Purpose Electro-Physiology (MPEP) catheter tested last. Studied success of placing the guiding catheter in a stable position inside the coronary sinus that would allow placement of a left ventricular lead for resynchronisation therapy.<br><br>Follow-up: Not stated<br><br>Inclusion criteria:<br>Patients undergoing implantation for 'standard indications'<br>> 17 years old<br>Not intolerant to contrast agents. | No serious adverse events involving coronary sinus injury requiring an intervention or prolonged hospital stay were observed.<br>Minor vascular staining in 2/27 patients could indicate damage to coronary sinus intima but this did not have any clinical implications.<br><br>Implantation success rate:<br>26/27 successfully implanted (1 was not implanted by any of the five quide catheters). Curved shaft catheters were associated with higher cannulation success rates 916/23 (70%) for the MPH and 17/23 for the CS-H. The standard MPEP which is also curved had the highest success rate 17/22 (77%). The straight shaft catheters had lower success rates 13/23 (56%) for the MPL and 12/23 (52%) for the CS-A6. Two of the catheters (CS-H and CS-A6) were more effective from a left hand rather than a right hand insertion site.<br><br>Perioperative: No clinically significant adverse events.<br><br>Postoperative: Not stated.<br><br>Patient characteristics:<br>Demographics stated to be representative of the heart failure population but no details presented. | Author's conclusions: The ability to switch between guiding catheters with different shapes and compound curves can improve the coronary sinus cannulation success rate.'<br><br>Comments:<br>Among the 29 patients, 2 did not undergo catheter testing, the complete set was evaluated in only 17/27 and for 10/27 the cardiologist prematurely stopped the testing.<br>The results were not subjected to statistical assessment.<br>The number of guiding catheters tested may have increased the risk of adverse events. That is, intimal tears may not have occurred with one guiding catheter.<br>Consecutive series.<br>Blinding: Not stated<br>Follow-up completeness: implantation results only<br>Participation rate = 27/29<br>No follow-up<br>Comparison group: no external group |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Linde et al 2002b)<br><br>Location:<br>15 centres in six European countries.<br><br>Study period:<br>1998-1999.<br><br>Study type:<br>Prospective cohort based on randomised, crossover study (Multisite Stimulation in Cardiomyopathies Trial-MUSTIC).<br><br>Level III-2 | Aim was to assess whether benefits of CRT were sustained over 12 months. 67 patients enrolled (in SR group). Follow-up study to Cazeau et al (2001) (see above) reporting outcomes with 12 months follow-up. Patients received their preferred pacing modality at the cessation of the crossover phase or, if no preference, at physician discretion.<br><br>Inclusion criteria:<br>Based on the MUSTIC study. | 48 patients completed crossover phase in SR group: 41/48 chose BiV pacing, five given BiV pacing at physician discretion, two chose non-pacing (VVI) option (both of whom died before the nine month f/ollow-up), one erroneously allocated to non-pacing option but reallocated to pacing option at nine months.<br><br>Postoperative: (i.e. between six and 12 months follow-up) deaths = 6 (sudden n=2, CVA n=1, heart failure n=1, septicaemia n=1, ICD n=1), EPT n=1 (transient).<br><br>Patient characteristics:<br>Mean age = 63 (10) years, 50/67 male. Mean QRS = 176 (19) ms, mean LVEF = 22 (8)%, rhythm = all patients in SR, NYHA class III only, aetiology = ischaemia (n=25 in the original study group for MUSTIC). | Author's conclusion:<br>'The clinical benefits of CRT appeared to be significantly maintained over a 12-month follow-up period.'<br><br>Comments:<br>Extension of MUSTIC trial.<br>Intention-to-treat analysis with Bonferroni correction for multiple analyses.<br>Total mortality 11 of 67 patients (16.4%) but study not powered for mortality.<br>Selected patients with defined criteria.<br>Satisfactory follow-up.<br>Single blind.<br>Historical control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(De Martino et al 2005)<br><br>Location:<br>Catholic University, Rome, Italy<br><br>Study period: not stated<br><br>Study type:<br>RCT<br><br>Level II | 83 patients were randomly assigned to two different venography techniques: contrast injection directly through guiding catheter versus venography obtained after occlusion of the coronary sinus by a Swan-Ganz catheter.<br><br>Follow-up: not stated – but short.<br><br>Inclusion criteria:<br>Left ventricular dysfunction<br>Intraventricular conduction delay (QRS>120ms)<br>NYHA Class III/IV despite optimal medical therapy | Implantation success rate: 82/83 (98%)<br><br>Perioperative:<br>Four dissections of the coronary sinus observed with the occlusive technique versus no complications with the direct venography technique (p=0.04).<br>Dose of contrast lower in direct group (p=0.03).<br>Total procedure time was not significantly different between the two groups (128 versus 139 minutes).<br><br>Postoperative: not stated<br><br>Patient characteristics:<br>Direct venography technique versus occlusive venography technique:<br>Mean age 62 years versus 61 years<br>Mean EF 24% versus 25%<br>Mean LVEDD 67 versus 66<br>Coronary artery disease 51% versus 50%<br>Dilated cardiomyopathy 49% versus 50%<br>CABG 24% versus 21% | Authors' conclusions:<br>'Direct venography technique shows a significantly lower incidence of complications and should be considered to be the first-line approach to coronary sinus venography during biventricular pacemaker implantation.'<br><br>Comments:<br>Randomisation after CS catheterisation using a computer-generated random-numbers series<br>Consecutive patients<br>Venography adequate in 40/41 assigned to the occlusive technique and 37 of 41 assigned to the direct technique. Crossover of the four failed direct technique patients led to adequate visualisation.<br>Blinding not stated.<br>Follow-up completeness: 82/83 patients.<br>Comparison group<br>Intention-to-treat analysis was conducted. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Sawhney et al 2004)<br><br>Location:<br>Washington University, St Louis, Missouri, USA<br><br>Study period:<br>Not stated.<br><br>Study type:<br>RCT | 40 patients with severe heart failure referred for CRT. All leads were implanted transvenously. Comparison of two methods of AV delay programming. Optimised AV delay by echo (n=20) versus an empiric AV delay of 120 msec (n=20).<br><br>Follow-up: 3 months<br><br>Inclusion criteria:<br>NYHA Class III/IV<br>Age >18 years<br>LV EF <35%<br>QRS duration >150 ms<br>Standard medical therapy for heart failure<br><br>Exclusion criteria:<br>Symptomatic bradyarrhythmias, medically refractory atrial arrhythmias, pregnancy, MI or coronary intervention within 3 months, or a significant co-morbid illness defined as severe obstructive pulmonary disease requiring chronic supplementation of oxygen, serum creatinine > 2.5, malignancy, or medically refractory anginal symptoms. | Implantation success rate: 40/40 (100%)<br><br>Postoperative: not stated<br><br>Postoperative:<br>Deaths: n=1 (1 death from cancer).<br>15 patients hospitalised during follow-up (no difference between groups n=6 and n=9).<br><br>Patient characteristics:<br>Age 59.8 years, Male (n=28, 70%), History of CAD 45%, NYHA Class 3.1, distance walked in 6 minutes 242m, EF 25.6%, QRS 176ms. ACE inhibitor/Angiotensin receptor blocker 100%, Diuretic 100%, Digitalis 65%, Aldactone 70%, Beta blocker 78%. | Authors' conclusions:<br>No safety related conclusions.<br>'Echo-guided AV delay optimisation improves clinical outcomes at 3 months compared to empiric AV delay.<br><br>Comments:<br>Primary aim was to determine if AV delay optimisation with continuous wave Doppler aortic velocity time integral is superior to an empiric program in patients treated with CRT.<br><br>Short follow-up period and small sample size.<br><br>Unclear if consecutive patients were used.<br><br>Blinding: single.<br>Follow-up completeness – 39/40 (due to the death).<br>Comparison group: yes randomised.<br>Intention-to-treat analysis was used. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(De Martino et al 2004)<br><br>Location:<br>Catholic University, Rome, Italy<br><br>Study period:<br>Not stated.<br><br>Study type:<br>RCT<br><br>Level II | 34 consecutive patients randomised to standard guiding catheter positioning strategy (GCA) or electrophysiology catheter aided positioning strategy (EPA).<br><br>Follow-up: Not stated – but likely short.<br><br>Inclusion criteria:<br>QRS >120 ms<br>NYHA Class III-IV despite optimal medical therapy | Time to successful catheterisation of CS was 5.0 minutes in the EPA group compared with 10.1 minutes in GCS group.<br><br>Implantation success rate:<br>15/16 (94%) in EPA group. 15/18 (83%) in GCS group.<br><br>Perioperative:<br>Three proximal and one distal CS dissections (n=4) with an uneventful course were observed.<br>Time to catheterisation: 5 minutes versus 10 minutes (p=0.004).<br>Dye volumes: 0 mls versus 14 mls (p<0.001).<br><br>Postoperative : not stated<br><br>Patient characteristics: Not stated. | Authors' conclusions:<br>'Cannulation of CS with the adjunct of an electrophysiology catheter to dedicated delivery systems significantly reduces procedural time, fluoroscopy time and contrast dye volume compared to a dye strategy.'<br><br>Comments:<br>Primary aim was to compare the use of an electrophysiology catheter aided positioning strategy with a conventional guiding catheter alone positioning strategy in terms of impact on CS cannulation time.<br><br>Consecutive patients<br>Randomisation using a computer generated random numbers series<br>Intention-to-treat analysis<br>Blinding not stated.<br>Follow-up completeness: full.<br>Comparison group: yes. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(O'Donnell et al 2005)<br><br>Location:<br>Austin Health, Heidelberg,Victoria, Australia<br><br>Study period: not stated.<br><br>Study type:<br>Prospective case series +comparison.<br><br>Level III-2 | Consecutive patients scheduled for CRT were invited to participate. 50 of 67 patients were selected with the other patients fulfilling exclusion criteria.<br>If a satisfactory LV lead position could not be attained, patients underwent implantation of a bifocal RV lead.<br><br>Follow-up:<br>12 months<br><br>Inclusion criteria:<br>NYHA Class II-IV despite optimal medical therapy<br>LV EF <35%<br>Ventricular dyssynchrony<br>Predominantly in sinus rhythm<br>LBBB with QRS >150ms, without over myocardial ischaemia.<br>Excluded patients with atrial fibrillation and patients receiving a combined CRT and ICD device. | Implantation success rate:<br>LV lead position was not successfully implanted in six patients (12%) because of coronary sinus occlusion in two, inability to obtain a stable lateral position in one and unacceptable capture threshold and/or diaphragm stimulation in three patients. These six patients underwent successful implantation of bifocal RV systems.<br><br>Perioperative: not stated<br><br>Postoperative:<br>Hospitalisation: Three patients were rehospitalised six times for heart failure (one with bifocal implant).<br>One patient with a BVT implant was rehospitalised four times and died of end stage heart failure.<br><br>Patient characteristics:<br>Bifocal versus biventricular systems:<br>Mean age 67 versus 64 years<br>Male 83% versus 82%<br>Previous CABG 50% versus 16%<br>Ischaemic aetiology 83% versus 48%<br>Mean LV EF 21% versus 23%<br>Mean QRS duration 168 ms versus 166 ms. | Authors' conclusions:<br>This non-randomised observational study suggests that clinical improvements conferred by BVT stimulation can be matched in selected patients by implanting a bifocal RV system. While the bifocal RV system should not be chosen as an initial treatment method, it may be an acceptable alternative in patients who have undergone unsuccessful LV lateral vein implantation attempts.<br><br>Comments:<br>Consecutive patients<br>Australian location.<br>Primarily reporting experience of implanting bifocal RV lead system when lateral LV pacing could not be achieved.<br><br>Blinding: unclear.<br>Follow-up completeness: unclear<br>Comparison: yes, internal. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Touiza et al 2001)<br>Location:<br>Brest University Hospital, Brest, France.<br><br>Study period:<br>Six-month period but dates not stated.<br><br>Study type:<br>Prospective comparative study with control.<br><br>Level III-2 | Aim was to assess the effects of LV alone versus CRT over six-month follow-up. Thirty-three patients receiving either LV (n=18) or CRT (n=15) pacing according to physician preference. Patient evaluations were performed at follow-up.<br><br>Follow-up:<br>Duration six month for all patients.<br><br>Inclusion criteria:<br><80 years, LBBB, no indication for pacing, severe heart failure, optimal pharmacological therapy. no recent myocardial infarction (<6 months), no recent bypass surgery, life expectancy (>1 year) due to non-cardiac causes, not a candidate for a heart transplant. | Postoperative events:<br>Deaths n=7 (CRT: n=3, LV: n=4, (1 sudden death, 6 due to cardiac decompensation). Pacemaker sepsis n=1 in CRT group (requiring explantation and re-implantation), lead dislodgement n=3 (CRT n=1, LV n=2).<br><br>Patient characteristics:<br>Mean age = 67 (6) years (CRT patients), 26/33 male, mean QRS = 187 (37) ms (CRT patients), mean LVEF = 22.1 (7) % (CRT patients), rhythm = SR (n=18) and AF (n=15), NYHA class III (n=13) and IV (n=20), aetiology = ischaemia n=13 (CRT n=7 and LV n=6), dilated n=20 (CRT n=8 and LV n=12). | Authors' conclusion:<br>'…a trend towards improvement was observed in objective parameters…following LV pacing. The two pacing modes …were associated with almost equivalent improvement of subjective and objective parameters.'<br><br>Comments:<br>Total mortality (21%) may reflect a sicker group of patients than some other studies.<br>Rhythm not specified in the patients with safety issues.<br>BiV and LV patients similar at baseline.<br>Satisfactory follow-up.<br>Consecutive patients.<br>Safety outcomes not a stated aim of the study.<br>No blinding.<br>External control group |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Bordachar et al 2004)<br><br>Location:<br>Hopital Cadiologique du Haut Levegne, Pessac, France<br><br>Study period:<br>Not stated<br><br>Study type:<br>Cohort with comparison<br><br>Level III-2 | 33 consecutive patients<br>LV lead inserted via a coronary sinus approach<br><br>Follow-up: 2 days<br><br>Inclusion criteria:<br>LVEF<40%<br>QRS>120msec<br>NYHA Class III/IV despite optimal medical therapy<br>PR interval ≥200msec<br>Exclusions: Atrial arrhythmias, primary mitral regurgitation, amyloidosis, previous valve replacement or reconstruction, hypertrophic obstructive cardiomyopathy, ongoing symptoms of myocardial ischaemia | Implantation success rate: 33/33 (100%)<br><br>Perioperative:<br>Acute LV lead dislodgement in one patient (3%).<br><br>Postoperative: not stated<br><br>Patient characteristics:<br>Age 69 years, Male n= 21 (64%), ischaemic heart disease 58%, previous MI 45%, primitive dilated cardiomyopathy 42%, NYHA class 3.2, LVEF 26%. ACE inhibitor 85%, AT1 receptor antagonist 15%, Beta blocker 79%, Diuretics 100%, Aldosterone antagonists 73%. | Authors' conclusions:<br>No safety-related conclusions<br><br>'Although LVP and BVP provide similar haemodynamic improvement, LVP results in more homogenous but substantially delayed LV contraction leading to shortened filling time and less reduction in post -ystolic contraction'.<br><br>Consecutive patients<br><br>No blinding<br>Follow–up: completeness unclear<br>Comparison group: LVP vs BVP |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Etienne et al 2001)<br><br>Location:<br>Brest University, Brest, France.<br><br>Study period:<br>Not stated.<br><br>Study type:<br>Prospective case series with sub-group comparisons between LV pacing and BiV pacing.<br><br>Level III-2 | Aim was to assess long-term effects of CRT on LV function and mitral regurgitation. 30 patients enrolled.<br>LV pacing n=18 or BiV pacing n=12. LV function evaluated by echocardiography and radionucleotide tests. Some comparisons between sub-groups who received just left ventricular pacing and those who received biventricular pacing<br><br>Follow-up:<br>Duration six months for all patients.<br><br>Inclusion criteria:<br>NYHA III or IV, stable over six months, LVEF <40%, LBBB, haemodynamic improvement during LV pacing, no other indication for pacing, informed consent. | Implantation:<br>Failure to catheterise CS n=5 (all received subsequent epicardial leads).<br><br>Postoperative:<br>Deaths n=7 (sudden death n=1, progressive heart failure n=6) of whom four had LV pacing and three CRT pacing. Three deaths in SR and four deaths in AF.<br><br>Patient characteristics (of the 23 survivors):<br>Mean age = 69 (7) years, 20/23 males. Mean QRS = 186 (31) ms, mean LVEF = 23.3 (7)%, rhythm = SR n=14 (7 receiving LV alone and 7 receiving BiV), AF n=9 (6 receiving LV alone and 3 receiving BiV), NYHA class III n=8, class IV n=15, aetiology = ischaemic (n=10), idiopathic (n=12), valvular (n=1). | Authors' conclusion:<br>'…LV-based pacing may significantly improve LV systolic function and decreases mitral regurgitation'.<br><br>Comments:<br>Only 10 received CRT pacing.<br>Sub-group comparison CRT versus LV pacing.<br>24 patients excluded prior to commencement as they did not improve in during an acute haemodynamic study. 7 patients died during the study period and were excluded from the study.<br>23 patients in LV and CRT groups comparable at baseline.<br>Adequate follow-up.<br>Consecutive patients.<br>Safety outcomes not a stated aim of the study.<br>No blinding.<br>Internal control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Zagrodzky et al 2001)<br><br>Location:<br>University of Texas, Fort Worth, USA.<br><br>Study period:<br>July 1998 – November 1999<br><br>Study type:<br>Prospective case series<br><br>Level III-3 | Aim was to assess the effect of BiV pacing on the inducibility of sustained monomorphic ventricular tachycardia. 14 patients enrolled: n=7 receiving CRT (test), n=7 receiving RV pacing (control). Controls were retrospective group of patients found to have inducible VT during the study period, test group was prospective.<br><br>Follow-up:<br>Duration not recorded (implantation and pacing modality study).<br><br>Inclusion criteria:<br>LVEF <35%, previous myocardial infarction, excluded if could not have sustained VT induced or if left ventricular pacing was not possible. | Implantation: No complications reported by authors.<br><br>Postoperative:<br>CRT pacing group: sustained VT no longer inducible in 5/7 patients c.f. no change (i.e. 0/7 patients) in control group. VF and/or ventricular flutter was induced in 3 patients receiving CRT.<br><br>Patient characteristics:<br>Limited descriptive information about patients. CRT group mean age = 62 years, 7/7 males, mean LVEF = 31%, mean QRS not given, rhythm not given, NYHA class not given.<br>All patients had inducible sustained VT. Aetiology = ischaemia (n=14). | Authors' conclusion:<br>'…acute CRT decreases the inducibility of sustained monomorphic VT in patients with ischaemic cardiomyopathy.'<br><br>Comments:<br>Comparability of groups not fully described.<br>Completeness of follow-up not stated.<br>Not stated if this was a consecutive series. Selected patients with some defined criteria.<br>Safety outcomes not a stated aim of the study.<br>No blinding.<br>Historical control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Res et al 2005)<br><br>Location:<br>Zans Medical Centre, Waterland Hospital, VU Medical Centre, The Netherlands<br><br>Study period:<br>Not stated.<br><br>Study type:<br>Comparison cohort<br><br>Level III-2 | Part of bifocal right ventricular apex pacing versus right ventricular outflow randomised trial comparing two positions for pacing. Bifocal RV pacing was performed in 40 consecutive patients with heart failure.<br>Positioning attempts, complications and overall procedure time were recorded.<br><br>Follow-up: up to 7 months.<br><br>Inclusion criteria: NYHA III, LVEF <35%, QRS >119 msec. | Implantation success rate: not stated<br><br>Perioperative:<br>AV block occurred in two patients during active fixation at the outflow tract.<br>Ventricular fibrillation was induced in one patient during advancement of the AP lead toward the apex, which was terminated with DC shock.<br><br>Postoperative:<br>One dislodgement of an active fixation atrial lead<br>One pocket haematoma<br>One late dysfunction of an outflow tract lead<br><br>Patient characteristics:<br>Mean age 69 years, Male (n=31, 78%), mean NYHA class 2.9, LV EF 24%, QRS width 180ms, PR interval 201ms. CAD 53%. Beta blocker 65%, ACE inhibitor, 88%, diuretics 75%, aldosterone blockade 30%, warfarin 100%, statins 33%, amiodorane 20%, digoxin 20%, long-acting nitrates 38%. | Authors' conclusions:<br>'Ease and success of lead implantation was similar in both positions.'<br><br>Comments:<br>Consecutive patients used<br><br>Blinding: unclear.<br>Follow-up completeness: unclear<br>Comparison group: internal control (crossover) group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Vogt et al 2004)<br><br>Location:<br>Ruhr University, Bochum, Germany<br><br>Study period:<br>Not stated.<br><br>Study type:<br>Cohort and comparison<br><br>Level III-2 | 313 patients followed post- implantation and measured event-free survival (sudden cardiac death, worsening heart failure requiring transplantation and implantation of ventricular assist devices). Description of single centre experience with CRT. Comparisons made with responders versus non-responders, sinus rhythm versus atrial fibrillation, dilated cardiomyopathy versus ischaemic origin.<br><br>Follow-up:<br>Mean follow-up 17.4 months<br><br>Inclusion criteria:<br>NYHA Class III-IV<br>LBBB with QRS ≥150 ms<br>LV EF <35%<br>LVEDD >60 mm<br>$VO_2$ peak <18 ml/min/kg | Implantation success rate: not stated<br><br>Postoperative: not stated<br><br>Postoperative:<br>Kaplan-Meier event-free survival 90% at one year and 80% at two years.<br><br>Patient characteristics:<br>Mean age 62 years, Male (n=234, 75%). Coronary heart disease n=110 (35%), dilated cardiomyopathy 56%, post valve replacement/end stage hypertrophic cardiomyopathy 9%. NYHA Class 3.1, peak $VO_2$ 13.0 ml/kg/min, 6-minute walking distance 312 metres, LVEDD 79.5 mm, LVEF 23.5%. | Authors' conclusions:<br>No safety-related conclusions.<br>'During midterm follow-up of 18months, dilated cardiomyopathy patients demonstrated a higher clinical benefit than patients with ischaemic heart disease. '<br><br>Comments:<br>Limited safety data<br>Coarse measure of event-free survival<br><br>Unclear if consecutive patients were used.<br>Blinding: not stated.<br>Follow-up completeness: unclear.<br>Comparison: internals comparisons. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Lecoq et al 2005)<br><br>Location:<br>Centre Hospitalier Universitaire, Rennes, France<br><br>Study period:<br>August 1994 – July 2001<br><br>Study type:<br>Case series with comparison group<br><br>Level III-2 | 139 consecutive patients successfully implanted with a CRT device. Endovenous LV lead used in all cases. Study population divided into two groups on the basis of the assessment of the clinical composite response.<br><br>Follow-up: 6 months<br><br>Inclusion criteria:<br>NYHA Class III or IV refractory to optimal medical management<br>LVEF<35% and LVEDD>60mm<br>Intraventricular conduction defect manifested by QRS>150 ms is patients with spontaneous ventricular activation or ≥200 ms in patients previously paced in the right ventricle. | Implantation success rate:<br>88% (Note: increased from 61% in 1994-6 to 98% in 2000-1).<br><br>Perioperative: not stated<br><br>Postoperative:<br>Deaths: total = n=6, endstage CHF n =4, one sudden death, one non-cardiac death.<br><br>Patient characteristics:<br>Mean age 68 years. Male (n=113, 81%). NYHA Class III 69%, NYHA Class IV 31%. Mean LVEF 21%. Mean QRS 188ms. Non-ischaemic dilated cardiomyopathy 54%, ischaemic heart disease 35%, miscellaneous disorders 11%, sinus rhythm n=94 (67%).. | Authors' conclusions:<br>No safety-related conclusions<br>'A positive response to CRT was observed in 73% of patients at 6 months and predicted by change in QRS.'<br><br>Comments:<br>Sinus rhythm in two-thirds of patients and atrial fibrillation in one-third of patients.<br>Consecutive patients<br>Retrospective study<br><br>Blinding: not stated.<br>Follow-up completeness: 99%<br>Comparison: internal comparison responders versus non-responders. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Reuter et al 2002)<br><br>Location:<br>University of Bordeaux, France & Broward General Hospital, Fort Lauderdale, USA.<br><br>Study period:<br>Unclear.<br><br>Study type:<br>Prospective case series, some comparisons between responders versus non-responders.<br><br>Level III-2 | Aim was to assess the clinical response to CRT over a 1-year follow-up and its relationship to echocardiograph and haemodynamic data. 102 patients enrolled. Echocardiography, quality of life and electrocardiography data included in a multivariate analysis.<br><br>Follow-up:<br>Duration12 months for all patients.<br><br>Inclusion criteria:<br>Severe drug resistant heart failure. No RBBB. | Implantation:<br>Failure to implant LV lead via transvenous approach n=13 (all received transseptal LV leads).<br><br>Postoperative events:<br>Deaths n=11 (progressive heart failure n=5, ventricular arrhythmias n=6), LV lead dislodgement n=4, CS dissection n=1 (received transseptal lead subsequently).<br><br>Patient characteristics:<br>Mean age = 64 (11) years, 87/102 male, mean QRS 184 (38) ms, mean LVEF = 24 (8)%, rhythm = SR n=83, AF n=19, NYHA class II n=8, class III n=63, class IV n=31, aetiology = not stated. Repeat hospitalisations = 0.5 (0.3) in responders to CRT cf 3.4 (1.2) in non-responders (no decrease in NYHA class and no decrease in Minnesota score). | Authors' conclusion:<br>'…study confirmed long-term beneficial haemodynamic and clinical effects of CRT. Patients who are not improved are likely to have had a myocaridal infarction, a low cardiac output, and no significant mitral regurgitation.'<br><br>Comments:<br>13 patients who received trans-septal leads received long-term anticoagulation.<br>Inclusion criteria: not fully stated.<br>Non-responders were defined as no clinical improvement (no decrease in NYHA class associated with no decrease in quality of life score) at 12 months follow-up.<br>No baseline comparison of study groups.<br>Satisfactory follow-up<br>Patients were consecutive.<br>Safety outcomes not a stated aim of the study.<br>Blinding of outcome assessment only.<br>Internal control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Bax et al 2004)<br><br>Location:<br>Leiden University Medical Centre, The Netherlands<br>University of Queensland, Australia<br><br>Study period:<br>Not stated<br><br>Study type:<br>Cohort with comparison<br><br>Level III-2 | 85 patients. LVEF, LV volumes and severity of mitral regurgitation measured before implantation. Clinical status assessed at baseline and 6 months: NYHA class, QoL, 6 minute walk test.<br>LV pacing lead inserted transvenously via subclavian route.<br><br>Follow-up:<br>1-year (hospitalisation and survival).<br><br>Inclusion criteria:<br>NYHA Class III/IV<br>LVEF≤35%<br>QRS≥120ms<br>Excluded: Patients with AF or previously implanted pacemaker. | No procedure related complications.<br><br>Implantation success rate: 85/85 (100%)<br><br>Perioperative: No complications.<br><br>Postoperative:<br>Six patients died with worsening heart failure within 6 months of implantation. Overall, there were seven deaths, including one non-cardiac death during the total follow-up. There were nine hospitalisations for decompensated heart failure.<br><br>Patient characteristics:<br>Age 66 years, Male (n=64, 75%), Previous MI 46%, NYHA class III 80%, Ischaemic aetiology 55%, QRS 178 ms, LVEF 23%. Diuretics 98%, ACE inhibitors 95%, Spironolactone 54%, Beta-blockers 84%, Amiodarone 41%. | Authors conclusions:<br>No safety related conclusions<br>'Patients with LV dyssynchrony > 65 ms respond to CRT and have an excellent prognosis after CRT.'<br><br>No results related to specific devices<br>N=48 receive ICD<br><br>Consecutive patients were used.<br><br>Blinding not stated<br>Follow-up completeness: 80/80 at 6 months and 5 deaths<br>Comparison group: responders versus non-responders |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Penicka et al 2004)<br><br>Location:<br>Presumed to be Belgium<br><br>Study period:<br>Not stated<br><br>Study type:<br>Cohort with internal comparison group<br><br>Level III-2 | Investigation into predictive factors of LV functional recovery and reversed remodelling using baseline and follow-up measurements from echocardiography and pulsed wave Doppler imaging. At 6 months comparisons were made between responders and non-responders to therapy.<br><br>Follow-up: 6 months<br><br>Inclusion criteria:<br>NYHA class II or greater for >12 months due to idiopathic or ischaemic cardiomyopathy. Stable medication for >3 months. Wide QRS complexes (QRS >130 ms), or BBB, LVEF <35%. Acute coronary syndrome or revascularisation were exclusions. | Safety results: 55 patients<br><br>Implantation success rate: 53/55 (96%)<br><br>Perioperative:<br>1 death a few hours after implantation due to cerebral bleeding.<br><br>Postoperative:<br>Diaphragmatic stimulation (n=1).<br><br>Mortality:<br>2 deaths due to ventricular fibrillation at 3 months and 4 months post-implant.<br><br>Patient characteristics: Age= 70 +/- 6 years, Male = not stated, ischaemic = 44% and idiopathic = 56%, NYHA = 3.2+/- 0.9, QRS = 182 +/- 30 ms, SR = 93%. | Authors' conclusions:<br>No safety conclusions.<br>'The combined index of intraventricular and interventricular asynchrony accurately predicts LV functional recovery and reversed remodelling after biventricular pacing. The use of such as a parameter may help to select patients who will benefit most from biventricular pacing. Its true clinical and prognostic benefit remains to be confirmed in a large prospective trial.'<br><br>Comments:<br>An uncertain number of patients also received an implantable defibrillator.<br>Baseline data that included the deaths not given (study primarily evaluated patients who achieved 6 mths follow-iup).<br><br>Consecutive series.<br><br>Blinding: no<br>Follow-up completeness: 49/55 (89%)<br>Comparison group: Internal |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Yu et al 2003a)<br><br>Location:<br>Chinese University of Hong Kong and University of Hong Kong, Hong Kong.<br><br>Study period:<br>Not stated<br><br>Study type:<br>Cohort with internal Comparison group<br><br>Level III-2 | Echocardiography with tissue Doppler was performed at baseline and 3 months after implantation of biventricular pacing. 17 responders to reverse remodelling (defined as a reduction in LV end-systolic volume by >15% ) were compared to 13 non-responders in relation to 6-minute walk distance, peak oxygen uptake, NYHA class, quality of life and ejection fraction, diastolic filling time, myocardial performance index, isovolumic relaxation time, systolic dyssnchrony. Univariate and multivariate analyses were undertaken.<br><br>Follow-up: 3 months<br><br>Inclusion criteria:<br>NYHA III or IV, LVEF <40%, QRS > 140 ms. | Implantation success rate:<br>'Pacemakers were successfully implanted in all (30/30) patients'.<br><br>Perioperative: not stated<br><br>Postoperative:<br>At 3 months follow-up biventricular pacing was successfully maintained in all patients. No patients were pacing dependent.<br><br>Patient characteristics:<br>21 (70%) male, mean age = 62 +/- 14 years, NYHA III = 18 (60%) and IV = 12 (40%). 17/30 (57%) had LBBB and 13 (43%) intraventricular conductional delay. PR >200 ms in 15 patients. Ischaemic aetiology =12 (40%) and non-ischaemic in 18 (60%). Mean 6-min walk = 328 metres. | Authors' conclusions:<br>No safety conclusions.<br>'Responders of LV reverse remodelling were associated with improvement in clinical status, cardiac function and systolic synchronicity. Direct assessment of systolic synchronicity by tissue Doppler imaging is highly accurate in predicting responders to therapy'.<br><br>Comments:<br>The study was primarily investigating predictors of left ventricular remodelling.<br>Selected series.<br><br>Blinding: No<br>Follow-up completeness: Full<br>Comparison group: Internal control |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Barbieri et al 2004)<br><br>Location:<br>Modena, Italy<br><br>Study period:<br>Nov 2001 – April 2003<br><br>Study type:<br>Cohort with concurrent controls<br><br>Level III-2 | 18 patients<br>Evaluations performed at baseline, day after and 3 and 6 months later. Evaluations included ECG, Echocardiography, 6-minute walk test, QoL.<br><br>Follow-up: 6 months<br><br>Inclusion criteria:<br>NYHA Class III/IV despite optimal medical therapy.<br>Clinically stable at time of implantation and without any modifications of their drug regimens in the previous month except minor dose adjustments to diuretics.<br>LVEF<35%<br>LBB with QRS>120ms<br><br>Exclusion criteria:<br>His ablation for atrial fibrillation within the past 3 months, unstable angina, revascularisation within 6 months, MI within 3 months, traditional indications for pacemaker or ICD. | One other patient needed a second procedure due to inability of identifying coronary sinus during the first procedure (second procedure used coronary angiography guidance).<br>Mean operative time: 65.4 minutes, mean fluoroscopy time: 33.6 minutes.<br>No hospital admissions in 6 months after implantation<br><br>Implantation success rate: not stated.<br><br>Perioperative:<br>One coronary sinus dissection.<br><br>Postoperative:<br>Number of hospitalisations:<br>6 months before = 1.5 and 0 after 6 months (p=0.08), number of inpatient days = 8 6 months before and 6 months post-implant (p=0.06).<br>Two patients died before the first outpatient examination.<br><br>Patient characteristics:<br>Age 67.5 years, Male (n=13, 72%), Ischaemic aetiology 67%, NYHA Class III (77%), LVEF 23%, Baseline QRS 157.9ms, Atrial fibrillation 33%. Past history MI 39%. Mean duration of heart failure 40.5 months. | Authors' conclusions:<br>No safety related conclusions.<br>'CRT reduces left ventricular volumes'.<br><br>Comments:<br>2 deaths prior to implantation<br>Atrial fibrillation 33%.<br>Small sample<br><br>Unclear if patients were consecutive or selected.<br><br>Blinding: No<br>Follow-up completeness: 16/16 (100%)<br>Comparison group: Yes, responders versus non-responders |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Oguz et al 2002b)<br><br>Location:<br>Trakya University, Edirne, Turkey.<br><br>Study period:<br>Not stated.<br><br>Study type:<br>Prospective case series some comparisons with responders versus non-responders.<br><br>Level III-2 | Aim was to assess whether long-term benefit of CRT could be assessed from echocardiographic parameters. Echocardiography assessments of 16 patients.<br><br>Follow-up: Duration 7.6 +/- 5 months.<br><br>Inclusion criteria:<br>NYHA class III or IV, LVEF <40%, symptoms despite optimised drug treatment, QRS >120 msec or >200 ms in those already implanted with a DDD pacemaker. | Implantation: No information given.<br>Postoperative: deaths n=3 (all due to progressive heart failure).<br><br>Patient characteristics:<br>Mean age = 59 (10) yrs, all males, mean QRS = 167 (25) ms, mean LVEF = 26 (8) %, rhythm = not stated but all patients had LBBB, NYHA class III n=4, class IV n=12, aetiology = ischaemia (n=10), idiopathic (n=5), previous valve disease (n=1). | Author's conclusion:<br>'Patients with longer QRS and mitral regurgitation are more likely to benefit from CRT.'<br><br>Comments:<br>Limited comparison of baseline characteristics of groups.<br>Responders defined as those with symptomatic improvement of one or more NYHA functional class compared to non-responders at follow-up.<br>Follow-up: Satisfactory.<br>Consecutive patients.<br>Safety outcomes: Not a stated aim of the study.<br>No blinding.<br>Internal control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Capasso et al 2005)<br><br>Location: Casaedi Cura, Maddaloni, Italy<br><br>Study period: not stated<br><br>Study type:<br>Case series with comparison<br><br>Level III-2 | Correlation of effects of CRT on LV systolic function with wall motion synchrony assessed by echocardiography.<br>Transvenous LV pacing performed in all patients.<br><br>Follow-up: 1 year<br><br>Inclusion criteria:<br>NYHA Class III/IV on optimal drug therapy<br>LV EF ≤ 35%<br>QRS ≥ 150ms with LBBB.<br><br>Exclusion criteria:<br>Acute coronary syndrome and/or coronary revascularisation in the previous 6 months. | Implantation success rate: not stated<br><br>Perioperative: not stated<br><br>Postoperative:<br>Deaths (n=3) from refractory heart failure after 6 months.<br><br>Patient characteristics:<br>Mean age 68.9 years. Male (n=11, 73%). Mean QRS 163ms, LVEF 25%, NYHA Class III (n=6), Class IV n=9), Ischaemic cardiomyopathy n=9, idiopathic cardiomyopathy n=6. | Authors' conclusions:<br>No safety conclusions<br>'Delayed long contraction was the best among intraventricular asynchrony indexes in predicting increases in LVEF after CRT'.<br><br>Comments:<br>Primary aim was to correlate the effects of CRT on LV systolic function with wall motion synchrony assessed by tissue doppler echocardiography.<br><br>4/15 received ICD<br><br>Consecutive patients<br><br>No blinding<br>Follow-up completeness: Unclear<br>Comparison group: responders versus non-responders. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Lunati et al 2002)<br><br>Location:<br>Nigurda Hospital, Milan, Italy.<br><br>Study period:<br>March 1999 – October 2000.<br><br>Study type:<br>Retrospective case series some comparisons between responders versus non-responders.<br><br>Level III-3 | Aim was to assess baseline pathophysiological characteristics of patients receiving CRT with outcome to identify patients most likely to benefit from this treatment.<br><br>Case series of 52 patients studied with echocradiography, functional activity and quality of life data. Very diverse group of patients: atrial + CRT (n=44) vs non-atrial CRT (n=8) only, epicardial (n=6) and transvenous pacing (n=46), CRT + ICD (n=11) vs CRT only (n=41), concomitant valvular surgery (n=4).<br><br>Follow-up:<br>Duration 348+/-154 days.<br><br>Inclusion criteria:<br>'Persistent heart failure symptoms with unacceptably poor quality of life despite optimised medical treatment'. | Implantation: No information given.<br><br>Postoperative:<br>Deaths n=5 (sudden n=1, 'noncardiac cause' n=1, progressive heart failure n=3). Actuarial survival = 87% at 12 months.<br><br>Patient characteristics:<br>Mean age = 61 (8) years, 46/52 male, mean QRS = 195 (33) ms, mean LVEF = 26.4 (8)%, rhythm = SR n=37, AF n=3 (further information not given), NYHA class II n=2, class III n=38, class IV n=12, aetiology = dilated cardiomyopathy n=26, ischaemia n=18, other n=8. | Authors' conclusions:<br>'Basal demographic, clinical, and functional characteristics do not appear to help in the preliminary selection of responders.'<br><br>Comments:<br>Retrospective assessment of responders versus non-responders.<br>Groups broadly similar at baseline.<br>Completeness of follow-up not stated.<br>Not stated if consecutive series and selection criteria not given.<br>Safety outcomes not a stated aim of the study.<br>No blinding.<br>Internal control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Tsurugaya et al 2004)<br><br>Location:<br>Gunma University Hospital, Japan<br><br>Study period:<br>Not stated.<br><br>Study type:<br>Case series and comparison.<br><br>Level III-3 | SPECT performed in 10 patients before and within one month after CRT implantation. Comparison made of responders versus non-responders on basis of clinical status and echo findings after follow-up.<br><br>Follow-up: 1 month.<br><br>Inclusion criteria:<br>NYHA Class III-IV despite maximal pharmacologic therapy.<br>LV EF <35%<br>QRS ≥ 140ms. | Implantation success rate: not stated<br><br>Perioperative: not stated<br><br>Postoperative:<br>Death: One death due to worsening heart failure<br>Hospitalisation: Three hospitalisations due to worsening heart failure.<br><br>Patient characteristics:<br>Mean age 62 years (range 52-76), Male (n=6, 60%). NYHA Class III 30%. Diuretics 100%, ACE inhibitor 80%, Beta blockers 90%. Idiopathic dilated cardiomyopathy 70%, ischaemic cardiomyopathy 30%. | Author's conclusions:<br>No safety related conclusions.<br><br>Comments:<br>Primarily evaluating the usefulness of quantitative gated SPECT to assess ventricular synchrony<br>2 in atrial fibrillation<br>LV lead placed surgically in an epicardial location in three patients.<br>Small sample size<br><br>Unclear if consecutive patients were used.<br><br>Blinding: unclear.<br>Follow-up completeness: unclear.<br>Comparison group: internal. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(De Cock et al 2004)<br><br>Location:<br>VU University Medical Centre, Amsterdam, The Netherlands<br><br>Study period:<br>Not stated<br><br>Study type:<br>Case series with comparison group<br><br>Level III-2 | 77 consecutive patients.<br>Description of experience with new technique. Triple puncture of left subclavian vein used to introduce separate guidewires for three leads under conscious sedation.<br><br>Follow-up: 6 months.<br><br>Inclusion criteria:<br>NYHA Class III/IV<br>LVEF<0.35 | Six patients had repetitive intraoperative lead dislocation. However, a retained guidewire technique was successfully applied in all six of these cases.<br><br>Implantation success rate: 73/77 (95%)<br><br>Perioperative: Major coronary sinus dissection (2 patients)<br>Perforation (1 patient)<br>Unacceptably high pacing threshold (1 patient)<br><br>Postoperative:<br>Deaths: Three deaths during 6-month follow-up (two sudden deaths, one refractory heart failure)<br>Hospitalisations: Six hospitalisations due to worsening heart failure.<br><br>Phrenic nerve stimulation (n=4) – 2 required repositioning<br>Lead dislocation (n=4)<br><br>Patient characteristics: Not stated. | Authors' conclusions:<br>The technique described for CRT implantation could be applied with all currently available over-the-wire leads. Its use should be only considered when all other measures to obtain a stable LV lead position have failed.<br><br>Comments:<br>No sample details<br>Consecutive sample<br>No blinding<br>Follow up rate 100%<br>Comparison group: Repetitive dislocation group versus rest. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Ellery et al 2005)<br><br>Location:<br>23 Centres, 8 countries:<br>Austria, Brazil, France, Germany, Hungary, Italy, The Netherlands, United Kingdom.<br><br>Study period:<br>October 2003 – June 2004<br><br>Study type:<br>Prospective case series<br><br>Level III-2 | Implantation of a new transvenous LV lead using either an over-the-wire technique or a stylet-driven lead in 96 patients. Comparisons with steroid and non-steroid eluting stylet.<br><br>Follow-up:<br>12 months<br><br>Inclusion criteria:<br>Indications for CRT and optimised drug treatment for heart failure. | Implantation success rate: (LV lead) 85/96 (89%). Coronary sinus not identified in one patient. Following successful LV lead implantation, 71 patients (84%) underwent implantation of CRT and 14 (16%) received ICD-CRT systems.<br><br>Perioperative:<br>Mean duration of successful implant procedures: 112 minutes.<br>Unsuccessful LV lead implantations and adverse events:<br>Small coronary venous system – n=1 (epicardial implantation succeeded)<br>Inability to advance the lead into target vessel (n=1)<br>Inability to find a stable lead position (n=4)<br>Lead dislodgement while removing guiding sheath (n=2)<br>Phrenic nerve stimulation (n=1)<br>Superior vena cava perforation/pneumothorax (n=1)<br><br>Postoperative:<br>Loss of LV capture (n=3)<br>Phrenic nerve stimulation (n=6)<br>Deaths (n=2) due to heart failure.<br><br>Patient characteristics:<br>Mean age 68 years (range 34-83), Male 76%. NYHA Class III 83%, NYHA Class IV 17%. Mean QRS 163 ms. Ischaemic heart disease 38%. | Authors' conclusions:<br>Ability to switch between over-the-wire and stylet-driven techniques during implantation offers procedural flexibility to the physician. The current follow-up period is too short to precisely assess the postoperative complication rate associated with the LV lead.<br><br>Comments:<br>Vague inclusion criteria<br>Unclear if consecutive patients were used<br>Follow-up completeness unclear but follow-up period limited to 12 months.<br>Blinding: not stated.<br>Comparison group: yes. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Ermis et al 2004)<br><br>Location:<br>University of Minnesota Medical School, USA<br><br>Study period:<br>Jan 1998 to December 2002<br><br>Study type:<br>Cohort<br><br>Level III-2 | 158 referred for CRT. Patients with a successful implantation were prospectively followed.<br>Comparison of mortality with patients receiving ICD (n=62) with pacing alone (n=64).<br><br>Follow-up:<br>Minimum 12 months<br>Mean: 18 months for pacing group.<br><br>Inclusion criteria:<br>Successful implantation of CRT-ICD or CRT<br>Refractory heart failure<br>Pacing indications included sick sinus, AV block and sinus bradycardia. | Implantation success rate: 126/158 (80%).<br><br>Perioperative:<br>No procedure-related deaths or complications that lengthened hospital stay.<br>LV lead repositioning required in one patient.<br><br>Postoperative:<br>Mean 1.8 hospitalisations for heart failure during follow up in the CRT group (comparable to ICD group with 1.2 hospitalisations).<br>26 deaths in the CRT group (41%). (Mortality lower in ICD group 13% mortality (8 deaths).<br><br>Patient characteristics (of the 126 successful implantations):<br>Mean age 69 years, Male (n=96, 76%). Mean LV EF 22%. NYHA Class III or IV 87%. | Authors' conclusions:<br>ICD offers survival benefit compared to pacing alone. Predominant survival benefit may become most evident after 12 months follow-up.<br><br>Comments:<br>CRT-ICD inserted in 62 and CRT in 64.<br>Mode of death is unclear.<br>Wide inclusion criteria.<br>Consecutive patients<br><br>Blinding: not stated.<br>Follow-up completeness: unclear.<br>Comparison of CRT-ICD and CRT |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Alonso et al 1999)<br><br>Location:<br>Centre Cardio-Pneumologique, Hôpital Pontchaillou, Rennes, France.<br><br>Study period:<br>August 1994 – June 1998.<br><br>Study type:<br>Retrospective case series with some comparative analysis between two groups.<br><br>Level III-3 | Aim was to assess if QRS modifications induced by CRT and the anatomical positioning of leads could predict the long-term effectiveness of CRT. 26 patients received CRT. Comparison between responders versus non-responders.<br><br>Follow-up:<br>Duration 7.5 (4) months.<br><br>Inclusion criteria:<br>Severe heart failure NYHA classes III or IV, refractory to optimised drug treatment, LVEF <35%, LVED>60 mm, QRS >120 ms. Successful implantation was also an inclusion criteria. | Implantation: None reported<br>Postoperative: Deaths n=4 (15%) (causes not reported).<br><br>Patient characteristics:<br>Mean age = 66 (7) yrs, male 24/26, mean QRS = 178 (24) ms, mean LVEF = 23 (8)%, rhythm = SR n=20, n=6 in AF, NYHA class III n=18, class IV n=8., aetiology: ischaemia (n=9), idiopathic (n=14), valvular (n=3). | Authors' conclusion:<br>'The only parameter that differed significantly … was the QRS duration under biventricular pacing.'<br><br>Comments:<br>May include data subsequently reported in Leclercq et al (2000a)5}a), Leclercq et al (2000b)1}c) and/or Alonso et al (2001)1}1).<br>Some comparisons were made between responders and non-responders to the therapy.<br>Responders were defined according to survival with improved symptoms (at least I class improvement in NYHA) and exercise tolerance (>10% on baseline $VO_2$).<br>Groups were broadly similar at baseline.<br>Completeness of follow-up not stated.<br>Selected patients with defined criteria.<br>Safety outcomes not a stated aim of the study.<br>No blinding.<br>Internal comparison group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author: Gasparini 2003 (Gasparini et al 2003e, Gasparini et al 2003b, Gasparini et al 2003f)<br><br>Location: Milano, Italy.<br><br>Study period: October 1999 – April 2002.<br><br>Study type: Cohort<br><br>Level III-2 | Longitudinal observational study patients with heart failure. Baseline electrocardiogram and echocardiograph evaluations. Comparisons between patients either with or without coronary artery disease. Re-evaluations at 3, 6 and 12 months then yearly.<br><br>Follow-up:<br>Median follow-up time = 11.2 +/- 4 months<br><br>Inclusion criteria:<br>NYHA II-IV, LVEF<40%, QRS>110ms, at least one hospitalisation for heart failure in last 12 months. | Safety results: 158 patients<br><br>Implantation success rate: 158/159 (99.5%)<br><br>Perioperative: not stated<br><br>Postoperative:<br>The hospitalisation rate before implantation was 21- 24 (95% CI: 19-22 and 22-26) per 100 patient-year. The rate after implantation was 2 – 2.9 (1.1-3.3 and 1.8-4.5) per 100 patient year.<br><br>Survival:<br>14 patients died. Mortality rates were 8.5-9.4 (4.1-17.9 and 4.5 -19.7) per 100 person-year. Cumulative probability of surviving one year was between 90-92.8% (79.2-96.2% and 83.4-96.9%).<br><br>Patient characteristics:<br>Males = 121 (77%), Mean age = 65 years, mean LVEF = 29%, mean QRS = 174ms, NYHA III = 127 (80%), IV = 31 (20%), coronary artery disease = 75 (47%). | Author's conclusions:<br>'The study shows that the benefits of CRT should not be denied to patients on the basis of the underlying cardiac pathology''; and 'Significant improvement was observed over time regardless of the LV stimulation site.'<br><br>Comments:<br>Studies designed to assess response to therapy in relation to presence or absence of coronary artery disease or placement site of lead.<br>Presence of coronary artery disease not clearly defined.<br>56 patients received an implantable defibrillator.<br><br>Selected series<br><br>Blinding: unclear<br>Follow-up assumed complete<br>Comparison group: Internal comparison group |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Leclercq et al 2004)<br><br>InSynch trial<br><br>Location:<br>France and Canada<br><br>Study period:<br>August 1997 – November 1998<br><br>Study type:<br>Case series with internal comparisons.<br><br>Level III-2 | 103 patients. This paper focuses on outcome in sub-groups of patients with and without coronary artery disease.<br><br>Follow-up: 12 months<br><br>Inclusion criteria:<br>NYHA Class III or IV persisting for > one month despite optimal medical therapy<br>LVEF<35% and LVEDD >60mm<br>Intraventricular conduction delay with QRS>150ms.<br>Stable sinus rhythm<br>Age >18 years<br>Signed informed consent. | Implantation success rate: 103/117 (88%)<br><br>Postoperative: not stated<br><br>Postoperative:<br>12-month survival 78% in both groups.<br>Deaths: n=21. Among the ischaemic group deaths = 10 (sudden n=6, heart failure n=2, non-cardiac n=2). Among the non-ischaemic group deaths n=11 (sudden n=4, heart failure n=5, non-ischaemic n=2).<br><br>Patient characteristics:<br>Ischaemic versus non-ischaemic:<br>Mean age 70 versus 65 years, Male 92% versus 67%, Mean QRS 180 ms versus 176 ms, LVEF 22 versus 22%, mean NYHA class 3.3 versus 3.3, 6-minute walking distance 289 versus 290 metres. Ischaemic aetiology n=48, non-ischaemia n=55. | Authors' conclusions:<br>There was no excess mortality in ischaemic patients compared with non-ischaemic patients. Pacing improves functional status regardless of aetiology.<br><br>Comments:<br>Primarily comparing outcome between patients with and without ischaemia.<br>Observational results from InSynch RCT<br><br>Selected series with criteria.<br><br>Blinding: unclear<br>Follow-up completeness: unclear.<br>Comparison group: ischaemia versus non-ischaemia. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author: Molh<br>(Molhoek et al 2004c)<br><br>Location: Leiden University Medical Centre, Rotterdam, Netherlands<br><br>Study period:<br>Not stated<br><br>Study type: Cohort with internal comparison group<br><br>Level III-2 | The aetiology of cardiomyopathy was defined at baseline as due to ischaemia (presence of >50% coronary stenosis) or non-ischaemia (no stenosis). Follow-up tests evaluated NYHA class, Minnesota Quality of Life, QRS duration, LVEF and mitral regurgitation (assessed by echocardiography). Long-term follow-up including survival and hospitalisation rates were obtained up to 3 years. Evaluation was made before and after implantation and up to 3 years.<br><br>Follow-up: Up to 3 years<br><br>Inclusion criteria:<br>NYHA class III or IV, LVEF <35%, QRS>120ms, LBBB. | Safety results: 74 patients<br><br>Implantation success rate: not stated<br><br>Perioperative: not stated<br><br>Postoperative:<br>Survival:<br>9 patients died during follow-up, 6 due to progressive heart failure, 1 sudden cardiac death, 2 non-cardiac causes.<br>Hospitalisation:<br>Among patients with idiopathic cardiomyopathy (n=40) hospitalisations decreased from an average of 3.8+/- 5.1 days/year before implantation to 0.6 +/-1.5 days/year (p<0.05). The number of annual hospitalisations per patient decreased from 0.7+/- 1 before to 0.2+/-0.3 after implantation (p<0.05). Mean follow-up 14.2 +/-7.8 months.<br>Among those with ischaemic cardiomyopathy (n=34), patients were hospitalised on average 3.9+/-4.8 days/year compared to 0.5+/-1.9 days/year after implantation (p<0.05). The number of annual hospitalisations per patient decreased from 0.8+/-1.2 before to 0.1+/-0.5 after implantation (p<0.05). Mean follow-up = 13.8+/- 6.8 months.<br><br>Patient characteristics: male = 54/80 (68%), mean age = 64+/- 8 years, NYHA III (85%), mean NYHA class = 3.2 +/- 0.5, mean QRS = 177 +/-29 ms, mean LVEF = 22%. 6-min walk = 280 metres. Diuretics all patients, ACE inhibitors = 85%, b-blockers = 60%, spironolactone = 42%, amiodarone = 30%. | Authors' conclusions:<br>'The underlying aetiology of heart failure was not related to the response to cardiac resynchronisation therapy.'<br><br>Comments:<br>34/74 patients also received an implantable defibrillator.<br>Discrepancies in the length of follow up: up to 2 and 3 yrs reported<br>Not possible to disentangle hospitalisations related to the procedure.<br>Appears that deaths were not related to the procedure.<br><br>Consecutive series.<br><br>Blinding: in assignment of mortality unclear<br>Follow-up completeness: Full<br>Comparison group: Internal |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Achilli et al 2003)<br><br>Location:<br>Belcolle Hospital, Viterbo, Italy and S Guiseppe Hospital, Albano Laziale, Italy.<br><br>Study period:<br>February 2000-March 2002.<br><br>Study type:<br>Prospective cohort with internal Comparison group.<br><br>Level III-2 | Patients with echocardiographic evidence of interventricular and intraventricular asynchrony were divided into 2 groups with either a QRS duration >120 ms or QRS <120 ms. Follow-up measurements included functional class, 6-min walk, EF, LVEDD, mitral regurgitation area, interventricular delay and deceralation time. Echocardiograph performed by 2 clinicians unaware of clinical status.<br><br>Follow-up:<br>Mean period = 546 +/- 277 days. Data collected at implantation, before discharge, then at 1, 3 and 6 months followed by every 6 months.<br><br>Inclusion criteria:<br>NYHA III or IV, dilated cardiomyopathy of any origin, SR or pacemaker induced rhythm. Exclusions were atrial fibrillation, restrictive or hypertrophic cardiomyopathy, valvular disease, acute coronary syndrome, severe chronic obstructive pulmonary disease or inability to walk.<br>EF≤35% and echo evidence of inter or intra ventricular synchrony.<br>Clinically stable for > 30 days. | Safety results: 52 patients.<br><br>Implantation success rate: 49/52 successfully transvenously implanted. Remaining 3 implanted epicardially.<br><br>Perioperative<br>Not stated.<br><br>Postoperative:<br>Survival: 10 deaths (19.2%), due to sudden cardiac deaths (n=5), progressive heart failure (n=4), non-cardiac death (n=1).<br><br>Patient characteristics:<br>Mean age = 69.6 +/- 9years, ischaemic origin n= 21 (40%), idiopathic n= 31, male = 60%, NYHA mean = 3.5 +/- 0.5, mean LVEF = 23.2 +/- 4.7%, mean QRS = 152.6 +/- 32 ms. Previous pacemaker 11.5%. | Authors' conclusions:<br>No safety related conclusions.<br>'Resynchronisation therapy determined clinical and functional benefit that was similar in patients with wide and narrow QRS. Resynchronisation therapy may be helpful in patients with echocardiographic evidence of interventricular and intraventricular asynchrony and incomplete left bundle branch block.'<br><br>Comments:<br>Biventricular pacing introduced transvenously in 49/52 patients.<br>Among the deaths it is unclear what proportion was attributed to implantation or the device.<br>Minor discrepancies in baseline characteristics.<br>Consecutive series.<br>Blinding. No<br>Follow-up completeness: Full<br>Comparison group: Internal comparison group |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Yu et al 2004)<br><br>Location:<br>Prince of Wales Hospital, Hong Kong<br><br>Study period:<br>Not stated.<br><br>Study type:<br>Prospective series.<br><br>Level III-2 | 58 patients. Compared patients with QRS 120-150 ms with patients with QRS >150 ms. Clinical assessment at baseline and 3 months after CRT. LV lead inserted transvenously.<br><br>Follow-up: 3 months.<br><br>Inclusion criteria:<br>NYHA Class III-IV on optimal medical therapy<br>LV EF <40% | Implantation success rate: not stated<br><br>Postoperative : not stated<br><br>Postoperative:<br>Deaths: Four deaths before 3 month assessment.<br><br>Patient characteristics:<br>Age 66 years, Male 66%. NYHA Class III 74%, NYHA Class IV 26%. | Authors' conclusions:<br>No safety related conclusions.<br>'Improvement in symptoms, exercise capacity and quality of life was observed in both QRS groups.'<br><br>Comments:<br>Primary focus was on efficacy of CRT in patients with mildly prolonged QRS duration.<br>4 received an ICD.<br>Limited safety related data<br>Unclear if consecutive patients were used.<br>Blinding: not stated.<br>Follow-up completeness: unclear.<br>Comparison group: internal. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Sciagra et al 2004)<br><br>Location:<br>University of Florence, Florence, Italy.<br><br>Study period:<br>Not stated<br><br>Study type:<br>Cohort with internal Comparison group<br><br>Level III-2 | Baseline perfusion gated SPECT before implantation and during follow-up. LVEF, EDD and wall motion index measured and compared with clinical outcome. Patients were classified according to presence/absence of a significant perfusion defect at baseline.<br><br>Follow-up: 3 months<br><br>Inclusion criteria:<br>NYHA III or IV, LVEF <35%, QRS > 120msec. CRT for persisting symptoms despite optimal medical treatment. | Safety results: 20 patients<br><br>Implantation success rate:<br>'Implantation successful and uncomplicated for all patients'.<br><br>Perioperative:<br>'Implantation successful and uncomplicated for all patients'.<br><br>Postoperative:<br>Survival: 1 patient died at 2 months follow-up due to pump failure.<br><br>Patient characteristics:<br>Male = 17 (85%), mean age = 66.8 +/- 12.6 years, NYHA III n=18 (90%), IV n= 2 (10%), ischaemic cardiomyopathy n=8 (40%). | Authors' conclusions:<br>No safety conclusions.<br>'Perfusion gated SPECT appears useful to characterise and follow-up candidates for resynchronisation therapy. Despite clinical improvement patients with severe resting perfusion did not show significant improvement'.<br><br>Comments:<br>Primarily evaluating SPECT.<br>Small sample.<br>Consecutive series.<br>Blinding. No<br>Follow-up completeness: 19/20<br>Comparison group: Internal comparison group |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Rossillo et al 2004)<br><br>Location:<br>Venice, Italy and Cleveland, USA<br><br>Study period:<br>Not stated.<br><br>Study type:<br>Prospective series<br><br>Level III-2 | 233 consecutive patients with a successful transvenous implant. Comparison of clinical response, mortality between 66 patients who received leads in anterior and anterolateral branches and 167 who received leads in lateral or posterolateral braches of coronary sinus.<br><br>Follow-up:<br>Mean follow up 546 days<br><br>Inclusion criteria:<br>NYHA Class III-IV<br>EF <35%<br>QRS > 120ms<br>≥1 hospitalisation for heart failure in the past year | Implantation success rate: 233/244 (95.5%)<br><br>Postoperative: not stated<br><br>Postoperative:<br>39 deaths over the mean follow-up period. No significant difference between groups 13.6% versus 17.9%.<br><br>Patient characteristics:<br>Mean age 66 years, Male (n=170, 73%). NYHA Class III 89%. Ischaemic cardiomyopathy 61%, ildiopathic dilated cardiomyopathy 39%. LVEF 19.0%. QRS duration 169 ms. | Authors' conclusions:<br>No safety related conclusions.<br>Placement of the CS lead in the lateral and posterolateral branches is associated with significant improvement in functional capacity and greater improvement in LV function compared with the anterior CS location. This improvement does not appear to influence mortality.<br><br>Comments:<br>102 had an ICD<br>Consecutive patients<br>Retrospective study<br>Blinding: not stated.<br>Follow-up completeness: unclear.<br>Comparison group: yes. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Mair et al 2005)<br><br>Location:<br>Munich University and Aachen Leuven, Germany and Belgium<br><br>Study period:<br>April 1999 – January 2003<br><br>Study type:<br>Cohort and comparison<br><br>Level III-2 | 86 patients (79 patients had coronary sinus leads implanted but 9 were subsequently converted to epicardial leads). A further 7 had epicardial LV leads implanted resulting in 16 with epicardial LV leads.<br><br>Follow-up:<br>Mean 16.4 months (range 0.1-45 months)<br><br>Inclusion criteria:<br>NYHA Class III/IV despite optimal medical therapy<br>Dilated ischaemic or non-ischaemic cardiomyopathy with LVEF<35% and LVEDD>60mm<br>QRS >120ms with LBBB. | Implantation success rate: 70/79 (89%) were successfully implanted transvenously<br><br>Perioperative:<br>Mean implantation time for transvenous group 198 minutes.<br>11 cases, failed attempt to place the IV lead in a tributary of the CS<br>4 cases coronary sinus dissection.<br><br>Postoperative:<br>Deaths: n=9, cardiac n=4, 1 death related to sepsis from insertion, 2 late deaths may be related to sepsis.<br>No complications involving adjustment of pacemaker sensitivity<br>Right atrial or right ventricular lead dislocation (n=4)<br>Two pleural or cardiac effusions required treatment<br>One pocket infection resulted in explantation of the CRT system<br>3 – unacceptable high pacing threshold with early depletion of battery<br>3 – diaphragmatic stimulations<br>3 – lead dislodgements<br><br>Patient characteristics:<br>Age 63 years, mean EF 24%, mean QRS 182 ms. | Authors' conclusions:<br>'Transvenous placement of the LV lead via the coronary sinus is the first choice approach. Nevertheless, surgically placed epicardial leads gave excellent long term results and a lower LV related complication rate than CS leads. '<br><br>Comments:<br>Primarily comparing coronary sinus versus epicardial stimulation.<br>Selection criteria varied slightly during study period (9 did not meet the inclusion criteria – 2 had an EF of ~40% and 7 were NYHA Class II-III)<br>38% received an ICD<br>Unclear of timing of results and whether they were peri-operative or postoperative.<br><br>Selected series.<br><br>Blinding: no<br>Follow-up completeness: unclear.<br>Comparison group: epicardial versus coronary sinus implant. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Koos et al 2004)<br><br>Location:<br>University Technology, Aachen, Germany<br><br>Study period:<br>January 1997 – March 2002<br><br>Study type:<br>Case series with internal controls.<br><br>Level III-2 | 81 patients. Long-term performance coronary sinus (n=56) versus limited thoracotomy (n=25) Retrospective analysis one year after implantation of CRT of LV pacing and sensing performance using echo and exercise testing and clinical data.<br><br>Follow-up:<br>One year.<br><br>Inclusion criteria:<br>Not stated. | Implantation success rate: 56/57 (98%)<br><br>Perioperative:<br>One coronary sinus dissection<br><br>Postoperative:<br>(coronary sinus implantation only)<br>Deaths: (n=7, 1 death within 30 days and 6 within 365 days)<br>Two heart transplants within 30 days<br>Developed atrial fibrillation (5 patients within 365 days)<br>Increased lead threshold (5 patients within 30 days)<br>Lead dislodgement (4 within 30 days and 5 within 365 days)<br>Phrenic nerve stimulation (1 within 30 days and 1 within 365 days)<br>Lead fracture (1 within 365 days)<br>Device dislocation (1 within 365 days)<br>Connector defect (1 within 30 days)<br>Haematoma (2 within 30 days)<br>Hospitalisation shorter after implantation 8 versus 12 days (p<-0.01).<br><br>Patient characteristics:<br>Mean age 65 years. Male (n=52, 64%). NYHA Class 3.0. LV EF 24%. Ischaemic cardiomyopathy 47%. QRS duration 166ms. Beta blocker (73%). | Authors' conclusions:<br>The small patient number allows no conclusions on mortality, although a trend toward a higher mortality was observed in the thoracotomy group.<br>Thoracotomy may lower reintervention rates, but hospitalisation rates are higher and there may be less functional improvement. Coronary sinus appears to be better than thoractomy.<br><br>Comments:<br>Primarily a comparison of LV lead placement via coronary sinus versus lateral thoracotomy approach (56 received coronary sinus placement and 25 received thoracotomy approach).<br>ICD inserted in 31 (38%)<br>Unclear if consecutive patients were used.<br>Small patient numbers.<br>Selected series.<br>Blinding: not stated.<br>Follow-up completeness: unclear.<br>Comparison group: thoracotomy versus coronary sinus. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Izutani et al 2002)<br><br>Location: Heart and Vascular Research Centre, and Cleveland Clinic Foundation, Cleveland USA.<br><br>Study period: June 2001 and February 2002<br><br>Study type: case series<br><br>Level III-3 | Series of patients evaluated before and after biventricular pacemaker insertion by means of functional class, electrocardiogram and echocardiograph assessment.<br><br>N=12, 4 received epicardial leads and 8 transvenous leads.<br><br>Follow-up: mean period = 9.1 +/- 2.2 months.<br><br>Inclusion criteria: None stated. | Safety results: 8 patients<br><br>Implantation success rate: not stated.<br><br>Perioperative:<br>Mean total procedure time = 266 +/- 117 minutes. No complications were noted. Mean time from procedure to discharge = 2.6 +/- 1.4 days, mean length of hospital stay = 4.8 +/- 2.8 days for transvenous approach.<br><br>Postoperative:<br>Survival: no deaths occurred.<br><br>Patient characteristics:<br>Male n=7 (88%), mean age = 69 years, median age = 71 years (range 55-80 years), mean LVEF = 21%, NYHA = IV, ischaemic cardiomyopathy = 3, dilated cardiomyopathy n= 5, LBBB n= 2, sick sinus syndrome n= 4. | Author's conclusions:<br>'Epicardial lead placement was performed safely with benefits equivalent to those of coronary sinus lead placement and with a shorter procedure time.'<br><br>Comments:<br>3 transvenous patients had atrial fibrillation bradycardia.<br>4 patients received epicardial leads.<br>Small sample<br>Unclear follow-up period.<br>Selected series.<br><br>Blinding: No<br>Follow-up completeness: Full<br>Comparison group: Yes (epicardial group) |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Bordacher et al 2004)<br><br>Location:<br>Hospital Cadiologique du Haut Levegne, Pessac, France<br><br>Study period:<br>Not stated<br><br>Study type:<br>Cohort with comparison<br><br>Level III-2 | 41 patients. Transvenous implantation.<br><br>Follow-up:<br>Evaluation conducted at 3 months after individually optimised CRT.<br><br>Inclusion criteria:<br>LVEF<40%<br>QRS > 120 ms, LBBB<br>NYHA class III/IV despite optimal therapy<br>PR interval ≥200 msec<br>Exclusions: atrial arrhythmias, primary mitral regurgitation, amyloidosis, ongoing symptoms of myocardial ischaemia. LV lead could not be positioned in a lateral or postero-lateral vein. | Implantation success rate: 41/41 (100%)<br><br>Perioperative:<br>LV lead had to be replaced one day after implantation in one patient due to an acute threshold increase.<br><br>Postoperative: not stated<br><br>Patient characteristics:<br>Age 69 years, Male 80%, Ischaemic heart disease 56%, previous MI 54%, Primitive dilated cardiomyopathy 44%, NYHA class 3.2, LV EF 28%, QRS 170 ms. ACE inhibitor 88%, AT receptor anatagonist 12%, Beta-blockers 76%, Diuretics 100%, Aldosterone antagonists 71%. | Authors' conclusions:<br>No safety related conclusions.<br>'Echo measures of dyssynchrony are correlated with haemodynamic changes and can be a useful adjunct in selection and optimisation of BVP.'<br><br>Comments:<br>Excluded patients whose LV lead could not be positioned in a lateral or postero-lateral vein.<br>Unclear if consecutive patients were included.\<br><br>Follow-up completeness: Unclear<br>Comparison group: Yes |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Molhoek et al 2004)<br><br>Location:<br>Leiden University Medical Centre, The Netherlands<br><br>Study period:<br>Not stated.<br><br>Study type:<br>Registry follow-up and comparisons.<br><br>Level III-2 | 60 patients (30 consecutive patients in SR and 30 consecutive patients in AF). All patients received a 3-lead pacing system (inserted transvenously).<br><br>Follow-up:<br>Mean follow-up of SR patients 25 months.<br><br>Inclusion criteria:<br>NYHA Class III/IV<br>LV EF<35%<br>QRS >120ms (>200ms for paced QRS)<br>LBBB | Implantation success rate: not stated<br><br>Perioperative: not stated<br><br>Postoperative:<br>3 deaths due to end-stage heart failure among patients in SR.<br>Annual hospitalisations per patient decreased from 0.8 before implantation to 0.2 after implantation amongst patients in SR. Hospitalisations for heart failure reduced from a mean of 3.9 days/year to a mean of 0.5 days /year after implantation.<br><br>Patient characteristics (patients in SR):<br>Age 68 years, Male (n=24, 80%). NYHA class 3.2, 6-minute walking test 262 m, LV EF 23%, LVEDD 7.4cm, LVESD 6.8cm. | Authors' conclusions:<br>The results in the present study indicate a comparable survival rate between patients who have SR and those who have AF. However, the number of patients evaluated is small and larger studies are needed to evaluate long-term survival rates after CRT in patients who have AF.<br><br>Comments:<br>Primarily a comparison of the use of CRT in patients with atrial fibrillation and patients in sinus rhythm.<br>28 patients received an ICD<br>Consecutive series.<br><br>Blinding: unclear.<br>Follow-up completeness: unclear.<br>Comparison group: Atrial fibrillation versus sinus rhythm and responders versus non responders. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(De Cock et al 2005)<br><br>Location:<br>VU University Medical Centre, Amsterdam, The Netherlands<br><br>Study period:<br>Jan 1999 – Jan 2004<br><br>Study type:<br>Case series with historical comparison<br><br>Level III-3 | 24 patients who underwent successful implantation of CRT. Selected from 214 patients with significant CAD but who were considered not to be appropriate for revascularisation due to diffuse disease (n=16) or severely depressed LV function with additional operative factors (n=9).<br><br>Follow-up:<br>Examination at 1, 3, 6 and 12 months. Mean 13 months<br><br>Inclusion criteria:<br>NYHA class III/IV heart failure refractory to medical therapy<br>LV EF<30%<br>LBBB<br>CAD | Implantation success rate: 24/25 (96%)<br><br>Perioperative: not stated<br><br>Postoperative:<br>Deaths: Two patients died suddenly and one patient died from progressive heart failure during 13 months follow up.<br><br>Patient characteristics:<br>Mean age 72 years, Male (n=19, 79%). Past MI (46%), past CABG (33%). NYHA class II (58%), NYHA Class III (24%). Mean LVEF 21%, Mean QRS 178 m\, Ischaemic heart disease = 100%. | Authors' conclusions:<br>'Patients with advanced heart failure, stable angina and documented myocardial ischaemia may undergo safe and successful implantations of CRT systems'.<br><br>Persistent atrial fibrillation 25%.<br><br>Selected series.<br>Blinding: not clear<br>Follow up: 100%<br>Historical comparison group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Dixon et al 2004)<br><br>Location:<br>Belfast Hospital, Northern Ireland<br><br>Study period: not stated.<br><br>Study type:<br>Case series with historical control.<br><br>Level III-3 | 27 patients who underwent CRT were studied in the 12 months prior to and following CRT implantation. Hospitalisation rates, exercise tolerance and NYHA changes and costs were examined post-implant.<br><br>Follow-up:<br>12 months<br><br>Inclusion criteria:<br>Dilated or ischaemic cardiomyopathy<br>QRS >130 ms<br>NYHA Class III/IV<br>EF<30%<br>Exclusions: acute coronary syndrome, needed revascularisation, PTCA or CABG had been performed in past 6 months. | Implantation success rate: not stated<br><br>Perioperative:<br>No pacemaker related complications<br><br>Postoperative:<br>No pacemaker related complications.<br>Deaths: 1 non cardiac, no cardiac related deaths.<br>Hospitalisation: days of hospitalisation for stabilisation decreased 98% from 472 to 9 days (p<0.001).<br>Cost savings of Euro $201,684 were recorded with overall savings of Euro $12,000.<br><br>Patient characteristics:<br>Mean age 64 years, Male (n=24, 89%), Ischaemic cardiomyopathy (n=14, 52%). Mean symptom duration 4.5 years. Mean QRS duration 177 ms. | Authors' conclusions:<br>CRT is a safe procedure, which significantly improves symptoms and exercise tolerance, reduces hospitalisation rates and provides significant cost savings.<br><br>Comments:<br>Unclear if consecutive patients were used<br>24 patients were in sinus rhythm (89%).<br><br>Selected series: unclear<br>Blinding: not stated.<br>Follow-up completeness: full.<br>Comparison group: before and after. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Knaapen et al 2004)<br><br>Location:<br>University Medical Centre, Amsterdam, The Netherlands<br><br>Study period:<br>Not stated.<br><br>Study type:<br>Case series with before/after comparison<br><br>Level III-3 | 16 consecutive patients<br>Three transvenous pacing leads were inserted in each patient. Serial and hyperemic myocardial blood flow measured at baseline, 3 months after CRT on and after cessation of pacing.<br><br>Follow-up:<br>3 months<br><br>Inclusion criteria:<br>NYHA Class III or IV<br>LV EF < 35%<br>QRS > 120ms<br>LVEDD >55mm<br>Sinus rhythm | Implantation success rate: 14/14<br><br>Perioperative:<br>Stated as uncomplicated in all 14 patients.<br><br>Postoperative:<br>Deaths: n=2 (one sudden death and one progressive heart failure).<br><br>Patient characteristics:<br>Mean age 58 years, Male (n=8, 57%). Idiopathic dilated cardiomyopathy (n=9), Ischaemic heart failure (n=7). NYHA Class III (n=12), NYHA Class IV (n=2). LVEF 25%. ACE inhibitor (n=14), angiotensin receptor antagonist (n=2), Beta blocker (n=13), diuretic (n=14), digoxin (n=3), QRS = 173 ms. | Authors' conclusions:<br>No safety related conclusions<br>'Resting mean blood flow is unaltered by CRT. Hyperemic mean blood flow are increased by CRT. '<br><br>Comments:<br>Consecutive patients<br>Primary aim of study was to assess serial changes in myocardial blood flow (MBF) and MBF reserve following insertion of CRT.<br>No data on adverse events post-procedure.<br><br>Blinding: unclear.<br>Follow-up complete for 14/16?<br>Comparison: historical comparisons. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Kautzner et al 2004))<br><br>Location:<br>Prague, Czech Republic<br><br>Study period:<br>June 1999 to December 2001<br><br>Study type:<br>Case series + comparisons.<br><br>Level III-3 | 46 patients with CHF and sinus rhythm who underwent an attempt at implantation of CRT. Divided the time period of study into periods of technological advancement and experience of the operator. Three technological periods were categorised: Phase 1, only one LV lead type available to the operators; Phase 2, other stylet-controlled LV leads; Phase 3, additional leads including over-the-wire design; Phase 4, electro-physiology guided.<br><br>Follow-up: implantation.<br><br>Inclusion criteria:<br>NYHA Class III/IV despite optimal medical therapy. | Implantation success rate: Phase 1: 82%, Phase 2 90%, phase 3 96%<br>Perioperative:<br>Early phase (n=46):<br>Procedural time: Phase 1 247.1 mins, Phase 2 219.4 minutes, Phase III 116.4 minutes.<br>Phase 1: Cardiac tamponade (n=1)<br>Phase 2: CS dissection (n=1) Resolved without any sequelae.<br>Lead dislodgement (n=1)<br>Phrenic nerve stimulation (n=1)<br>Phase 3: Phrenic nerve stimulation (n=1)<br>Pocket haematoma (n=2)<br>CS dissection (n=1) described as "non-significant".<br>Advanced phase (n=92): Pocket haematoma (n=5), phrenic nerve stimulation (n=2), LV lead dislocation (n=3), atrial lead dislocation (n=2), infection (n=2) AV block during manipulation with introducers (n=4), asymptomatic CS dissection (n=4), nonsignificant leak of contrast medium into pericardial space (n=1)<br>Total complications: haematoma n=5, phrenic nerve stimulation n=2, leads dislocated n=5, infection n=2, AV block n=4, dissection n=4, peroration and effusion n=1.<br>Postoperative:<br>No complications described.<br>Patient characteristics:<br>Early phase: Mean age 61 years (range 44-80). Male (n=40, 87%). NYHA Class III/IV, QRS duration ≥150 ms, LV EF ≤ 30%.<br>Advanced phase: Mean age 61 years (Range 38-81), Male (n=76, 83%). CAD (n=48), Dilated cardiomyopathy (n=38), Valvular heart disease (n=6). Mean LVEF 21.8%. Mean LVEDD 73.8mm. | Authors' conclusions:<br>Both individual learning curve and technical advances influence the success rate, procedural times and fluoroscopic times for CRT implantation. Complication rates remain relatively low.<br><br>Lead types were most often: Attain 4189 and 4193.<br><br>Comments:<br>Assessment of learning curve comparing early experience with more advanced experience.<br>Essentially two studies and unclear if there is overlap between patients in the two subcomponents.<br><br>Unclear if consecutive patients used.<br><br>Blinding: not stated.<br>Follow-up complete but short.<br>Comparison group: yes, internal. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Mortensen et al 2004)<br><br>Location:<br>29 centres in Europe and Canada<br><br>Study period:<br>Not stated<br><br>Study type:<br>Prospective cohort<br><br>Level IV | Prospective observational study of safety, performance and efficacy of InSync III biventricular pacing device capable of sequential RV and LV activation. Open label study.<br><br>Follow-up:<br>1, 3 and 6 months, mean = 112 days, median = 102 days.<br><br>Inclusion criteria:<br>NYHA II-IV, LVEF <36%, LVEDD >54mm, QRS > 129 ms (>180 ms for pacemaker dependent people).<br>Exclusion criteria were: indication for an ICD, chronic atrial tachyarrhymias or mechanical right heart valves. | Safety results: n= 198 patients<br><br>Implantation success rate:<br>Successfully implanted in 189 (95.9%) of patients, unable to be implanted in 8 patients and one was excluded as he did not meet inclusion criteria. Of the 189 implanted, 3 were initially unsuccessful and were required to be implanted within 2-7 days of the initial procedure.<br><br>Perioperative:<br>Total implant time was 126 +/- 63 minutes<br><br>Postoperative:<br>Survival: 8 deaths 7 due to cardiac causes (heart failure n= 3, ventricular arrhythmia n=2, unknown n=2) and one due to pulmonary infection. Survival was 97+/- 2% at 3 months and 94+/- 2% at 6 months.<br>No device malfunctions were noted.<br>Some 20 patients experienced 22 complications including: problems with the stimulator (n=3), pocket swelling (n=1), pocket haematoma (n=2), LV lead dislodgement (n=12) requiring repositioning in 10 and explanting in 2, phrenic nerve stimulation (n=2) resolved by repositioning.<br><br>Patient characteristics:<br>Male = 72.5%, age = 66.3 +/- 10.6 years, LVEF = 24.4 +/- 6.9%, ischaemic heart disease = 41.8%, NYHA II= 17.5%, III = 68.3%, IV = 14.3%, LVEDD = 68.8 +/- 9.1mm, QRS = 176.3 +/- 27 ms, ACE inhibitors = 81%, anti-arrhythmias 25%, anticoagulant drugs 53%, beta-blockers 50%. Mean 6-min walk = 339 metres. | Authors' conclusions:<br>'The InSync III biventricular stimulator has been found to be safe and effective for the treatment of patients with symptomatic systolic heart failure and prolonged QRS complex duration.'<br><br>Comments:<br><br>3 patients received an implantable defibrillator.<br>Incomplete reporting of adverse events only 17/22 complications described.<br><br>Selected series with defined criteria<br><br>Blinding: No<br>Follow-up completeness: 176/189 (13 left early)<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Ricci et al 2000)<br>(Zardini et al 2000)<br>(Porciani et al 2000)<br><br>Location:<br>39 centres in Italy.<br><br>Study period:<br>Jan 1998 – April 2000.<br><br>Study type:<br>Prospective case series.<br><br>Level IV | 212 patients enrolled, 190 studied. Study aimed to examine feasibility, safety and reliability of CRT.<br><br>Follow-up:<br>Mean duration 10.4 (5.6) months (range 1-28 months).<br><br>Inclusion criteria:<br>None presented. | Implantation:<br>Implant success rate was 189/212 patients (89%). Implant failure was due to no CS catherisation, no lead progression into the CS, lead instability, or high EPT (exact numbers for each not given). 1 failed endocardial insertion requiring epicardial leads.<br><br>Perioperative:<br>acute cardiac tamponade n=2, CS dissection n=6, CS dissection + pericardial effusion n=2, cardiac arrhythmias n=6 (asystole n=3, VF n=3).<br><br>Postoperative:<br>Follow-up early (<2/52) LV lead dislodgement n=8, late (>2/52) LV lead dislodgement n=6 (all successfully repositioned), LPN stimulation n=4 (3 treated by decreasing ventricular stimulation, 1 requiring repositioning), far field P wave oversensing n=3 (2 treated by re-programming, 1 requiring repositioning), sepsis requiring explantation n=2, life threatening VT requiring implantable defibrillator n=1.<br>Postoperative – follow-up death n=13 (sudden death n=5, progressive heart failure n=6, AMI n=1, CVA n=1).<br>Mean implantation duration: 2.63 (1.1) hours.<br><br>Patient characteristics:<br>Age = 68 (8) years, 157 males, mean QRS = 172 (34) ms, mean LVEF = 25 (7)%, n=158 in SR, 32 in AF. Only mean NYHA class given in Ricci (3.15+/-0.61); proportions in NYHA classes stated in NYHA class II n=23, class III n=116, class IV n=51. Aetiology: ischaemic 47%, idiopathic 38%, valvular 8%, other 7%. | Authors' conclusion:<br>'CRT can be effectively obtained transvenously with an acceptable complication rate.'<br><br>Comments:<br>InSync study (3-part report – with Porciani et al (2000)1}0) and Zardini et al (2000)4}0)). May also include patients from Gras (2002a).<br><br>Enrolment given as 190 patients, but implantation success rate uses 212 patients as unexplained denominator. Presume that 190 = 189 with transvenous leads + 1 with epicardial leads.<br>Note: 39 patients were either a NYHA class <3, LVEF>35% or QRS width <120ms.<br>Rhythm not specified for patients with safety issues.<br>Not consecutive and no selection criteria presented.<br>No blinding.<br>Follow-up completeness: unclear.<br>No external control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Purerfellner et al 2000)<br><br>Location:<br>Phase 1:<br>16 centres (1 to 6 patients per centre), Austria and Belgium.<br><br>Phase 2:<br>63 European centres.<br><br>Study period:<br>Pha se 1 :<br>April 1999 –<br>Sept 1999<br><br>Phase 2:<br>Nov 1999 –<br>Jan 2000.<br><br>Study type:<br>Prospective case series.<br><br>Level IV | Two phases of trial: Phase I to obtain European Commission approval for marketing; phase II results from insertion in first 150 patients from CONTAK European registry.<br>European Registry aimed to report performance, adverse events and complications associated with CRT from feedback voluntarily provided by clinicians. 197 patients eligible for CRT pacing.<br><br>Follow-up:<br>Duration six weeks (phase I) and 0 weeks, ie implantation data only (phase II).<br><br>Inclusion criteria:<br>Phase I: Symptomatic heart failure, >18 years old, no implantable defibrillator.<br><br>Phase II: Symptomatic heart failure, sinus rhythm, LBBB, QRS >150ms. | Phase I (n=47):<br>Excluded prior to implantation n=3 (1 alternative therapy chosen, 1 unable to tolerate procedure under LA, 1 subclavian fibrosis precluding L sided insertion).<br>Implantation: 36/44 (82%) successfully implanted: reasons for failure; unstable catheter placement (n=4), EPT (n=2), tortuous coronary venous anatomy (n=1), coronary venous dissection (n=1, from balloon catheter for venography of CV). In successful implants, 2/36 atrial wall dissections and 1/36 induced VF from steering catheter insertion.<br>Postoperative:Lead dislodgement n=1 (time not given), pocket stimulation n=1, EPT n=2.<br><br>Phase II (n=150)<br>Implantation success rate: 135/150 (83%) (if CS identified success rate was 92%).<br>Postoperative:<br>Immediate post-implantation only reported. lead dislodgement n=1, LPN stimulation n=2 (all cases successfully repositioned).<br>Average implantation duration: 169 (81) minutes (range 53 – 480 minutes).<br><br>Patient characteristics:<br>Phase I<br>Mean age 70 years +/- 10, male = 67%, average QRS not given, average LVEF = 35%. 35/36 patients in phase 1 were in AF, NYHA classes not given. Aetiology: not stated.<br><br>Phase II<br>Males 78% mean age = 64 +/- 10 yrs, average QRS = 165 (35) ms, average LVEF not given, patients all SR as protocol was for patients with SR and BBB (QRS>150ms), 70% NYHA class III, 21% IV and 8% II, Ischaemic: 30%, dilated cardiomyopathy 47%. | Authors' conclusion:<br>Easytrack system is a suitable and safe tool for CRT.<br><br>Clear learning curve effect noted – centres implanting 1-2 devices success rate = 81%, centres implanting 3 or > success rate = 88%.<br>Follow-up completeness unclear<br>EASYTRAK leads with CONTAK TR (phase I), or EASYTRAK leads with one of CONTAK TR or CONTAK CD pacemakers (phase II).<br><br>41% also received an ICD (i.e. CONTAK CD)<br>41% (unclear: n=150 (61) or n=135 (55)) received and 59% (unclear n=150 (89) orn=135 (80)) received CONTAK devices.<br>63 centres involved, 37 centres implanted 1 patient only, 18 implanted 2, and 8 centres implanted 3 or more.<br><br>Implant success was clearly correlated with experience – demonstrated by duration of the procedure: centres with no experience needed average >3 hours whereas those with >3 implants finished in 2-2.5 hours.<br>Selected patients using some criteria. Selection processes may have varied at different centres in both studies.<br>No blinding in either study.<br>Completeness of follow-up: not stated.<br>No external control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Hansky et al 2002)<br><br>Location:<br>University of Bochum, Germany.<br><br>Study period:<br>1999 – 2001.<br><br>Study type:<br>Retrospective case series.<br><br>Level IV | Aim was to report results of use of CRT, especially lead selection at authors' institution. 116 patients (121 leads) received transvenous leads (another 13 patients received epicardial leads).<br>A variety of endocardial leads used. Broadly two types:<br>(1) pre-shaped distal lead body and a microporous electrode.<br>(2) electrodes positioned with coronary wires in a 'side wire' or 'over the wire'.<br>Type 2 leads were used for torturous target veins.<br>29 patients received type 2 leads.<br><br>Follow-up: Not stated.<br><br>Inclusion criteria: None stated. | All endocardial lead types (n=121 leads and 116 patients):<br>Implantation:<br>CV dissections n=6, VT induction n=3, CS thrombus formation n=3, LPN stimulation n=16, repeat attempts to place CV lead n=2, failed CS cannulation n=1, implantation was achieved in 115 patients.<br>Postoperative:<br>EPT n=5, lead dislodgement n=5 (all replaced successfully in same vein), PE n=1 (1st post-op day), pacemaker sepsis (requiring system explantation and re-implantation) n=1.<br><br>Patient characteristics:<br>Age, gender, QRS, LVEF, SR/AF, NYHA class not given and aetiology not stated. | Authors' conclusion:<br>'By selecting the CV lead model most suitable for each individual patient we achieved successful implantation in 99.1% of patients.'<br><br>Comments:<br>Some patient selection occurred including angiography and haemodynamic testing. Non-responders did not receive pacing.<br>Only data on lead insertion and postoperative complications relating to lead insertion was presented.<br>LPH stimulation required repositioning Guidant lead in a different vein or using different type of lead.<br>Authors' comment that Guidant leads were particularly useful for tortuous veins.<br>Heparinisation (100IU/kg) instituted after 3 CV thrombus: no further cases of thrombus occurred after this.<br>Results for epicardial versus endocardial leads not fully explicit.<br>Patient follow-up methods and adequacy not described.<br>Selected patients no criteria.<br>Safety outcomes not a stated aim of the study.<br>No blinding.<br>Retrospective comparisons with internal control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Gras et al 2002b) Preliminary results presented in (Gras et al 1998).<br><br>Location:<br>Multi-centre study based at European and Canadian Centres.<br><br>Study period:<br>August 1997 – November 1998.<br><br>Study type:<br>Prospective series.<br><br>Level IV | Aim was to assess the safety, feasibility and long-term effects of CRT. 117 patients enrolled.<br><br>Follow-up:<br>Duration 12 months for all patients.<br><br>Inclusion criteria:<br>Symptomatic heart failure NYHA III or IV refractory to medical treatment, QRS >150ms, LVEF<35%, LVEDD>60mm, stable medical regimen for >1 month, age >18 years, no contraindications to DDD pacing, no AMI or unstable angina in past 3/12, not in permanent AF, no ICD present, not participating in other trial, no diagnosis of life-threatening disease other than heart failure. | Implantation:<br>Success rate 103/117 (88%). Causes of failure to implant: unable to catheterise CS n=2, unable to advance lead to final destination n=5, unstable lead position n=3, EPT n=4. Other complications: perforation of CS tributary (no treatment required).<br><br>Postoperative:<br>Withdrawals from study n=9 (loss of capture n=3, cardiac transplantation n=3, infection of RV lead n=1, LPN stimulation n=1, painful pulse generator pocket n=1.) Dislodgement of LV lead n=10 patients and n=13 procedures to reposition or replace equipment.<br>Deaths n= 21 (sudden n=10, progressive heart failure n=7, pneumonia n=1, CVA n=1, leukaemia n=1, PE n=1). Actuarial survival = 78 (+/-8)%.<br><br>Patient characteristics:<br>Mean age = 67 (10) years, males = 81/103, mean QRS = 178 (28) ms, mean LVEF = 22 (6) %. Rhythm = all in SR, NYHA class III n=70, class IV n=33 aetiology = ischaemia (n=49), non-ischaemia (n=54). Medications: Diuretics (93%), ACE inhibitors (70%), angiotensin II receptor agonists (16%), digoxin (58%), beta-blockers (17%), vasodilators (17%), calcium channel blockers (15%), amiodorone (50%), anticoagulants (34%), intravenous inotropic support (2%). | Authors' conclusion:<br>'CRT long-term … can be safely and reliably achieved...'<br><br>Comments:<br>InSync (Medtronic) study. May include data subsequently reported in Leclercq et al (2000a), Leclercq et al (2000b) &/or Alonso et al (2001).<br>Follow-up satisfactory.<br>Selected patients using defined criteria.<br>Safety a stated aim of study but insufficiently powered to assess mortality.<br>No blinding.<br>No external control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Alonso et al 2001)<br><br>Location:<br>Cardio-Pneum-ologique Hôpital Pontchaillou, Rennes, France.<br><br>Study period:<br>August 1994 – February 2000.<br><br>Study type:<br>Retrospective case series.<br><br>Level IV | Aim was to assess the technical feasibility and long-term results (over 6 years) of CRT. 116 patients enrolled.<br><br>Follow-up:<br>Mean duration 15+/- 13 months.<br><br>Inclusion criteria:<br>Severe heart failure NYHA III or IV despite optimised medical treatment including at least ACE inhibitors or angiotensin receptor blockers, diuretics and recently beta-blockers, LVEDD >60 mm, LVEF <35%, QRS >150 ms. | Implantation:<br>102/116 successfully implanted (88%), coronary sinus dissection n=2/102 (successful repeat implantation).<br><br>Postoperative:<br>Reimplantations n=26 (between day 2 and 48 months post-implantation) for LV EPT (n=15), LPN stimulation (n=3), RV EPT or RV lead dislodgement (n=7) (1 case not specified); sepsis requiring explantation n=3.<br>Ambiguous paragraph: 'In 15 cases it was necessary to remove the left ventricular lead, either because of infection or to relocate it or replace it with another one. Eight such extractions were performed.'<br><br>Patient characteristics:<br>Mean (SD) age = 67 (9) yrs, gender not given, mean QRS = 185 (26) ms, mean<br>LVEF = 22 (5)%, rhythm = SR n=71, AF n=31, NYHA class III n=71, class IV n=31, aetiology = ischaemia (n=37), idiopathic (n=50), other causes (n=15). | Authors' conclusion:<br>'Transverse left ventricular pacing through the coronary sinus is feasible and safe.'<br><br>Comments:<br>Operator training and use of specific tools resulted in an increase in success rate. Lead dislodgement reduced over time (30% <1999 down to 11% >1999).<br>Unclear what percentage of patients were followed-up fully.<br>Consecutive series using defined selection criteria.<br>One study aim was to examine safety.<br>No blinding.<br>No control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Schuchert et al 2004)<br><br>Location:<br>Hamburg, Germany<br>(six medical institutions)<br><br>Study period:<br>August 1999 – August 2001<br><br>Study type:<br>Case series<br><br>Level IV | 102 patients with heart failure and bundle branch block who underwent CRT implantation. Follow-up of patients who receive a new pre-shaped lead dedicated to LV stimulation.<br><br>Follow-up:<br>24 months<br><br>Inclusion criteria:<br>NYHA Class III or IV despite optimal medical therapy<br>LVEF <0.35<br>QRS duration >130ms | Implantation success rate: 96/102 (94%).<br><br>Perioperative:<br>Reasons for failure: instability of the lead in the CS tributary (n=2), failure of CS catheterisation (n=4).<br><br>Postoperative:<br>Reintervention for phrenic nerve stimulation (n=2).<br>Phrenic nerve stimulation was present in six patients.<br>Haematoma (n=1)<br><br>Patient characteristics:<br>Age 67 years, Male 70%. Two thirds were NYHA Class III, one third Class IV. Non-ischaemic dilated cardiomyopathy (n=74), ischaemic cardiomyopathy (n=28). LBBB and mean QRS 148ms in 96 patients, RBBB and mean QRS 151 ms in 6 patients. Mean PR interval in patients in sinus rhythm was 210 ms. | Authors' conclusions:<br>Few lead related adverse events were observed during follow-up. The CS dissections were observed when a rigid ablation catheter was used to catheterise the CS ostium. This complication could probably be eliminated by the systematic use of different instrumentation.<br><br>Comments:<br>Primary aim was to assess the two-year performance of a new pre-shaped lead designed for LV stimulation.<br>90 patients in sinus rhythm and 12 patients in atrial fibrillation at time of implantation.<br><br>Unclear if consecutive patients were used.<br><br>Blinding: no.<br>Follow-up completeness: unclear.<br>Comparison group: no. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Gaita et al 2000)<br><br>Location:<br>Ospedale Civile of Asti, Florence, Italy.<br><br>Study period:<br>July 1998 – April 2000.<br><br>Study type:<br>Retrospective case series.<br><br>Level IV | Aim was to consider if CRT for heart failure should be combined with defibrillator therapy. 96 patients studied. 67 received CRT, 29 received CRT and ICD.<br><br>Follow-up:<br>Duration 283+/-170 days.<br><br>Inclusion criteria:<br>Interventricular conduction delay, no acute myocardial infarction, NYHA II-IV, full drug treatment including diuretic, digoxin, ASCE inhibitor and beta-blocker, QRS >140 ms, LVEF <35%. | Implantation:<br>No complications reported by authors.<br><br>Postoperative:<br>Deaths n=13 (CRT only n=8, CRT and ICD n=5): causes; progressive cardiac failure n=11 (CRT only n=7, CRT and ICD n=4), sudden death n=1 (CRT only), noncardiac death n=1 (CRT and ICD).<br><br>Patient characteristics:<br>Mean age = 66 (8) years, 88/96 males, mean QRS = not given, mean LVEF = 22 (6)%. Mean NYHA class = 2.8 +/- 0.7 (numbers per class not given). Aetiology: not stated. | Author's conclusions:<br>'Ischaemic heart disease patients with reduced left ventricular ejection fraction and ventricular tachyarrhythmia are good candidates for CRT with ICD back-up'.<br><br>Comments:<br>Selected patients with defined criteria.<br>No blinding.<br>Completeness of follow-up not stated.<br>No external control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Mascioli et al 2002b)<br><br>Location: University of Brescia, Italy<br><br>Study period: October 1998-April 2002<br><br>Study type: Registry cohort with follow-up<br><br>Level IV | Echocardiograph measures undertaken at baseline, 1, 3, 6 months and 6 monthly thereafter.<br><br>Follow-up:<br>68/96 followed for at least 6 mths<br>Mean 676 days +/- 240 days<br><br>Inclusion criteria: not stated | Safety results: 96 patients<br><br>Implantation success rate: 95/96 (99%)<br><br>Perioperative: not stated<br><br>Postoperative:<br>Survival: during the first year there were 8 deaths. Due to: sudden cardiac deaths (n=3), heart failure (n=3), non-cardiac causes (n=2).<br>Overall, there were 15 deaths. Due to: sudden cardiac death (n=7), heart failure (n=5), non-cardiac causes (n=3). Mortality rates at 2 and 3 years were 25%.<br>Hospitalisation rates were reduced by 78%, hospital stay was decreased by 84% comparing one year before implantation with one year after implantation.<br><br>Patient characteristics:<br>Male = 53 (78%), mean age = 68+/- 8 years, atrial fibrillation (n=6, 9%), idiopathic dilated cardiomyopathy (n=33, 49%), mean NYHA class = 3.2 +/- 0.5, mean QRS = 177 ms, mean LVEF = 23%. | Authors conclusions:<br>No safety conclusions.<br>"Biventricular pacing is effective in improving the clinical and instrumental statuses of patients with severe heart failure. The treatment could reduce the mortality rate.'<br><br>Comments:<br>15 received an implantable defibrillator.<br>2 patients received an epicardial lead.<br>Selected series.<br>Blinding: no<br>Follow-up completeness: 68/96 (71%)<br>Comparison group: no |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Ollitrault et al 2003)<br><br>Location: 10 hospitals in France<br><br>Study period: March 99 – May 2000<br><br>Study type:<br>Case series<br><br>Level IV | Descriptive study of experience with a new Situs LV pacing lead. Two different lead implantation methods used (conventional approach and sheath assisted). Three different lead designs. Coronary sinus angiogram was performed at the time or before implantation.<br><br>Follow-up:<br>Mean period of 15 months (0- 35 months). 8 patients had 2 years of follow up.<br><br>Inclusion criteria: NYHA III-IV and QRS > 150 ms. | Safety results: 62 patients.<br><br>Implantation success rate: 20% success with first design then the horn shape tip was inserted with 24/38 (63%) success. With the use of an introduction sheath and hydrogel coating 12/14 were successful (86%). Overall success rate = 38/62 (61%).<br><br>Perioperative:<br>Mean total implantation time = 115 +/- 34 minutes.<br><br>Postoperative:<br>Survival: 8 (21%) deaths, none linked to the pacing system.<br>Dislodgements (n=2) one requiring lead explantation, phrenic nerve stimulation corrected by decreasing amplitude (n=1), pericardial effusion (n=1), infection (n=1) requiring explantation and pocket drainage (n=1). One loss of capture corrected by repositioning (n=1). Total n=15 adverse events. Electrical parameters at follow-up indicated that the pacing threshold rose from 0.73 +/- 0.54 to 1.57 +/- 0.6 volts.<br><br>Patient characteristics:<br>Male = 81%, SR = 33/38, mean age = 71 +/- 10 years. | Author's conclusions:<br>The implant success rate of the Situs lead improved as its design was gradually modified, and with the addition of dedicated tools facilitated the catheterisation of the CS tributaries. The pacing characteristics of the new lead were good at implant and follow-up, and were expected to be associated with a low battery current drain and hence a durable pulse generator longevity.<br><br>Comments:<br>Atrial fibrillation 5/38<br>Different implantation success rates for different designs.<br><br>Selected series.<br><br>Blinding: unclear<br>Follow-up completeness: ?Unclear<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Pitzalis et al 2005)<br><br>Location:<br>University Bari, Italy<br><br>Study period:<br>June 2000 – September 2003<br><br>Study type:<br>Case series<br><br>Level IV | 60 patients. Echocardiography recordings used to measure septal to posterior wall motion delay. Transvenous LV pacing performed in all patients.<br><br>Follow-up:<br>Median follow-up 14 months (minimum 6 months).<br><br>Inclusion criteria:<br>NYHA Class III<br>LBBB with QRS >130ms<br>LVEF ≤ 35%<br>Exclusions: unstable condition, spontaneous or provoked angina or the need for revascularisation procedures. | Implantation success rate: 63/65 (97%)<br><br>Perioperative: not stated<br><br>Postoperative:<br>Deaths: Four deaths from congestive heart failure.<br>Hospitalisations: 12 hospital admissions<br><br>Patient characteristics:<br>Age 62 years, Male (n=32, 53%), Ischaemic cardiomyopathy 22%. QRS duration 171 ms, LVEF 25%. ACE inhibitors 80%, angiotensin 2 receptor antagonists 22%, Beta blocker 80%, Digitalis 72%, Diuretics 100%, Aldosterone antagonists 88%. | Authors' conclusions:<br>No safety related outcomes.<br>"Baseline of echo septal motion post wall motion delay is a strong predictor of long-term clinical improvement after CRT.'<br><br>Comments:<br>Primary aim was to assess whether clinical benefit of CRT can be predicted by baseline evaluation of left ventricular asynchrony.<br>65 met the enrolment criteria but only 60 were included in the study (2 failed implantation, 3 had poor image quality)<br>30 received ICD<br><br>Blinding: no.<br>Follow-up completeness: unclear.<br>Comparison group: no. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Walker et al 2000b)<br><br>Location:<br>Harefield Hospital, UK.<br><br>Study period:<br>February 1998 – April 1999.<br><br>Study type: Retrospective case series.<br><br>Level IV | 54 patients enrolled; 47 received CRT and 7 received CRT with an ICD. Aim was to describe experience with CRT.<br><br>Follow-up:<br>Duration three months.<br><br>Inclusion criteria:<br>Consecutive series at one centre no other criteria reported. | Implantation: 49/54 (91%) successful implantations.<br><br>Postoperative:<br>Lead repositioning n=5/49 (LV lead only n=4, both LV and RV n=1) mean 43 days (range 1-90), unsuccessful left side implantation but successful right side implantation n=2/49. 5/54 failed implantations due to; no accessible left sided CS tributary (n=3), persistent lead instability (n=1) and LPN stimulation (n=1).<br>Deaths: n=1 (sudden, cause VF).<br>Mean total implantation time: 116 (43) minutes.<br><br>Patient characteristics:<br>Limited description of patients. Mean age = 64 (12) years, gender not given, mean QRS and LVEF not given, n=25 in AF (8 of whom receiving CRT after His ablation of refractory AF), n= 29 in SR enrolled. NYHA class proportions not given. Underlying diagnoses: ischaemic heart disease (n=21), dilated cardiomyopathy (n=21), valvular disease (n=3), hypertrophic cardiomyopathy (n=1), medically refractory atrial fibrillation (n=8). | Authors' conclusions:<br>'With appropriate previous experience in complex and coronary sinus pacing and with access to up-to-date pacemaker and lead technology, a biventricular implantation service can be instituted with good medium-term results.'<br><br>Comments:<br>Short follow-up may reflect low mortality (1.8% shown).<br>Learning curve effect: all implantation failures were in first 12 implants.<br>Patient who died also included in study of uni- vs BiV pacing after His ablation: at time of death was receiving univentricular pacing (RV only).<br>Consecutive series.<br>No blinding.<br>Follow-up <80% at three months.<br>No control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Leclercq et al 2000a)<br><br>Location:<br>Cardio-Pneumologique Hôpital Pontchaillou, Rennes, France.<br><br>Study period:<br>August 1994 – February 2000.<br><br>Study type:<br>Pilot prospective case series.<br><br>Level IV | Aim was to assess long-term benefits of CRT. 50 patients received CRT, 43 via transvenous leads and seven via epicardial leads.<br><br>Follow-up:<br>Mean duration 15.4+/-10.2 months (range 1-40 months).<br><br>Inclusion criteria:<br>NYHA III or IV, optimised medical treatment (ACE inhibitors and diuretics at maximal doses), LVEF <35%, LVEDD >60 mm, QRS >120 ms. | Implantation:<br>One sudden death during epicardial lead insertion due to VF.<br><br>Postoperative:<br>20 deaths (2 in NYHA class III, 18 in NYHA class IV) during follow-up, mean 8+/-7.2 months post-implantation (range 1-38 months). Causes of death: progressive pump failure (n=11), sudden cardiac death (n=6, 3 from VT or VF) and noncardiac (n=3). Survival rate was significantly better (no p value given) in class III c.f. class IV patients.<br>Re-operation (re-implantation) required in 16 (32%) of patients, 13 of whom due to faulty connector between the two ventricular leads (non-dedicated CRT pacemakers used).<br><br>Patient characteristics:<br>Mean age = 68 (8) years, 45/50 male, mean QRS = 197 (32) ms, Mean LVEF = 20 (6)%, SR (n=36) and AF (n=14), NYHA class III (n=16) and IV (n=34, including 17 in terminal phase requiring permanent inotropic support). Aetiology of heart failure: idiopathic (n= 20), ischaemic (n=24), other (n= 6). | Author's conclusion:<br>'CRT appears to improve the functional status of patients with dilated cardiomyopathy with advanced heart failure'.<br><br>Comments:<br>May include data subsequently reported in Alonso et al (2001)1}1).<br>Total mortality (40%) may reflect a sicker group of patients than other studies.<br>Rhythm not specified in patients with safety issues.<br>Note: Seven patients had epicardial LV leads.<br>Consecutive series and defined selection criteria.<br>Completeness of follow-up: not stated.<br>No blinding.<br>No external control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Daubert et al 1998)<br><br>Location:<br>Cardiologie Ahotel Dieu/CHRU Rennes and Chirurgical du Val d'Or, Saint-Cloud, France.<br><br>Study period:<br>Unclear.<br><br>Study type:<br>Prospective case series but some comparisons were made group of patients who received non-specific leads and those who received specific leads.<br><br>Level IV | 47 patients included. The study described experience with transvenous insertion between 1994-1997.<br><br>Some, mainly electrophysiological, comparisons made between an early group of 8 patients who received non-specific uni-polar leads (inserted between 1994-1996) and those who received specially designed leads (n=27) (inserted 1996-1997). Aimed to assess CRT safety, feasibility and performance.<br><br>Follow-up:<br>Duration of f/u 10.2 +/- 8.7 months (range 1 to 28 months).<br><br>Inclusion criteria:<br>NYHA III or IV, failure or intolerance to drug treatment including ACE inhibitors, diuretics, and digoxin, LVEF <35%, LVEDD >60mm, QRS >150ms. | Implantation success rate 35/47 (74.5%). Causes of failure: unable to catheterise CS (n=1), unable to catheterise LV veins from CS (n=4), and unacceptably high pacing thresholds (n=7).<br><br>Postoperative: acute early LV lead dislodgement n=2 (day 2 and 15) – successfully repositioned. 1 lead failed due to exit block after pacing threshold increase - patient refused reoperation.<br><br>Postoperative: follow-up deaths n=10 (mean f/u 6.0 +/- 4.5 months, range 1-17 months) from progressive cardiac failure (n=5), sudden death (n=4) and cancer (n=1), EPT n=1 (non-specific lead).<br><br>Patient characteristics:<br>Average age = 68 (9) years, 42/47 male, average QRS = 187 (27) ms, average LVEF = 17 (4)%, rhythm not given, NYHA class III n=6, class IV n=41. 9 patients received VVIR pacemaker, 15 DDD and four-chamber pacemaker in 11. Aetiology: ischaemia (n=25), idiopathic (n=20), other (n=2). | Authors conclusions: 'Permanent LV pacing is possible for most patients with excellent safety and long-term results'.<br><br>Comments:<br>May include data subsequently reported in Alonso et al (2001)1}1), Leclercq et al (2000a), Leclercq et al (2000b)1}c), Alonso et al (1999)9}9) &/or Leclercq et al (1998)8}8).<br>All patients were anticoagulated.<br>Improved implantation rate 82% vs 53% when using specifically designed CS leads.<br>Specially designed leads used from 1996.<br><br>Selected series.<br>No blinding.<br>Follow-up completeness unclear.<br>No control group |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(al-Khadra 2003)<br><br>Location:<br>Prince Sultan Cardiac Centre, Riyadh, Saudi Arabia.<br><br>Study period:<br>Unclear: stated as November 2001 – May 2001<br><br>Study type:<br>retrospective case series<br><br>Level IV | 47 patients underwent implantation of permanent pacemaker, defibrillator or biventricular pacing. Record review of the safety of implantation among patients who received a new pacemaker, defibrillator, device/lead revision or generator replacement while receiving oral anticoagulation (warfarin) therapy with INR < 3.5. Implantations involved cannulation of the left axillary vein and all leads were actively fixated. The implantation involved a modified axillary approach and pressure dressings.<br><br>Follow-up: 6 weeks<br><br>Inclusion criteria: Currently on warfarin. | Safety results: 3 patients<br><br>Implantation success rate:<br>All procedures were reported as successful.<br><br>Perioperative and postoperative:<br>No major bleeding problems and no major procedure or device related complications (including pneumothorax, wound drainage, dehiscence or infection). One patient sustained a small haematoma which resolved without treatment within a week. It is not clear if this patient received a biventricular pacemaker.<br><br>Patient characteristics:<br>47 patients, 27 (57%) male, mean age = 56.5 +/- 13 years, LVEF = 42% Indications for warfarin included mechanical prosthesis (11), atrial fibrillation (33), stroke (1), myocardial infarction (1) and DVT (1). Mean INR = 2.3 +/0.4). No separate description of the 3 patients who received a biventricular pacemaker. | Authors conclusions: 'In experienced centres, patients requiring treatment with warfarin may undergo implantation of pacemakers with minimal risk despite continuation of anticoagulation with INR <3.5'.<br><br>Comments: Only 3 patients received a biventricular pacemaker.<br><br>Selected series.<br><br>Blinding: No<br>Follow-up completeness: unclear<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Ammann et al 2004)<br><br>Location:<br>University Hospital Basel, Switzerland<br><br>Study period: not stated<br><br>Study type:<br>Case series<br><br>Level IV | Ventricular electrode implanted via cephalic or subclavian vein. Electrode for left ventricular pacing introduced over a guidewire into the coronary sinus. CRT device was connected with the electrodes and implanted subcutaneously or subpectorally.<br><br>Follow-up:<br>Follow up on vital status, device integrity, clinical signs of heart failure, need for hospitalisation due to heart failure and assessment of LV EF was assessed at 3 month intervals. Mean duration: 12 months.<br><br>Inclusion criteria:<br>NYHA Class III/IV heart failure,<br>QRS ≥ 130ms | Safety results: 47 patients.<br><br>Implantation success rate: 43/47 (91%). One failed implantation due to technical difficulties. Adequate pacing site could not be found during implantation (n=1) and left ventricular capture failure developed shortly after implantation (n=2).<br><br>Perioperative: not stated<br><br>Postoperative:<br>12 (28%) patients died during follow up (6 sudden deaths, 5 heart failure).<br>Hospitalisation for heart failure before were 18 days versus 1 day after ($p<0.0001$).<br><br>Patient characteristics:<br>Age 65 ± 10 years, male n=36 (84%), ischaemic heart disease n=22 (51%), mean QRS 172 ms, mean LVEF 20%, SR n=36 (84%), Diuretics 91%, Beta blockers, 66%, Amiodarone 37%, Spironolactone 55%, ACE inhibitor 100% | Authors' conclusions:<br>'CRT is feasible and safe. It improved dyspnoea and LVEF and reduced hospital stay for heart failure during long term follow-up'.<br><br>Comments:<br>Only followed 43/47 patients who had successful implantation<br>56% received ICD-CRT<br>Atrial fibrillation present in 16%.<br><br>Selected series with criteria<br><br>Blinding. No<br>Follow-up completeness: Unclear<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Santomauro et al 2004)<br><br>Location:<br>Federico University, Naples, Italy<br><br>Study period:<br>Martch 2001-June 2003<br><br>Study type:<br>Case series<br><br>Level IV | 45 male patients with severe drug refractory CHF. Technetium scintigraphy performed at 14 days and 24 and 36 months following pacemaker insertion to analyse relationship between ventricular contractile synchrony and LVEF.<br><br>Follow-up: 36 months<br><br>Inclusion criteria:<br>LVEF < 35%<br>Sinus rhythm<br>QRS > 120 ms<br>LBBB<br>NYHA Class II-IV despite optimal medical therapy. | Implantation success rate: not stated<br><br>Postoperative:<br>No complications related to lead placement or CRT.<br><br>Postoperative:<br>No complications related to lead placement or CRT.<br><br>Patient characteristics:<br>Mean age 64 years. Male 100%, ischaemic heart disease n=3. | Authors' conclusions:<br>No safety conclusions.<br>The data from this study suggest that CRT, by correcting interventricular contractile dyssynchrony may in part contribute to improve the ventricular function.<br><br>Comments:<br>Primary aim was to evaluate the usefulness of Fourier analysis when estimating the electromechanical resynchronisation in CHF patients with CRT.<br><br>Unclear if consecutive patients were used<br><br>Blinding: unclear.<br>Follow up completeness unclear.<br>Comparison group: no. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(O'Donnell et al 2005)<br><br>Location:<br>Austin Health, Heidelberg,Victoria, Australia<br><br>Study period: not stated.<br><br>Study type:<br>Case series<br><br>Level IV | 40 recipients of CRT devices were studied before, during and at specified intervals over 9 months after implant. Groups were studied to determine optimal programme setting.<br><br>Follow-up:<br>9 months<br><br>Inclusion criteria:<br>NYHA Class II-IV despite optimal medical therapy<br>LV EF <35%<br>Ventricular dyssynchrony<br>Predominantly in sinus rhythm<br>LBBB with QRS >150 ms, without over myocardial ischaemia.<br>Limited to patients who had undergone a successful implantation of a transvenous lead in a true lateral or postero-lateral epicardial vein. | Implantation success rate: full. Reasons for exclusions from this study were unsuccessful transvenous LV lead placement in 5 (implying an implantation success rate of 88%) and death during follow up in one patient.<br><br>Perioperative: not stated<br><br>Postoperative:<br>Death n=1.<br><br>Hospitalisation:<br>1,163 days over 9 months before implantation and 17 days after (excluding implantation days).<br><br>Patient characteristics:<br>Not stated. | Authors' conclusions:<br><br>No specific safety conclusions.<br>'Optimal stimulation parameters in CRT devices vary over time. Though temporal trends were observed in the overall population, they could not be accurately predicted in individual patients. Detailed, regular reevaluations and reprogramming of optimal parameters may be appropriate.'<br><br>Comments:<br>Primary study aim was to quantify the temporal variations in programming parameters to optimise follow up of CRT devices.<br>Australian location.<br><br>Consecutive patients<br><br>Blinding: yes.<br>Follow-up completeness: Full.<br>Comparison group: no. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Leclercq et al 2000b)<br><br>Location:<br>Cardio-Pneumologique Hôpital Pontchaillou, Rennes, France.<br><br>Study period:<br>Unclear.<br><br>Study type:<br>Prospective case series.<br><br>Level IV | 37 patients receiving CRT pacing, all with transvenous leads. Study aimed to examine long-term effects of CRT among patients with either SR or atrial fibrillation.<br><br>Follow-up:<br>Mean duration 13.5+/-8.4 months (SR) & 14.4+/-10.9 months (AF).<br><br>Inclusion criteria:<br>LVEDD > 60 mm, LVEF< 35%. All types of aetiology for heart failure, NYHA III or IV, medications included diuretic, ACE inhibitor at maximal doses and QRS >120 ms. | Implantation: None specified<br><br>Postoperative:<br>9 deaths (4 in SR and 5 in AF sub-groups; 7 in NYHA class IV).<br>Re-operation required in 5 (2 LV dislodgements, 3 adaptor problems).<br><br>Mean implantation duration: 150 (80) minutes.<br><br>Patient characteristics:<br>Mean age = 67 (8) yrs, gender not given, mean QRS = 178 ms (23), mean LVEF = 22% (6), includes patients in SR (n=22) and AF (n=15), NYHA class III (n=26, 16 in SR) and IV (n=11, 6 in SR). Aetiology: ischaemia (n=14, 10 in SR), idiopathic (n=18, 10 in SR), other (n=4, 2 in SR), 1 not stated. | Authors' conclusions:<br>CRT significantly improves exercise tolerance in patients with SR or permanent atrial fibrillation.<br><br>Comments:<br>May include data subsequently reported in Leclercq et al (2000a)5}a) and/or Alonso et al (2001)1}1).<br>Total mortality (24%) may reflect greater risk if in AF (33% of AF c.f. 18% SR patients died).<br>5 in sinus rhythm group had a previous pacemaker.<br>Selected series with defined criteria.<br>No blinding.<br>Completeness of follow-up: not stated.<br>No external control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Chan et al 2003b)<br><br>Location:<br>Princess Margaret Hospital, Hong Kong and Stanford University Medical Centre, California, USA.<br><br>Study period:<br>1 January 2000 – 30 June 2001<br><br>Study type:<br>Descriptive case series<br><br>Level IV | Description of experience with contrast venography guided axillary vein puncture, which avoids the possibility of subclavian crush phenomenon associated with lead placement using a subclavian puncture.<br><br>Follow-up: 12 months<br><br>Inclusion criteria:<br>Admitted for biventricular pacing or implantable defibrillator therapy. | Safety results: n= 35 patients – axillary puncture technique was used to attempt the implantation of all 3 leads in every patient.<br><br>Implantation success rate:<br>34/35 patients (97%) one failure was reported to be due to a small axillary vein, subclavian puncture was then performed successfully.<br><br>Perioperative:<br>No contrast related complications, no puncture related complications, no lead related problems<br><br>Postoperative:<br>No contrast related complications, no puncture related complications, no lead related problems<br><br>Patient characteristics:<br>29 (83%) male, mean age = 57.1 +/- 14.7 years, ischaemic cardiomyopathy = 12, dilated cardiomyopathy = 21, hypertrophic cardiomyopathy = 1. NYHA II = 6 (17%), III = 20 (60%), IV = 8 (24%). Mean LVEF = 23%. 6 BVP alone. | Authors' conclusions:<br>'Axillary vein puncture technique is effective and safe for biventricular pacing<br><br>Comments: 29 received ICD.<br>Axillary puncture was assessed.<br><br>Consecutive series<br><br>Blinding: No<br>Follow-up completeness: Not stated, presumed to be full<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Toussaint et al 2003)<br><br>Location:<br>Hôpital Européen Georges Pompidou, Paris, France<br><br>Study period:<br>January 1997 – May 2000.<br><br>Study type:<br>Cohort<br><br>Level IV | Patient group studied by radionucleiotide Angioscintigraphy before, eight days after implantation with a biventricular pacemaker. Further evaluations undertaken at every 3 months follow-up. All received transvenous biventricular pacing.<br><br>Follow-up: 20 +/- 7months.<br><br>Inclusion criteria:<br>Age > 18 and < 80 years, NYHA III or IV, LVEF < 40%, EDD > 60 mm, QRS > 150 ms, LBBB, symptomatic despite optimal medications, exclusions were unstable angina or recent myocardial infarction within last 3 months, requiring surgery, 2nd or 3rd degree heart block. | Safety results: 34 patients<br><br>Implantation success rate: Not stated.<br><br>Perioperative: Not stated.<br><br>Postoperative:<br>Survival: 3 deaths. Deaths were due to: electromechanical dissociation during orthopaedic surgery at 18 months follow-up (n=1), heart failure at 28 months follow-up (n=1), sepsis at 30 months follow-up (n=1).<br><br>Patient characteristics:<br>Male (n=31), mean age = 64.5 +/- 11 years, ischaemic cardiomyopathy (n=18, 53%), idiopathic cardiomyopathy (n=15), valvular cardiomyopathy (n=1), mean LVEF = 20.2 +/- 8.1%, mean QRS = 179 ms, mean NYHA 3.4 +/- 0.5. | Authors' conclusions:<br><br>No safety related conclusions.<br>'Biventricular pacemaker resynchronises ventricles early and in the longer term while ejection fraction improves progressively. Patients with large electromechanical dyssnchrony benefit most.'<br><br>Comments:<br>Unclear if any deaths were related to the procedure or device.<br><br>Consecutive series.<br><br>Blinding. No<br>Follow-up completeness: Full<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Teo et al 2003)<br><br>Location: Indonesia, Thailand, Singapore.<br><br>Study period: August 1999 – December 2001<br><br>Study type: Prospective cohort?<br><br>Level IV | Description of experience with resynchronisation therapy. NYHA class, treadmill exercise time, LVEF, symptoms and survival assessed during follow-up. Cephalic vein cut down or subclavian puncture. LV lead secured followed by implantation of RV and RA leads.<br><br>Follow-up: 1- 28 months<br><br>Inclusion criteria:<br>NYHA III or IV, QRS > 130ms, LVEF ≤ 40%, on optimum medical therapy, not a candidate for heart transplant. Exclusions were: myocarditis, unstable coronary syndromes or planned for revascularisation. | Safety results: n= 29 patients<br><br>Implantation success rate:<br>All left ventricular leads were reported as successfully implanted.<br><br>Perioperative:<br>Pocket haematoma (n=1), transient worsening of heart failure (n=1) requiring inotropic support over a few hours.<br>Mean procedure time was 167 +/- 79.6 minutes.<br><br>Postoperative:<br>Complications: lead dislodgement (n=2) symptoms improved after repositioning (1), 1 declined.<br>Survival:<br>3 deaths, 1 related to sudden death and 2 due to progressive heart failure.<br><br>Patient characteristics:<br>Mean age = 59.6 +/- 12.8 years, male = 26 (90%), 62% ischaemic cardiomyopathy, NYHA all III or IV, mean LVEF =22 +/- 8%, LBBB (n=23), RBBB (n=4), mean QRS = 161 +/- 21 ms. | Author's conclusions:<br>'Biventricular pacing can be safely performed and results in improvement in symptoms and exercise tolerance in heart failure patients with ventricular dyssynchrony not responding to drug therapy.'<br><br>Comments:<br>5 patients received an implantable defibrillator.<br>Small sample.<br><br>Selected series.<br><br>Blinding: No<br>Follow-up completeness: Variable<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Medina-Ravell et al 2003)<br><br>Location:<br>Unclear - ?Venezula and ?US<br><br>Study period:<br>Not stated<br><br>Study type:<br>Case series<br><br>Level IV | Examination of pacing site-dependent changes in QT interval, JT interval and transmural dispersion of repolarisation and their potential role in the development of torsades de pointes. Measurements were obtained with right ventricular endocardial pacing, biventricular pacing and left ventricular epicardial pacing. Data collected perioperatively, 24 hrs postop and 1-2 weeks later.<br><br>Follow-up:<br>Up to 2 weeks<br><br>Inclusion criteria:<br>None stated | Safety results: n= 29 patients<br><br>Implantation success rate: not stated<br><br>Perioperative:<br>4/29 frequent R on T ventricular extrasystoles (inhibited by RVEndoP)<br>1 recurrent non-sustained polymorphic VT.<br>1 incessant torsade de pointes (TdP) (also had ICD)<br><br>Postoperative: not stated<br><br>Patient characteristics:<br>Male= 23 (79%), mean age = 71 +/- 8 years, ischaemia n=23, non-ischaemia n=6, LVEF = 23 /-7%, none had history of polymorphic ventricular tachycardia or torsades de pointes, QRS = 154 +/- 19 ms, LBBB=n=14, RBBB n=2, NYHA III or IV. | Author's conclusions:<br>'Biventricular pacing increase QT, JT and transmural dispersion of repolarisation by altering the transmural sequence of activation of the intrinsically heterogeneous ventricular myocardium. Our data suggests that the resultant exaggeration of arrhythmic substrates can lead to the development of torsades des pointes in a sub-set of patients.'<br><br>Comments:<br>Some patients received an implantable defibrillator.<br><br>Consecutive series.<br><br>Blinding: Yes – blinded measures<br>Follow-up completeness: 12/29 (41%)<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Galvao et al 2002)<br><br>Location:<br>Sao Paula, Brazil.<br><br>Study period:<br>April 1999 – August 2000.<br><br>Study type: Retrospective case series.<br><br>Level IV | Aim was to report results of use of CRT at authors' institution. Case series of 28 patients.<br><br>Follow-up:<br>Duration five months (range 10 days to 14 months).<br><br>Inclusion criteria:<br>Dilated cardiomyopathy, QRS >140 ms, uncontrolled heart failure despite optimal medical therapy. | Implantation:<br>No complications or failure to implant information given.<br><br>Postoperative:<br>Deaths n=3 (sudden death n=2, pulmonary fungal infection n=1), cardiac transplantation n=3, lead dislodgement n=1, pacemaker site infection n=1 (requiring explantation and reimplantation), LPN stimulation n=1, EPT n=2 (both in epicardial leads).<br><br>Patient characteristics:<br>Mean age = 58 years, 23/28 male, mean QRS = 187 ms, mean LVEF = 20 (7)%, rhythm = SR and AF numbers not stated (at least one patient in AF). NYHA class III n=12, class IV n=16, aetiology = not stated. | Authors' conclusion:<br>'CRT … improved significantly the Functional Class (sic) and, therefore, the quality of life.'<br><br>Comments:<br>Specific triple-chamber pacemaker used in four patients. One patient in AF + ventricular arrhythmia received BiV + ICD.<br>Note: Three patients had epicardial leads (one subsequently reimplanted with transvenous leads due to EPT). Complications are presumed to be transvenous unless otherwise stated.<br>Inclusion criteria not clearly stated: uncertain if criteria listed here were selection criteria or patient characteristics.<br>Follow-up information unclear and incomplete follow-up data on seven patients.<br>Unclear if consecutive or selected.<br>Safety outcomes not a stated aim of the study.<br>No blinding.<br>No control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(O'Cochlain et al 2001b)<br><br>Location:<br>Emory University Hospital, Atlanta, USA.<br><br>Study period: September 1999 – May 2000.<br><br>Study type:<br>Prospective case series.<br><br>Level IV | Studied effects of variation in activation time between right and left ventricle using paced QRS duration at implantation. 26 patients enrolled.<br><br>Follow-up:<br>Duration 0 days (implantation and pacing modality study only).<br><br>Inclusion criteria:<br>None stated. | No complications reported.<br><br>Patient characteristics:<br>Mean age = 63 (11) years, 20/26 male, average QRS = 160 (16) ms. Mean LVEF not given, all patients in LBBB, SR/AF not given. NYHA class III n=12, class IV n=14. Aetiology: ischaemia (n=15), idiopathic (n=11). | Author's conclusion:<br>The ability to programme the left and right ventricle interval may be useful to optimise the effects of CRT.<br><br>Comments:<br>Consecutive patients.<br>No blinding.<br>Follow-up full but brief.<br>No external control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Sogaard et al 2001)<br><br>Location:<br>Skejby Hospital, Denmark.<br><br>Study period:<br>Study period = 1 year Which period not stated.<br><br>Study type:<br>Prospective case series.<br><br>Level IV | Echcardiography and tissue velocity imaging used to evaluate the effect of CRT on left ventricle performance and volumes. 25 patients enrolled.<br><br>Follow-up:<br>Duration 0 days (implantation and pacing modality study only).<br><br>Inclusion criteria:<br>Sinus rhythm, bundle branch block, NYHA III or IV despite medical treatment patients referred for CRT. | No complications reported.<br><br>Patient characteristics:<br>Average age = 61 (10) years, 22/25 males, mean QRS = 184 (24) ms, mean LVEF= 23.2 (6) %. All patients in SR. NYHA class III n=14, class IV n=11. Aetiology = ischaemia (n=16), non-ischaemia (n=9). Medications: ACE inhibitor (100% of patients), diuretic (100%), beta-blocker (88%), digoxin (80%), aldosterone antagonist (76%). | Author's conclusion:<br>CRT improves left ventricular systolic performance and reduces left ventricular volumes.<br><br>Comments:<br>Consecutive patients and defined criteria.<br>No blinding.<br>Follow-up: full but brief.<br>No external controls. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Yu et al 2002)<br><br>Location:<br>Queen Mary Hospital, Hong Kong.<br><br>Study period:<br>Unclear.<br><br>Study type:<br>Prospective series.<br><br>Level IV | Aim was to investigate the effect of CRT on reverse modelling and the underlying mechanisms. 25 patients enrolled. Serial echocardiography, exercise and quality of life assessments.<br><br>Follow-up:<br>Duration 4 months (3 months of pacing followed by 1 month off).<br><br>Inclusion criteria:<br>NYHA III or IV, LVEF <40%, QRS > 140ms. | Implantation:<br>Authors report all patients successfully implanted.<br><br>Postoperative:<br>Deaths n=1 progressive heart failure, acute deterioration in heart failure (n=1) when pacemaker turned off, resolved when pacemaker turned back on.<br><br>Patient characteristics:<br>Mean age = 65 (12) years, 18/25 male, mean QRS = 162 (30) ms, mean LVEF = 28 (10)%, rhythm = not stated, NYHA Class III = 11, IV = 14, aetiology = idiopathic dilated cardiomyopathy (n=11), ischaemia (n=9), hypertension (n=3), alcoholic cardiomyopathy (n=1), chemotherapy induced (n=1). | Authors' conclusion:<br>'CRT … reverses LV remodelling and improves cardiac function.'<br><br>Comments:<br>Six patients received Easytrak leads, four patients received Contak TR pacemakers and two received Guidant model 1241 with ICD.<br>Follow-up: satisfactory.<br>Consecutive patients using a few defined selection criteria.<br>Safety outcomes: not a stated aim of the study.<br>No blinding.<br>No control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Bax et al 2003b)<br><br>Location:<br>Unclear – The Netherlands, Australia?<br><br>Study period:<br>Not stated<br><br>Study type:<br>Case series<br><br>Level IV | Before implantation clinical and echocardiographic parameters including LVEF, peak systolic velocities and septal to lateral dyssynchrony were derived using myocardial tissue Doppler imaging. The parameters were assessed again after implantation. Transvenous insertion LV pacing lead via subclavian approach. Biventricular DDD-R system used in all patients.<br><br>Follow-up: 3 months<br><br>Inclusion criteria:<br>NYHA III or IV, LVEF ≤35%, QRS >120 ms. | Safety results: 22 patients.<br><br>Implantation success rate:<br>"The procedure was uncomplicated in all patients'<br><br>Perioperative:<br>"The procedure was uncomplicated in all patients'<br><br>Postoperative: not stated<br><br>Patient characteristics:<br>Male =15 (68%) men, mean age = 63 years, mean LVEF = 19+/- 8% or 21 +/- 7%, mean QRS = 172 +/- 33 ms. | Authors' conclusions:<br>No safety related conclusions.<br>"Tissue doppler imaging allowed evaluation of LV dyssynchrony and subsequent resynchronisation after biventricular pacemaker implantation.'<br><br>Comments:<br>7/22 patients received a biventricular implantable defibrillator.<br>Discrepant baseline results were reported.<br><br>Consecutive series.<br><br>Blinding: No<br>Follow-up completeness: Full (assumed)<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author<br>(Leclercq et al 1998)<br><br>Location:<br>Centre Cardio-Pneumologique, Hôpital Pontchaillou, Rennes, France.<br><br>Study period:<br>Unclear.<br><br>Study type:<br>Prospective case series. Comparisons made using same patient and different pacing modalities.<br><br>Level IV | 18 patients receiving CRT pacing.<br><br>Follow-up:<br>Short haemodynamic study.<br>Duration none (only acute effects reported). Assessed acute haemodynamic effects of the best mode of DDD pacing.<br><br>Inclusion criteria:<br>Age <18 >80 years, sinus rhythm, NYHA III or IV, LVEF <35%, LVEDD >60mm, QRS >120 ms, ischaemic or idiopathic origin. | Implantation:<br>None reported.<br><br>Patient characteristics:<br>Average age = 65(5), 17/18 male, mean QRS= 170 (37) ms, mean LVEF = 19 (5)%, all patients had LBBB and all assumed to be in SR, NYHA class III n=4, class IV n=14. Ischamic origin in 2 cases, idiopathic in 14, 1 vavlular and 1 sarcodiosis.<br>All patients received ACE inhibitors and diuretics at maximally tolerated doses. Digoxin was prescribed to 60%. | Authors' conclusions:<br>Biventricular DDD pacing may improve cardiac performance compared with intrinsic conduction and single site RV DDD pacing.<br><br>Comments:<br>May include data subsequently reported in Leclercq et al (2000a)5}a), Leclercq et al (2000b)1}c), Alonso et al (1999)9}9) &/or Alonso et al (2001)1}1).<br><br>Selected series.<br>No blinding.<br>Follow-up: 15/18 (83%) patients received haemodynamic assessment.<br>No control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Braunschweig et al 2000)<br><br>Location:<br>Karolinska Hospital, Stockholm, Sweden.<br><br>Study period:<br>June 1998 – May 1999.<br><br>Study type:<br>Prospective case series.<br><br>Level IV | Aimed to assess hospital days, safety, and efficacy of CRT comparing one year before implantation with one year after. 16 patients enrolled.<br><br>Follow-up:<br>Duration of f/u mean 291+/-76 days (range 120 to 365 days).<br><br>Inclusion criteria:<br>NYHA III or IV despite optimised medications including an ACE inhibitor or beta-blocker. Stable over last month. LVEF < 40%, QRS > 150 ms. | Implantation: All 16 successfully implanted.<br><br>Postoperative events:<br>Deaths n=2 (progressive heart failure 1, pneumonia secondary to hip fracture 1), lead dislodgement n=2 (one of whom requiring 3 repositionings), pacemaker pocket haematoma n=1.<br>Mean operation time = 71 (30) minutes and mean hospital stay = 2.5 (0.7) days.<br><br>Hospitalisations:<br>Number of hospitalisations = 42 before and 8 after. Number of hospital days before CRT = 253, after implantation = 45.<br><br>Patient characteristics:<br>Average age = 64 (12) years, 15/16 males, mean QRS = 181 (22) ms, mean LVEF = 22 (7)%. n=7 in AF (3 with His ablations) and n=9 in SR. NYHA class III n=14, NYHA class IV n=2. Aetiology = ischaemia (n=11), idiopathic (n=5). | Author's conclusion:<br>Need for hospital care is significantly reduced after implantation.<br><br>Comments:<br>All pacemaker insertions performed by one operator.<br>Selected patients, criteria given.<br>No blinding.<br>Follow-up described and complete.<br>No external control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Sayad et al 2003)<br><br>Location:<br>Florida Cardiovascular Institute and Tampa General Hospital, USA.<br><br>Study period:<br>Not stated.<br><br>Study type:<br>Case series<br><br>Level IV | Description of experience with new method to cannulate coronary sinus which involves cutting the proximal end of the conventional 5Fr left Amplatz catheter and passing the coronary sinus sheath over the catheter and then removing it. Infraclavicular incision.<br><br>Follow-up: Not stated.<br><br>Inclusion criteria:<br>Drug refractory heart failure. | Safety results: 15 patients<br><br>Implantation success rate:<br>'Implantation successful in all patients'<br><br>Perioperative:<br>No complications – specifically no dissection or perforation.<br><br>Postoperative: not stated<br><br>Patient characteristics: 10 men (67%), mean age = 67 +/- 7 years, SR (n=11), atrial fibrillation (n=4) and received a conventional VVIRpacemaker. | Authors' conclusions:<br>'Simple, safe and fast technique for coronary sinus cannulation. Encourage manufacturers to make an additional guiding sheath with an Amplatz curve that can be used for coronary sinus engagement.'<br><br>Comments:<br>3 patients intraventricular conduction delay related to an implanted right ventricular pacemaker.<br>Atrial fibrillation in 4 patients.<br>Unclear recruitment.<br>Small sample.<br><br>Selected series.<br><br>Blinding: No<br>Follow-up completeness: Unclear<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Pappone et al 2001)<br><br>Location:<br>Hospital San Raffaele, Milan, Italy; Technicron Israel Institute, Haifa, Israel; and Beth-Israel Hospital, Boston, USA.<br><br>Study period:<br>Unclear.<br><br>Study type:<br>Prospective case series.<br><br>Level IV | Assessment of safety and efficacy of cardiac contractility modulating signals for CRT. 15 patients enrolled.<br><br>Follow-up:<br><br>Duration 0 days (implantation and pacing modality study only).<br><br>Inclusion criteria:<br>None stated. | No complications reported.<br><br>Patient characteristics:<br>Mean age = 62 (8) years, 12/15 males, mean QRS not given, mean LVEF = 28(5)%, AF/SR not given, NYHA class I n=2, class II n=9, class III n=4. Aetiology: ischaemia (n=7), non-ischaemic (n=8). | Author's conclusions:<br>CRT increased myocardial contractility and improved haemodynamic performance.<br><br>Comments:<br>Selected patients no criteria.<br>No blinding.<br>Follow-up was full but brief.<br>No external comparison group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Kim et al 2001)<br><br>Location:<br>Aarhus University Hospital, Skejby Sygehus, Denmark.<br><br>Study period:<br>Unclear.<br><br>Study type:<br>Prospective case series.<br><br>Level IV | Study aimed to quantify the short-term haemodynamic effects of CRT using echocardiography. 15 patients enrolled.<br><br>Follow-up:<br>Duration.9 days (range 2-7 days).<br><br>Inclusion criteria:<br>Bundle branch block (QRS >120 ms), NYHA III or IV despite current medical treatment. | No complications reported.<br><br>Patient characteristics:<br>Average age = 63.5 (9) yrs, 15/15 males, mean QRS = 182 (23) ms, average LVEF= 26.4 (6)%. All patients in SR and LBBB. NYHA class III n=9, class IV n=6. Aetiology: ischaemia (n=11), idiopathic (n=3), valvular (n=1). | Author's conclusions:<br>5/15 patients with CRT reduced their left ventricular chamber size and mitral regurgitation.<br><br>Comments:<br>Consecutive patients some defined criteria.<br>Blinding of echocardiography assessment.<br>Full follow-up (10/15 for 2-7 days and 5/15 for 1 day).<br>No external comparison group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Kasravi et al 2005)<br><br>Location:<br>Long Beach Memorial Medical Centre, California, USA.<br><br>Study period:<br>January 2002 to February 2004<br><br>Study type:<br>Retrospective database review of case series<br><br>Level IV | Pacemaker lead extraction from coronary sinus (14 had a CRT device). Leads extracted using nonsurgical techniques. Both subclavian and femoral vein approaches have been employed for extraction, which is performed under general anaesthetic. Database review at a single centre.<br><br>Follow-up:<br>Mean 17 months.<br><br>Inclusion criteria:<br>Not stated. | Implantation success rate: not stated<br><br>Perioperative: not stated<br><br>Postoperative:<br>14 leads extracted without difficulty. One lead was retrieved from the lateral branch of the CS but its tip was attached to the ostium of the CS. This lead was extracted using a locking stylet and a looping exchange wire.<br><br>Indications for lead extraction:<br>Infection: n=7<br>Lead malfunction: n=7<br>Exit block: n=2<br>(Two patients were described as having both malfunction and exit block as the indication for extraction).<br>All leads able to be reimplanted.<br><br>Patient characteristics:<br>Restricted to the 14 with a CRT:<br>Median age 71.5 years (range 61-83). Male (n=13, 93%) | Authors' conclusions:<br>'As experience grows with leads implanted for longer duration and with newer active fixation design leads, we will gain more insight into the safety of their removal from the branches of the CS.'<br><br>Comments:<br>6 of 14 CRT devices also had ICD.<br>Mean duration of implantation: 17 months<br>Unclear if consecutive patients were used.<br><br>No blinding<br>Full follow-up<br>No comparison group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Kerwin et al 2000)<br><br>Location:<br>University of California, United States.<br><br>Study period:<br>July 1997 – April 1998.<br><br>Study type:<br>Prospective case series.<br><br>Level IV | The aim was to evaluate the effects of CRT on contractile synchrony and ejection fraction. Total n=13 patients: 11 received either permanent CRT pacing (n=6) or acute CRT pacing in the laboratory (n=5) via endocardial leads; another 2 received CRT post-CABG via epicardial leads.<br><br>Inclusion criteria:<br>Dilated cardiomyopathy, NYHA II-IV, SR, had a CRT device, referred for electrophysiologuy, or open-heart surgery and epicardial pacing. | Authors state that no '…complications regarding lead insertion, CRT or radionuclide image acquisition…' occurred.<br><br>Patient characteristics:<br>Mean age = 58 (13) yrs, 9/13 male, mean QRS = 156 (48) ms, mean LVEF = 17 (8)%, all patients were in SR, NYHA II n=7, NYHA III n= 6. Aetiology: Ischaemia (n=2), idiopathic (n=9), valvular (n=1), alcoholic cardiomyopathy (n=1). | Author's conclusions:<br>'Improvements in interventricular dyssnychrony during CRT correlated with acute improvements in left ventricular ejection fraction'.<br><br>Comments:<br>The six patients receiving permanent CRT were part of the VIGOR trial.<br>Note: Two patients had epicardial leads.<br>Patients were consecutive.<br>No blinding.<br>Completeness of follow-up: Not stated.<br>No external control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Hamdan et al 2000)<br><br>Location:<br>Dallas Veterans Affairs Medical Centre, Dallas, USA.<br><br>Study period:<br>Unclear.<br><br>Study type:<br>Prospective case series.<br><br>Level IV | 13 patients enrolled. Aim was to compare CRT with single-site pacing in relation to the effect on haemodynamics and sympathetic activity.<br><br>Follow-up:<br>Duration 0 days (implantation and pacing modality study only).<br><br>Inclusion criteria:<br>LVEF<35%, 'indications for CRT'. | No complications reported.<br><br>Patient characteristics:<br>Mean age = 66 (8) years, all males, mean QRS = 123 (31) ms, mean LVEF = 28 (7)%, NYHA class and AF/SR rhythm data not provided. Aetiology: not stated. | Author's conclusion:<br>'LV based pacing improves haemodynamics and decreases sympathetic activity compared with right ventricle-based pacing'.<br><br>Comments:<br>Selected patients some criteria.<br>No blinding.<br>Follow-up complete but brief.<br>No external controls |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Garrigue et al 2001b)<br><br>Location:<br>University of Bordeaux, Bordeaux-Pessac, France.<br><br>Study period:<br>Unclear.<br><br>Study type:<br>Prospective case series.<br><br>Level IV | Aim was to assess the usefulness of CRT in patients with heart failure and RBBB. Twelve patients enrolled. Mainly echocardiography data.<br><br>Follow-up:<br>Duration 12 months for all patients.<br><br>Inclusion criteria:<br>NYHA II or III despite diuretics, ACE inhibitor and beta-blockers at maximally tolerated doses, LVEF <35%, LVEDD >or=60 mm, complete RBBB with QRS >140 ms age >18 or <80 years, no unstable angina in last 2/12, no AMI in last 6/12, no coronary angioplasty and/or CABG in past year. | No complications reported.<br><br>Patient characteristics:<br>Mean age = 64 (10) yrs, 11/12 male, mean QRS = 189 (26) ms, mean LVEF = 24 (6)%. Rhythm = SR n=8, AF n=4, all patients had RBBB, NYHA class II n=2, class III n=10, aetiology = ischaemia (n=5), idiopathic (n=7). | Authors' conclusion:<br>'…only patients with a RBBB associated with a major left intraventricular asynchrony detected echocardiographically are likely to respond to pacing therapy'.<br><br>Comments:<br>Adequate follow-up.<br>Selected with defined criteria.<br>Safety outcomes not a stated aim of the study.<br>No blinding.<br>No external control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Lau et al 2000)<br><br>Location:<br>Queen Mary Hospital, Hong Kong.<br><br>Study period:<br>Unclear.<br><br>Study type:<br>Prospective case series.<br><br>Level IV | Eleven patients enrolled. Aim was to assess if CRT reverses left ventricular remodelling.<br><br>Follow-up:<br>Duration 3 months.<br><br>Inclusion criteria:<br>LVEF<35%, refractory to optimal medical therapy. | No complications reported.<br><br>Patient characteristics:<br>Mean age = 61 (8) yrs, 7/11 males, mean QRS = 165 (37) ms, mean LVEF = 21.6 (10)%, All patients in SR. All patients in NYHA class III or IV (numbers and mean not specified). Aetiology of disease: idiopathic (n=6), ischaemic (n=3), hypertensive cardiomyopathy (n=1), chemotherapy induced (n=1). Use of medications: ACE inhibitors (n=9), angiotensin antagonists (n=2), beta-blocker (n=6), digoxin (n=5), diuretics (n=11). | Authors' conclusion:<br>'CRT over three months was associated with haemodynamic improvements, reversal of left ventricular remodelling.'<br><br>Comments:<br>Consecutive patients.<br>No blinding.<br>Completeness of follow-up not stated.<br>No external control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Baker et al 2004)<br><br>Location:<br>Ohio State University College of Medicine, Columbus, Ohio, USA<br><br>Study period: not stated<br><br>Study type:<br>Case series<br><br>Level IV | Eleven patients who met the criteria for CRT were included. Systolic and diastolic time intervals were measured along with QoL, 6-minute walk test and ECG.<br><br>Follow-up:<br>Evaluated at 1 and 3 months post CRT implantation.<br><br>Inclusion criteria:<br>NYHA Class III-IV on optimal medical therapy.<br>LVEF<35%<br>LBBB or intraventricular conduction block with QRS >130 ms.<br>Patients with atrial fibrillation, another major life threatening illness or carotid artery disease were excluded | Safety results: 11 patients<br><br>Implantation success rate: 11/11 (100%)<br><br>Perioperative: not stated<br><br>Postoperative: not stated<br><br>Patient characteristics:<br>Median age 62 years (range 46-70), Male n=8 (73%), mean LVEF 21%. Dilated cardiomyopathy of uncertain aetiology (n=5), familial dilated cardiomyopathy (n=1), dilated cardiomyopathy after remote MI (n=2), dilated cardiomyopathy after long standing systemic hypertension (n=2) | Authors' conclusions:<br>No safety related conclusions<br>'CRT shortened pre-ejection period.'<br><br>Unclear if patients were consecutive or selected<br><br>No blinding<br>Follow-up completeness unclear<br>No comparison group |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Pires et al 2005)<br><br>Location:<br>St John Hospital, Detroit, Michigan, USA<br><br>Study period:<br>July 2002 – April 2004<br><br>Study type:<br>Case series<br><br>Level IV | Studied 10 patients in whom the right internal jugular vein was used for placement of the coronary sinus leads.<br><br>Follow-up: 12 months.<br><br>Inclusion criteria: Not stated. | Implantation success rate: not stated<br><br>Perioperative:<br>Mean procedure duration = 124 minutes.<br>One haematoma – no specific intervention required.<br>No other complications.<br><br>Postoperative: not stated<br><br>Patient characteristics:<br>Age 66 years (range 42-82), Male (n=6, 60%), LV EF 19%, QRS duration 183 ms. | Authors' conclusions:<br>In situations where the more traditional CAS venous approach cannot be used (left side) or is technically difficult (right side), it is reasonable, in experienced centres, to employ the right internal jugular venous approach to deploy CS leads before resorting to the more invasive epicardial approach.<br><br>Comments:<br>Unclear if patients were consecutive<br>Unclear if haematoma was in a patient receiving CRT alone<br>Seven patients received an ICD.<br><br>Blinding: not stated.<br>Follow-up completeness: unclear.<br>Comparison group: no. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Nelson et al 2000)<br><br>Location:<br>Johns Hopkins Medical Institution, Baltimore, USA.<br><br>Study period:<br>Unclear.<br><br>Study type:<br>Prospective case series.<br><br>Level IV | Ten patients enrolled. Aim was to test if CRT changes cardiac oxygen consumption.<br><br>Follow-up:<br>Duration 0 days (implantation and pacing modality study).<br><br>Inclusion criteria:<br>NYHA calss II-IV, LVEF <35%, LBBB with QRS > 140 ms, PR interval >160ms, sinus rhythm, <20% stenosis in left coronary circulation, evidence of contractile improvement from pacing. | No complications reported.<br><br>Patient characteristics:<br>Mean age 57 (4) years, 5 males, mean QRS = 179 (3) ms, mean LVEF = 20 (3)%, all patients were in LBBB (SR/AF not reported). NYHA class III n=8, NYHA class IV n=2. Aetiology: ischaemic cardiomyopathy (n=2) and dilated cardiomyopathy (n=8). Medications included digoxin, diuretics, an ACE inhibitor, and in 5 cases a beta-blocker. | Authors' conclusion:<br>CRT increases systolic function with a minimal increase in energy.<br><br>Comments:<br>Haemodynamic study.<br>Selected patients with defined criteria.<br>No blinding.<br>Follow-up presumed complete but brief.<br>No external control group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(de Cock et al 2004)<br><br>Location: VU University Medical Centre, Amsterdam, The Netherlands.<br><br>Study period: January 1998 – December 2001<br><br>Study type: Case series<br><br>Level IV | Description of outcomes from 103 implanted patients. Patients were noted to have sustained coronary artery dissection due to the presence of extravasation of contrast and in whom balloon occlusive venography was repeated using multiple projections. A major dissection was defined as a dissection equal to or exceeding the luminal diameter of the dissected vessel. Balloon occlusive venography was repeated 2-3 months after the procedure and parameters such as minimal luminal diameter and minimal luminal cross sectional area were calculated.<br><br>Follow-up:<br>2-3 months<br><br>Inclusion criteria:<br>NYHA III or IV, QRS ≥140 ms, LVEF ≤35%. | Safety results:<br>7 cases of dissection (6.8%) among 103 consecutive attempts at implantation.<br><br>Implantation success rate: not stated.<br><br>Perioperative:<br>During 103 attempts, 7 patients (6.8%) had angiographic signs of a major coronary sinus dissection. In one patient, pericardial extravasation was observed. Clinical follow-up was uneventful for all patients except one who complained of prolonged chest discomfort for several hours after the procedure. In none of the patients were there signs of pericardial effusion or tamponade demonstrated on echocardiography.<br><br>Postoperative:<br>Follow-up venography did not reveal any significant differences in vessel parameters although in one patient a small partial dissection was still present.<br><br>Patient characteristics:<br>Male n=5, mean age = 62 +/- 12 years. | Author's conclusions:<br>'Although dissection of the coronary sinus following lead implantation is not an uncommon complication, it is usually well tolerated. Long term angiographic follow-up demonstrated no significant vessel damage or vessel remodelling.'<br><br>Comments:<br>2 operators.<br><br>Consecutive series.<br><br>Blinding: No<br>Follow-up completeness: Full<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Ohkusu et al 2003)<br><br>Location:<br>Yokohama City University School of Medicine, Yokohama, Japan.<br><br>Study period:<br>Not stated<br><br>Study type: case series<br><br>Level IV | Methods:<br>Cardiac glucose metabolism was measured using PET scanners.<br><br>Follow-up:<br>Mean duration = 7.8 +/- 2.7 months (range 5-12 months).<br><br>Inclusion criteria:<br>CHF any cause despite optimal medical therapy including ACE inhibitor or angiotensin-receptor blockade, exclusions included recent atrial or ventricular tachyarrhythmia, except atrial fibrillation, recent myocardial infarction, recent or pending coronary revascularisation, severe valvular disease and dependence on intravenous inotropes. | Safety results: 5 patients<br><br>Implantation success rate: not stated<br><br>Perioperative: none stated<br><br>Postoperative:<br>Survival: 2 deaths.<br><br>Patient characteristics:<br>Mean age = 68.8 +/- 8.1 years, male = 4 (80%), mean LVEF (after BVP) = 30.8 +/- 12.7%, mean NYHA = 3.67+/- 0.5, SR = 2. | Authors conclusions:<br>No safety conclusions. An evaluation of the effects of biventricular pacing on glucose metabolism in the subacute phase may help identify patients with a favourable long-term response to this therapy.<br><br>Comments:<br>Small study<br>Primary purpose was to measure cardiac glucose metabolism.<br><br>Selected series.<br><br>Blinding: No<br>Follow-up completeness: Full<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Gasparini et al 2003d)<br><br>Location: Milano, Italy.<br><br>Study period: October 1999 – April 2002.<br><br>Study type: Cohort<br><br>Level IV | Longitudinal observational study patients with heart failure.<br><br>Follow-up: median follow-up time = 11 +/- 4 months<br><br>Inclusion criteria:<br>Unclear other than heart failure and superior vena cava. | Safety results: 4 patients<br><br>Implantation:<br>No complications, 100% implantation success assumed.<br><br>Perioperative: not stated<br><br>Postoperative: not stated<br><br>Patient characteristics:<br>Male = 2/4 (50%), ages 51-77 years, NYHA class III (all), mean QRS = 174 ms, LVEF = 20-27%, 1 atrial fibrillation, 3 SR (with LBBB). | Author's conclusions:<br>'The experience gained from these four cases of persistent LSVC shows that the direct lead placement in large CS tributaries, like the MCV or posterolateral vein, is feasible and safe provided that leads with adequately angled tips are used. Successful LV stimulation can be accomplished, which, in turn, resynchronises cardiac contraction with its expected advantages.<br><br>Comments:<br>Small sample<br><br>Consecutive series: unclear<br><br>Blinding: unclear<br>Follow-up assumed complete<br>Comparison group: no |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Akiyama et al 2002)<br><br>Location:<br>Gunman University School of Medicine, Maebashi, Japan.<br><br>Study period:<br>Not stated<br><br>Study type:<br>Single case report<br><br>Level IV | Description of series of sinus cycles that occurred without p-wave tracking, causing symptoms for a patient due to adverse haemodynamics.<br><br>Follow-up: 6 months<br><br>Inclusion criteria:<br>Not stated | Safety results: Single patient<br><br>Implantation success rate: not stated<br><br>Perioperative: not stated<br><br>Postoperative:<br>Symptomatic arrhythmia generated by pacemaker- patient admitted after 6 months the premature ventricular response algorithm was activated after capture of the LV only by sensed ventricular events falling in the ventricular refractory period, reflecting the transeptal wavefront propagation from LV to RV. This then caused extension of the postventricular atrial refractory period starting from the VR, preventing the proper sensing of the subsequent P wave. Even after shortening of the postventricular atrial refractory period down to the programmed value, the postponement of the atrial refractory period due to first degree AV block of the cycles without ventricular tracking regularly prevented sensing of the subsequent P wave during sinus tachycardia. Sinus cycles without P wave tracking were completely eliminated by turning off the premature ventricular complex response.<br><br>Patient characteristics:<br>45-year-old man, severe heart failure, LBBB, QRS = 180 ms. | Author's conclusions:<br>'When using a biventricular pacing system with a 'Y' adapted left lead it is advisable to program a shorter postventricular atrial refractory period or to program the premature ventricular complex algorithm off'.<br><br>Comments:<br>Selected case.<br><br>Blinding: No<br>Follow-up completeness: Full<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Sbragia et al 2003)<br><br>Location:<br>Hopital Nord, Paris, France.<br><br>Study period:<br>July 2001<br><br>Study type:<br>Single case report<br><br>Level IV | Description of a complication that affected a patient who underwent resynchronisation therapy for heart failure.<br><br>Follow-up: 6 months<br><br>Inclusion criteria:<br>Not stated | Safety results: n=1<br><br>Implantation success rate: not stated<br><br>Perioperative: not stated<br><br>Postoperative:<br>Report 6/12 post implantation of intra-atrial thrombus and pulmonary embolism associated with the pacemaker leads. The complication was successfully treated with thrombolytic therapy.<br><br>Patient characteristics:<br>65-year-old male with heart failure. No prior infection. Narrow QRS complexes (100 ms). LVEF = 30%. | Author's conclusions:<br>'Pacemaker lead thrombus with pulmonary embolism is a potentially serious complication of pacemaker implantation. Long-term anticoagulation should be considered in patients with depressed left ventricular function particularly those undergoing resynchronisation therapy'.<br><br>Comments:<br>Case report<br><br>Selected case.<br><br>Blinding: No<br>Follow-up completeness: Full<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Van Erven et al 2004)<br><br>Location:<br>Leiden University Medical Center, Leiden, Netherlands<br><br>Study period: Implanted January 2002<br><br>Study type:<br>Single case report<br><br>Level IV | Single case report of patient who developed an atrial tachycardia during device implantation.<br><br>Follow-up: None<br><br>Inclusion criteria:<br>Not stated | Implantation success rate: not stated<br><br>Perioperative:<br>Developed atrial tachyarrhythmia with 2:1 conduction at implantation. Mode switching and back switching of the biventricular pacemaker occurred, due to special timing of the atrial and ventricular deflections.<br><br>Postoperative: not stated<br><br>Patient characteristics:<br>53-year-old woman with dilated cardiomyopathy, LVEF =14%, NYHA III, LBBB, past history of paroxysmal atrial tachyarrhythmias, QRS 180 ms. | Author's conclusions:<br>"The case emphasises the dilemma of atrial tachyarrthmia in this population. The primary goal must be to maintain sinus rhythm. The report stresses the importance of strenuous treatment of atrial arrhythmias in patients with resynchronisation devices'.<br><br>Comments:<br>Case report<br><br>Selected series.<br><br>Blinding: no<br>Follow-up completeness: 1 case no follow up<br>Comparison group: no |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Oguz et al 2002a)<br><br>Location:<br>Istanbul, Turkey.<br><br>Study period:<br>Not stated<br><br>Study type:<br>Single case report<br><br>Level IV | Single case description of far-field sensing of left atrial activity the pacemakers ventricular channel resulted in ventricular pacing inhibition.<br><br>Follow-up: 24 months<br><br>Inclusion criteria:<br>Not stated | Safety results: Single case<br><br>Implantation success rate: not stated<br><br>Perioperative:<br>Far-field sensing of left atrial activity the pacemakers ventricular channel resulted in ventricular pacing inhibition. Placing of the left ventricular pacing electrode in the proximal part of the coronary sinus tributary resulted in the far-field sensing problem which was resolved following decreasing ventricular sensitivity.<br><br>Postoperative: not stated<br><br>Patient characteristics:<br>65-year-old male with severe heart failure and intraventricular conduction delay. | Author's conclusions:<br>''The far-field sensing of the left atrial activity should be kept in mind for troubleshooting of an atrio-ventricular pacing system'.<br><br>Comments:<br>Single case report<br><br>Selected case.<br><br>Blinding: No<br>Follow-up completeness: Full<br>Comparison group: No |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Kanhai et al 2004)<br><br>Location:<br>Groene Hart Hospital, Gouda, The Netherlands<br><br>Study period: Not stated.<br><br>Study type:<br>Case report<br><br>Level IV | Case report. CRT implanted – traditional placement of right atrial and ventricular leads. Left ventricular lead positioned in posterolateral branch of coronary sinus using a transvenous over the wire approach.<br><br>Follow-up: Three days.<br><br>Inclusion criteria:<br>Severe heart failure, reduced ejection fraction, QRS>120 ms. | Implantation success rate: 1/1 (100%)<br><br>Perioperative:<br>No problems with implantation.<br><br>Postoperative:<br>Chest pain related to an increase in LV threshold. Death ascribed to cardiogenic shock secondary to a myocardial infarction.<br><br>Patient characteristics:<br>78-year-old male. Past history of 2 MIs. NYHA Class III. LV EF 17%. LVEDD 78mm. QRS>120 ms with LBBB. | Authors' conclusions:<br>Additional studies required but assessment of patients eligible for CRT will be needed to verify whether the region targeted for left ventricular pacing is viable.<br><br>Comments:<br>Case report.<br>Selected series.<br><br>No blinding<br>Full follow-up<br>No comparison group. |

**Table 47 Studies included under safety (continued)**

| Study | Methods | Results | Conclusions |
|---|---|---|---|
| Author:<br>(Geske et al 2005)<br><br>Location:<br>University Hospital, Cleveland, Ohio, USA<br><br>Study period:<br>Not stated.<br><br>Study type:<br>Case report<br><br>Level IV | Methods:<br>Case report of the use of a novel steerable telescoping catheter system for implantation of left ventricular leads<br><br>Follow-up: Not stated.<br><br>Inclusion criteria:<br>Not stated. | Implantation success rate: 1/1 (100%)<br><br>Postoperative: not stated<br><br>Postoperative: not stated<br><br>Patient characteristics:<br>51 year old male with non-ischaemic cardiomyopathy, LV EF 30%, NYHA Class III despite optimal medical therapy. LBBB with QRS 185ms. | Author's conclusions:<br>'The new adjunctive implant tool described in this report for placing LV transvenous leads may be useful in shortening procedure times, reducing complications and improving implant success rates.'<br><br>Comments:<br>Selected case report<br><br>No blinding<br>Full follow-up<br>No comparison group. |

**Table 48 Studies included under effectiveness**

| Source | Study design and aim | Data sources | Study selection<br>Data extraction | Data synthesis<br>Meta-analysis results | Conclusions and comments |
|---|---|---|---|---|---|
| (Bradley et al 2003)<br><br>Level I | Meta-analysis of randomised controlled trials<br>To determine whether cardiac resynchronisation reduces mortality from progressive heart failure. | MEDLINE (1966-2002), EMBASE (1980-2002), Cochrane Controlled Trials Register (2nd Quarter, 2002), National Institutes of Health Clinical Trials.gov database, US Food and Drug Administration website). Search terms included: pacemaker, pacing, heart failure, dual-site, multisite, biventricular, resynchronisation, and left ventricular preexicitation. Additional searches were conducted using 65 author names and 24 trial acronyms. | Inclusion criteria:<br>Randomised controlled trials of cardiac resynchronisation versus control group for treatment of chronic left ventricular dysfunction. For crossover trials only data from the first crossover period were included. Studies were excluded if another report with more complete data was available, when follow-up during the randomised period was <3 months, if no separate data for the first crossover period was present. Reports in formats other than journal articles and non-English language studies were included.<br>Eligible studies reported outcomes including death or hospitalisation for heart failure, death from any cause.<br>Study quality was assessed according to intention-to-treat analysis and reported allocation generation, allocation concealment and blinding. Disagreements between reviewers were resolved by consensus.<br>Of the 6,883 potentially relevant reports initially identified, 11 reports of 4 randomised controlled trials with 1,634 patients were included. | The 4 trials included in the meta-analysis were: CONTAK CD, InSnyc ICD, MIRACLE, and MUSTIC.<br>Baseline characteristics were similar in the four trials mean ages = 63-66 years, mean LVEF = 21-23%. Most patients were NYHA III or IV. Apart from MUSTIC, most trials included patients with ischaemic cardiomyopathy. Baseline QRS was similar in the trials mean = 158-176ms. LBBB was present in the majority of patients in all trials. Baseline angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use was similarly high in all trials (87-96%). Baseline beta-blocker use was variable range 28-60% in the trials. Patients with conventional indications for pacemaker insertion were excluded from all four trials. Patients with atrial fibrillation were only included in MUSTIC. 54 of the 490 patients in CONTAK CD underwent epicardial lead placement. Follow-up varied between 3-6 months. Measures of methodological quality were similar between the four studies. | Searches performed in May and June 2002.<br>Included patients with implantable cardioverter defibrillators (2 of the 4 RCTs).<br>54 of 490 underwent epicardial lead placement in one study (CONTAK CD).<br>Unscheduled crossover 0-6.9% in group originally receiving CRT and 3.4-8.5% in group originally receiving no CRT.<br>Drop out for reasons other than death or heart transplantation: 0.4-2.7% for patients originally receiving CRT and 0.8-2.7% in group originally receiving no CRT.<br>Results of interest were part of two sub-analyses only. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design and aim | Data sources | Study selection<br>Data extraction | Data synthesis<br>Meta-analysis results | Conclusions and comments |
|---|---|---|---|---|---|
| (Bradley et al 2003)<br><br>Level I | | Search for reports at scientific meetings of American College of Cardiology, American Heart Association, European Society of Cardiology, North American Society of Pacing and Electrophysiology (1994-2002). Bibliographies of reviews articles were searched. Searches were limited to years 1994-2002. | Data extraction:<br>Trial reports were reviewed independently by 2 investigators in an unblinded standardised manner.<br><br>Data analysis:<br>Odds ratios were the principle measure of effect. ORs were pooled using random effects models that used weighting based on inverse variance calculated by DerSimonian and Laird method. Chi-square test for hetereogeneity was conducted. Sensitivity analyses assessed statistical models, baseline severity, individual trials and missing data. | Pooled results: Death from progressive heart failure (Pacemaker trials only): OR 0.40 (0.12-1.29) – 590 patients<br>Secondary outcomes:<br>All cause mortality (Pacemaker trials only): OR 0.79 (0.39-1.58) | All intention-to-treat analyses.<br><br>All industry funded.<br><br>One trial single blind, others double blind.<br><br>Allocation generation not reported. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design and aim | Data sources | Study selection<br>Data extraction | Data synthesis<br>Meta-analysis results | Conclusions and Comments |
|---|---|---|---|---|---|
| (Oduneye 2003)<br><br>Level I | Systematic review of randomised controlled trials<br><br>To assess the effects of cardiac resynchronisation in people with heart failure | MEDLINE (1966-2002), EMBASE (1980-2002), Cochrane Controlled Trials Register (1st Issue, 2003), Clinical Evidence Issue 8, Centre for Reviews and Dissemination Databases. Search terms not described. No additional searches were conducted using author names and trial acronyms. No search for reports at scientific meetings. Bibliographies of reviews articles were not searched. | Inclusion criteria:<br>Randomised controlled trials of permanent pacemaker to left and right ventricles with ventricular resynchronisation versus medication or any other therapy group for treatment of chronic heart failure and no other indication for ventricular pacing. Studies were excluded if people had indications for pacing based on rhythm disturbance; or if the comparator was univentricular pacing; or if the intervention included an implantable cardioverter defibrillator. Reports in formats other than journal articles and non-English language studies were not included.<br>Eligible studies reported outcomes including: death or hospitalisation for heart failure death from any cause, disability, functional outcomes, exercise tolerance, quality of life and any clinical outcome.<br>Study quality was assessed according to undisclosed methods.<br>From an unstated number of potentially relevant reports initially identified, 9 potentially relevant randomised controlled trials were considered. One RCT (the MIRACLE study) met the inclusion criteria and was evaluated.<br><br>Data extraction:<br>Trial reports were reviewed independently by 2 investigators in a standardised manner.<br><br>Data analysis:<br>Study results were presented from the single included trial. | The single included trial = MIRACLE study.<br>Baseline characteristics of the study participants were not described. Follow-up was for a 6-month period in the trial. An assessment of methodological quality indicated that the study was of high quality (randomisation method not fully described; allocation concealed until after device inserted; baseline characteristics and co-interventions similar; inclusion criteria described; double blinding; well described outcomes; adverse effects were presented; follow-up reasonable but not long term; large study appropriate sample size; low losses to follow-up and intention to treat analysis).<br><br>Results: Resynchronisation therapy increased six-minute walk distance (39 versus 10 metres, (p=0.005).<br>Improved quality of life: median decrease in Minnesota Living with Heart Failure Score = 18 versus 9, p=0.001).<br>Death rates similar between groups (intervention group = 5.3% versus 7.1% hazard ratio = 0.73, 95% CI = 0.34 – 1.54.<br>8% could not be implanted.<br>Adverse events included permanent heart block requiring pacing, coronary sinus dissection (4%), perforation (2%), need to replace leads (6%), infection. | Search performed January 2003.<br><br>Results from a single trial (MIRACLE study) were reported.<br><br>Authors' conclusion: 'Good evidence that cardiac resynchronisation improved symptoms after 6 months. However, in a high proportion of study participants, insertion of the device failed or adverse events occurred. Long term effects of cardiac resynchronisation are unknown.' |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design and aim | Data sources | Study selection<br>Data extraction | Data synthesis<br>Meta-analysis results | Conclusions and comments |
|---|---|---|---|---|---|
| (Brophy 2004)<br><br>Level I | Systematic review/meta-analysis of randomised controlled trials and economic evaluation<br><br>Aim not stated. | MEDLINE, EMBASE, Pubmed, Cochrane Controlled Trials Register, HTA databases (dates not stated). Search terms included: biventricular pacing, biventricular pacemaker, resynchronisation, pacing and heart failure. Websites on clinical trials were searched. No additional searches were conducted using author names and trial acronyms. No search for reports at scientific was conducted. Bibliographies of reviews articles were not searched. No restriction was made for dates of publication. Restricted to European languages. | Inclusion criteria: not stated.<br>Outcomes: not stated.<br>Method of study quality assessment was not stated.<br>The number of potentially relevant reports initially identified was not stated. 7 randomised controlled trials were included.<br>Data extraction: not described.<br>Methods: not stated.<br><br>Data analysis<br>Odds ratios were the principle measure of effect. ORs were pooled using fixed-effect models that used weighting based on inverse variance using Revman. Chi-square test for hetereogeneity was conducted. A simple economic analysis involving a cost comparison was conducted based on local McGill University Health Centre/Canadian Health care data. Sensitivity analyses and discounting were not considered. | The 7 trials included in the review were: COMPANION (limited data), MIRACLE, MUSTIC and Linde et al (2003) follow-up data, MIRACLE ICD, Higgins et al (2003), Leclercq et al (2002).<br>Meta-analyses of results from the MIRACLE, Insync ICD, Contak CD and MUSTIC trials were performed.<br>9 non-randomised studies were also included.<br><br>Baseline characteristics of the participants in the separate studies were presented but not closely compared.<br><br>Pooled results:<br>Mortality: (Based on MIRACLE and unpublished COMPANION results) no significant reduction in all-cause mortality at 6 months OR = 0.91, 95% CI: 0.61-1.34.<br>Re-hospitalisation: (MUSTIC and MIRACLE) significant 57% reduction in heart failure hospitalisations after 6 months OR = 0.43, 95% CI: 0.25-0.75.<br>Quality of life: Larger improvement in Minnesota Living with Heart Failure Questionnaire among intervention groups approximately 17 point decrease with pacing compared to 9 point decrease with control groups.<br>6-minute walk: Approximate average improvement of 52 metres in pacing group compared to 34 metres in control groups. | Search date not stated<br><br>Included patients with implantable cardioverter defibrillators.<br><br>Included patients who received epicardial lead placement.<br><br>Results of interest were part of sub-analyses only.<br><br>Methods not fully described.<br><br>Included a limited economic evaluation using local data. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design and aim | Data sources | Study selection<br>Data extraction | Data synthesis<br>Meta-analysis results | Conclusions and comments |
|---|---|---|---|---|---|
| (McAlister 2004a)<br><br>Level I | Systematic review/meta-analysis of randomised controlled trials<br><br>To determine efficacy and safety of cardiac resynchronisation therapy in adults with advanced systolic heart failure. | MEDLINE (1980-2003), EMBASE (1980-2003), Cochrane Controlled Trials Register (2002 Vol 4), International Pharmaceutical Abstracts, Web of Science, Pubmed, HTA electronic databases, US FDA Reports. Search strategies were provided and terms included: biventricular pacing, biventricular pacemaker, resynchronisation, pacing and heart failure. Websites on clinical trials were searched. Additional information was requested from primary authors and manufacturing companies. A search for reports at scientific meetings was conducted. Bibliographies of reviews articles were searched. No restriction was made for dates of publication. Not restricted by language. | Inclusion criteria: RCTS for efficacy and safety plus prospective cohort studies for safety. Study duration > 2 weeks.<br>Outcomes: all-cause mortality or heart failure hospitalisation.<br>Method of study quality assessment was not stated.<br><br>The number of potentially relevant reports initially identified was not stated.<br><br>Data extraction: two independent reviewers abstracted data. Discrepancies were resolved by consensus and third party consultation.<br><br>Nine trials were included in the review of efficacy along with some 3,216 patients. An additional 10 cohort studies evaluated safety.<br><br>Data analysis<br>Relative risks and weighted mean differences were the principle measure of effect. Data were pooled using random effects models using STATA 7. Chi-square and $I^2$ tests for hetereogeneity were conducted. A priori sensitivity analyses were considered. | The 9 trials included in the review were: COMPANION (limited data), MIRACLE, MIRACLE ICD, MUSTIC, MUSTIC AF, PATH CHF, CONTAK CD, RD-CHF, (Garrigue et al, 2002).<br>10 non-randomised studies were also included.<br><br>Baseline characteristics of the participants in the separate studies were presented and closely examined. The baseline characteristics were generally similar across studies: all trials enrolled patients with prolonged QRS and restricted LVEF < 40%. The mean age across the trials was 64 years, 74% of patients were male, 58% had ischaemic cause of heart failure, 75% had NYHA class III, 10% had NYHA class IV. However, Garrigue et al, 2002 and MUSTIC AF only included patients with atrial fibrillation. MIRACLE ICD, CONTAK CD and COMPANION included a study group who received pacing + ICD therapy. The PATH CHF trial included patients who were only implanted with a transthoracic approach.<br>The demographic characteristics of the cohort study patients were similar to those in the trials. | Authors' conclusion: 'In selected patients with heart failure, cardiac resynchronisation therapy improves functional and haemodynamic status, reduces heart failure hospitalisations and reduces all-cause mortality.'<br><br>Search date not stated<br><br>Included patients with implantable cardioverter defibrillators.<br><br>Included patients who received transthoracic lead placement.<br><br>Results of interest were part of a sensitivity analysis only.<br><br>All intention-to-treat analyses.<br><br>All trials were industry supported.<br><br>4 trials were double blind, 3 single blind, 2 were open label. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design and aim | Data sources | Study selection<br>Data extraction | Data synthesis<br>Meta-analysis results | Conclusions and comments |
|---|---|---|---|---|---|
| (McAlister 2004a)<br>*(continued)*<br>Level I | | | | Pooled results:<br>All-cause mortality: CRT reduced all-cause mortality by 21% RR=0.70, 95% CI: 0.66-0.96. This result included all 9 trials. A sensitivity analysis was conducted using meta-regression to examine the effect of ICDs on the efficacy of resynchronisation therapy. The benefits of CRT did not appreciably differ between patients with or without an ICD (p>0.2). But the data from the COMPANION trial was preliminary and did not include data on patients with and without an ICD.<br>Heart failure hospitalisations: non-significant reduction among 6 trials RR=0.68, 95% CI: 0.41-1.12. Heterogeneous result p=0.01, I2 = 65%. Sensitivity analysis again indicated no significant difference between patients with or without an ICD. | |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample, inclusion criteria | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Cleland 2005)<br><br>CARE-HF multicentre study<br><br>Recruit-ment Jan 2001 to march 2003.<br><br>Level II | Random-ised controlled trial compar-ing medical therapy alone (n=404) with medical therapy plus cardiac resynch-ronisation therapy (n=409) in patients with NYHA class III or IV heart failure.<br>Random-isation stratified by NYHA class. | Mean follow up 29.4 months (range 18.0-44.7)<br><br>Austria, Belgium, Denmark, Finland, France, Italy, The Netherlands, Sweden, Switzerland, United Kingdom.<br>(82 European study sites) | ***Inclusion criteria***<br>≥ 18 years<br>Heart failure for at least six weeks<br>NYHA Class III or IV despite receipt of standard pharmacologic therapy<br>LVEF ≤ 35%<br>LVEDD ≥ 30mm<br>QRS ≥ 120 msec<br>Patients with QRS 120-149 msec were required to meet two of the following three additional criteria for dyssynchrony:<br>-aortic pre-ejection delay of > 140 msec<br>-interventricular mechanical delay of > 40 msec<br>-delayed activation of posterolateral left ventricular wall | CRT plus standard medical therapy versus standard medical therapy alone<br><br>Transvenous implantation of cardiac resynchronisation device (Medtronic InSync or InSync III) with three pacing leads. Atrial based biventricular stimulation using standard right ventricular and Attain (Medtronic) left ventricular leads. Left ventricular lead was positioned to pace the lateral or posterolateral left ventricular wall. Radiographic confirmation of lead placement was undertaken. The atrioventricular delay was optimised echocardiographically. Back-up atrial pacing was set at 60 beats per minute. | Primary outcome:<br>Time to death from any cause or an unplanned hospitalisation for a major cardiovascular event.<br><br>Secondary outcomes:<br>Death from any cause<br>Death from any cause and unplanned hospitalisation with heart failure<br>Quality of life(assessed by Minnesota Living with Heart Failure Questionnaire and European Quality of Life -5 Dimensions instrument) at 90 days | Primary composite endpoint:<br>reached by 159 patients in intervention group compared with 224 in the control group (39% vs 55%; hazard ratio, 0.63; 95% CI, 0.51-0.77, p<0.001).<br><br>Secondary endpoints:<br>In the pacing group 82 patients died as compared with 120 patients assigned to the control group (20% vs 30%; hazard ratio, 0.64; 95% CI: 0.48-0.85, p<0.002). The main cause of death was cardiovascular (143 patients, non-cardiovascular in 34 patients and unknown in 25. The cause of death was attributed to worsening heart failure in 56/120 deaths in the control group and 33/82 in the resynchronisation group. The mode of death was sudden in 38/120 patients in the control group and 29/82 of the intervention group.<br>0.70+/- 0.28 compared with 0.63 +/-0.29 in the control group (hazard ratio = 0.08, 95% CI: 0.04 – 0.12, p<0.001). | Study was unblinded but members of the endpoints committee were not aware of patients' treatment assignments.<br><br>Patients in the control group were not scheduled to receive a device.<br><br>Medtronic Corporation funded the trial and provided a study manager to supervise its conduct. The sponsor had no access to the database and did not participate in the study analysis or study writing.<br><br>Emergency heart transplantation counted as a death.<br>First hospitalisation with documented worsening heart failure, MI, unstable angina, arrhythmia, stroke, or other major cardiovascular event or hospitalisation owing to or prolonged by a serious procedure related event was counted in the primary end point. Hospitalisations within 10 days of randomisation did not count toward the primary endpoint. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample, inclusion criteria | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Cleland 2005)<br><br>CARE-HF multicentre study<br><br>Recruit-ment Jan 2001 to March 2003.<br><br>Level II | Medtonic InSynch or InSynch III devise inserted.<br>LV lead positioned to pace the lateral or postero-lateral left ventricular wall. | | ***Exclusion criteria***<br>Major cardiovascular event in previous six weeks<br>Conventional indications for pacemaker or ICD<br>Heart failure requiring continuous IV therapy<br>Atrial arrhythmia<br>***Sample***<br>Median age: 66 years v. 67 years (no CRT v. CRT)<br>Male sex 73% v. 74% (no CRT v. CRT)<br>NYHA class IV 7% v. 6% (no CRT v. CRT)<br>Dilated cardiomyopathy 48% v. 43% (no CRT v. CRT)<br>IHD 36% v. 40% (no CRT v. CRT)<br>Median LVEF 25% v. 25% (no CRT v. CRT)<br>QRS duration 160msec v. 160msec (no CRT v. CRT)<br>ACE inhibitor or angiotension receptor blocker 95% v. 95% (no CRT v. CRT) | The interventricular delay was set to zero. Patients were monitored overnight. Efficacy analyses were based on time to event using Kaplan-Meier method and analysed with Cox proportional hazard models that included NYHA class as a covariate. | | Compared with the control group the intervention reduced the risk death from any cause or hospitalisation for worsening heart failure (hazard ratio, 0.54; 95% CI: 0.43-0.68, p<0.001).<br><br>Patients in the intervention group had a better quality of life (p<0.001) at 90 days. Mean Minnesota Questionnaire score was 31+/-22 compared with 40+/-22 in the control group (hazard ratio = -10, 95% CI: -8 - -12, p<0.001). Mean EuroQoL EQ-5D score in intervention group = 0.70+/- 0.28 compared with 0.63 +/-0.29 in the control group (hazard ratio = 0.08, 95% CI: 0.04 – 0.12, p<0.001). | Death was given a notional NYHA class of V for the analysis of changes in class.<br><br>Intention-to-treat analysis.<br><br>Implantation of a device was attempted in 404 of 409 patients assigned to the CRT group.<br><br>Implantation of CRT (without ICD) was attempted in 43 patients and of CRT with ICD in 23 patients. The device was activated in 50 patients including 19 patients (5%) before they reached the primary endpoint.<br><br>Authors' conclusions:<br>CRT is an effective therapy for patients with left ventricular systolic dysfunction and cardiac dyssynchrony who have moderate or severe heart failure and who are in sinus rhythm. Data on patients who underwent elective heart transplantation were censored seven days after the procedure.<br>Emergency heart transplantation was counted as a death. Hospitalisation with worsening heart failure was defined as the occurrence of increasing symptoms and the need for intravenous diuretics or a substantial increase in oral diuretic dosage, or the initiation of a combination of a thiazide and a loop diuretic.<br><br>Method of randomisation and allocation to groups not fully described. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample, Inclusion criteria | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Cleland 2005) *(continued)* CARE-HF multicentre study<br><br>Recruit-ment Jan 2001 to March 2003.<br><br>Level II | | | Beta-blocker 74% v. 70% (no CRT v. CRT)<br>Spironolactone 59% v. 54% (no CRT v. CRT)<br>High-dose loop diuretic 44% v. 43% (no CRT v. CRT)<br>Digoxin 45% v. 40% (no CRT v. CRT) | | | | Sample size: trial was designed with 80% power to detect a relative reduction of 14% or a 5.7% reduction in the rate of events, alpha = 0.025 and predicted 300 events.<br><br>Survival status was known about all patients at the end of the study.<br><br>8 patients received a defibrillator in addition to a pacing device.<br><br>Based on the hazard ratios, for every 9 devices implanted, one death and 3 hospitalisations for major cardiovascular events were prevented.<br><br>Sub-group analyses suggest that the benefits of therapy were similar among patients with ischaemic or non-ischaemic disease. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Bristow et al 2004)<br>*(continued)*<br>COM-PANION<br><br>Level II | Multi-site RCT (optimal medical therapy alone vs optimal therapy + bi-ventric pacing vs optimal therapy + biventricpacing + implantable defibrillator in 1: 2: 2 ratio)<br><br>Single (outcome assessment) No blinding of patients or physicians | 128 centres in the US.<br>January 2000 to November 2002.<br>Comparison of Medical Therapy, Pacing and Defibrillation in heart failure (COMPANION) Study. | 925 patients with heart failure were randomised to control group (n=308) and pacemaker group (n=617). Follow-up withdrawal rates differed between the groups: 26% of patients in the medication-only group withdrew compared to 6% in the pacemaker group. There were no significant differences in the baseline characteristics of the medication-only group between those who withdrew from the study and those who did not, with the exception of the prevalence of ischaemic cardiomyopathy (68% versus 55%).<br>Patients were randomised in a 1:2 ratio to control or intervention groups.<br>No significant baseline differences in demographic, electrophysiological haemodynamic characteristics between study groups.<br>Mean age: (control group) = 68 years, (intervention group) = 67 years, mean LVEF (control group) = 22%, (intervention group) = 22% ; mean QRS (control group) = 158 ms, (intervention group) = 160 ms, NYHA class III n=790 (control n=253, pacing n=537), NYHA class IV n=43 (control n=20, pacing n=23), male = 413/617( intervention), 213/308 (control). Ischaemic cardiomyopathy: control group = 59%, intervention group = 54%.<br>All in SR at time of enrolment. | **Transvenous** implantation of cardiac resynchronisation device (Contak TR model 1241, Guidant) with 3 pacing leads. An over–the-wire lead (Easytrak, 4510-3, Guidant) was placed with the aid of a guiding sheath. Radiographic confirmation of lead placement was undertaken. The programmed atrioventricular delay was calculated from a proprietary algorithm based on measures of the intrinsic PR interval, the QRS interval, and the intracardiac atrioventricular interval at implantation.<br>Efficacy analyses were based on time to first event using log-rank statistic and Kaplan-Meier method. | Primary outcome was a composite of death from any cause or hospitalisation for any cause analysed from the time of randomisation to the time of first event. Unscheduled intravenous administration of inotropic or vasoactive drugs for > 4hrs as an outpatient was considered to be an instance of the primary end point. Hospitalisation for implantation was not the primary end point.<br><br>Secondary endpoints included: Death from any cause; death from or hospitalisation for cardiovascular causes; and death from or hospitalisation for heart failure. | Primary composite endpoint:<br>12-month rate of death or hospitalisation from any cause = 68% in medication only group compared to 56% in the pacemaker group (hazard ratio = = 0.81, 95% CI = 0.69 – 0.96, p=0.014, adjusted p = 0.015).<br><br>Secondary endpoint:<br>In the medication-only group 77/308 (25%) patients died during the study 58 (75%) were due to cardiac causes. The one-year mortality rate in the medication-only group = 19%. The implantation of a pacemaker was associated with a marginally significant reduction in the risk of death from any cause (hazard ratio = 0.76, 95% CI = 0.58 – 1.01, p=0.059, adjusted p = 0.06).<br><br>The 12-month event rate for death or hospitalisation for cardiac causes was 60% in the medication-only group and was reduced by 25% in the pacemaker group (hazard ratio = 0.75, 95% CI= 0.63 – 0.9, p=0.002). | During the study an unanticipated large number of patients withdrew from the medication only group to join the implant groups. To mitigate the withdrawal rate patients who had withdrawn before December 2002 were asked about vital status and hospitalisations for the duration of the study. For mortality and hospitalisation end point analyses, data on patients who withdrew before an endpoint who did not die and for whom the complete post-withdrawal information on hospitalisation could not be obtained by this means were censored at the time of elective hospitalisation for implantation or the date of last contact. For mortality endpoint analyses, data on patients whose vital status was not known at the end of the study were censored on the date of last contact. All analyses were censored at the time of cardiac transplantation.<br>All analyses were intention-to-treat.<br><br>Sample size: trial was designed to detect a reduction of 25% in the primary endpoint and in the rate of death from any cause, alpha = 0.02 – 0.03. Target = 1000 primary events. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Bristow et al 2004)<br>*(continued)*<br>COM-PANION<br><br>Level II | | | Inclusion criteria:<br>Severe heart failure (NYHA heart failure III or IV) due to ischaemic or non-ischaemic cause, LVEF<35%, QRS > 120 ms, PR interval > 150msec, sinus rhythm, no clinical indication for a pacemaker or implantable defibrillator, and a hospitalisation for the treatment of heart failure or the equivalent in the preceding 12 months.<br>Optimal therapy used in all groups consisted of: diuretics, angiotensin-converting enzyme inhibitors, beta-blockers and spironolactone. Medication was not given if not tolerated or contraindicated. Digoxin and other medication could be used at the **investigator's** discretion. | Both nominal p values and p values adjusted for sequential monitoring were reported for the primary endpoint. | Adverse events (including undesirable clinical outcomes and device related events as well as events related to the patients' general condition were also reported. | The 12-month event rate for death or hospitalisation due to heart failure in the medication-only group was 45% compared to a reduction of 34% in the pacemaker group (hazard ratio = 0.66, 95% CI = 0.53 – 0.87, p=0.002).<br><br>Subgroup analyses:<br>The addition of a pacemaker resulted in progressive lowering of the hazard ratio with increasing QRS interval.<br>The resynchronisation therapy in combination with beta-blockers or spironolactone reduced the risk further than the combination of the therapy and any other agents. | Power = 90% for primary endpoint and 80% for secondary endpoint. Stopping guidelines based on O'Brien-Fleming monitoring boundaries. Trial stopped early on November 18 2002 after steering committee indicated likely reached 1000 events also the pacemaker-defibrillator group had crossed primary and secondary endpoints and pacemaker group secondary endpoint. Follow-up stopped on December 1 2002.<br><br>No clinically significant differences in baseline variables between study groups.<br><br>Status of the primary end point was know for 91% of patients in the medication-only group and 99% of the pacemaker group; data on mortality was complete for96% of the medication group and 99% of the pacemaker group. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Bristow et al 2004)<br>*(continued)*<br>COM-PANION<br><br>Level II | | | | | | Other outcomes:<br>Significant reductions in distance walked in 6 minutes at 3 and 6 months (170 versus 422, p<0.001; 142 versus 373 metres, p<0.001); percentage improvements in quality of life at 3 and 6 months (243 versus 510, p<0.001; 207 versus 460, p<0.001); per centage improvements in NYHA class symptoms at 3 and 6 months (242 versus 551, p<0.001; 199 versus 489, p<0.001). | Patients, physicians, statisticians and members of the data-management group and the data safety and monitoring board were not blinded to treatment assignments, whereas the steering committee, endpoints committee and the sponsor were unaware of treatment assignments.<br><br>Industry supported<br><br>Intention-to-treat analyses<br>Randomisation method unclear. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Abraham et al 2002)<br>*(continued)*<br>MIRACLE<br><br>Level II | Multi-site RCT (bi-ventric pacing vs no pacing)<br><br>Double blind | 45 centres in the US and Canada.<br>November 1998 to December 2000.<br>Multicentre InSync Randomised Clinical Evaluation (MIRACLE) Study. | 571 patients with heart failure were enrolled. Withdrawals (n=4) due to unstable condition. Implantation failures (43/567) were excluded. Remaining patients (524) were randomised by permuted block to intervention or control groups. Note 71 implanted patients participated in a 3-month pilot. Results here pertain to remaining 453. 453 patients randomised to control (no pacing n=225) and pacing (n=228).<br>No significant differences in demographic, electrophysiological/haemodynamic characteristics between study groups.<br>Mean age (intervention group): 63.9 (SD=10.7) years, mean LVEF (intervention group) = 21.8 (SD=6)% mean QRS (intervention group) = 167 (21) ms, NYHA class III n=410 (control n=205, pacing n=205), NYHA class IV n=43 (control n=20, pacing n=23),136/453 male.<br>All in SR at time of enrolment.<br><br>Inclusion criteria:<br>Severe heart failure (NYHA heart failure III or IV) due to idiopathic or ischaemic cause, EF<35%, EDD >55mm. QRS > 130 ms, 6-minute walk >450m, receiving optimal therapy (diuretics, ACE inhibitor at max doses stable for >1 month) | Transvenous implantation of cardiac resynchronisation device (Insync Model 8040, Medtronic) with three pacing leads.<br>After randomisation patients were assigned to active or inactive pacing for a period of 6 months by an electrophysiologist not otherwise involved with patient care. Baseline variables were assessed at one, three and six months of follow-up.<br>Crossover was prohibited. | Primary outcomes were: NYHA class, Minnesota Living with Heart Failure quality of life score, and the distance walked in six minutes.<br>Secondary outcomes were: peak oxygen consumption, time on treadmill, electrophysiological and haemodynamic outcomes, and death or number of days spent in hospital. | Primary outcomes:<br>Change in distance walked in six minutes:<br>(Intervention group) +39 versus +10 (controls), p=0.005.<br>Change in Minnesota Living with Heart Failure median score:<br>-18 versus -9, p=0.001.<br>Percentage no change in NYHA class:<br>30% versus 59%, p<0.001.<br><br>Secondary outcomes:<br>Change in median peak oxygen consumption:<br>+1.1 versus +0.2 ml/kg/min, p=0.009.<br>Change in median total exercise time:<br>+81 versus +19 secs, p=0.001.<br>Deaths from any cause:<br>12 versus 16, hazard ratio = 0.73 (0.34 – 1.54). | Follow-up: 24 controls were not followed up – 16 died, two received a heart transplant, one had complications related to the device, and five missed the final visit. 13 were not followed up in intervention group – 12 died and one had complications related to the device.<br>Optimal medical therapy: patients received digitalis (78-79%), diuretic (93-94%), ACE inhibitor (90-93%), beta-blocker (55-62%).<br>Minnesota Living with Heart Failure score has been validated elsewhere.<br>Follow-up period was limited – only six months.<br>Significant placebo/trial participation effects were noted in the Quality of Life and six-minute walk results.<br>Study did not have adequate power to assess mortality.<br>Groups were comparable at baseline.<br>Sample size adequate.<br>Intention-to-treat analysis. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Abraham et al 2002)<br><br>MIRACLE<br><br>Level II | | | Exclusion criteria:<br>Pacemaker or cardioverter/defibrillator or a contraindication to pacing, cardiac or cerebral ischaemic event within last three months, or atrial arrhythmia within last month. Excluded if BP >170 or <80 mmHg, heart rate >140bpm, serum creatinine > 3.9mg/dl, serum aminotransferase more than 3x normal. | | | Hospitalisations for worsening heart failure:<br>15% versus 8%, hazard ratio = 0.50 (0.28 – 0.88). | Checks for contamination/crossover – 10 in control group were re-assigned.<br>Method of allocation to study groups was described.<br>Follow-up fully described and used objective tests.<br>No losses to follow-up related to worsening heart failure or death.<br>Double blind. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample, Inclusion criteria | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Adamson 2003)<br><br>MIRACLE<br><br>Level II | RCT | USA | Inclusion criteria:<br>NYHA Class III/IV<br>EF < 35%<br>QRS ≥ 130ms<br>Atrial rate histogram data available<br><br>Sample:<br>n=76<br>Mean age 61 yrs<br>Male 70%<br>QRS width 161.3 ms<br>NYHA Class III 92%<br>ACE inhibitor use 94%<br>Beta blocker use 48%<br>NSD between groups | CRT on versus CRT off | Primary outcome:<br>Heart rate variability (standard deviation of the atrial cycle length over 2 mths of continuous monitoring)<br><br>Secondary outcomes:<br>Plasma catecholamine,<br>LV volume,<br>LV EF,<br>Mitral regurgitation jet area. | Effectiveness<br>SD of ACL 25% higher in CRT-on group (148 v 118, p=0.02)<br><br>Secondary outcomes:<br>Changes in Echo parameters from baseline to 3 mths f/up (CRT off v CRT-on):<br>LVEDV ($cm^3$) 15.2 v –20.2 P=0.02<br>LVEDD (cm) 0.01 v –0.41 P=0.02<br>LVESD (cm) 0.11 v –0.42 P=0.04<br>MR jet area ($cm^2$) –0.7 v –4.2 P=0.03<br><br>Plasma catecolamines (n=36 19 CRT on and 17 CRT off)<br>NSD between groups (adrenaline, noradrenaline, dopamine). | Pilot phase of MIRACLE study<br>Double blind<br>50 of 76 (66%) finished 3 mths follow-up. Only 36 tested for catecolamines (47%).<br>Intermediate outcome measures<br>HRV may reflect non-autonomic as well as autonomic influences<br>Industry supported<br>Authors conclusions: CRT favourably impacts cardiac autonomic control, thus resulting in less sympathetic dominance in patients with severely symptomatic heart failure. This was associated with a reversal of ventricular remodelling and may contribute to improvement in long-term functional capacity and quality of life.<br>Reviewers' issues: low follow-up and intermediate outcome measures allow few conclusions. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample, Inclusion criteria | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (St John Sutton 2003)<br><br>MIRACLE<br><br>Level II | Prospective, double-blind RCT<br><br>Echo performed at baseline, before device implantation, 3 mths and 6 mths. | USA | Inclusion criteria:<br>Optimal HF medical regimen that was unchanged for a minimum period of 1 month in the case of diuretics, ACE inhibitors, and digitalis, and 3 mths for beta blockers<br>QRS ≥ 130ms<br>LV EDD ≥ 55 mm<br>EF ≤ 35%<br><br>Sample:<br>Mean age 64 yrs<br>Male 66.9%<br>NYHA Class III 92.3%<br>QRS duration 165.6 msec<br>LV EF 24.4%<br>6-minute walk 301.7 m<br><br>NSD between CRT and control group. | CRT on v CRT off | Primary outcome:<br>LV end diastolic volume, LV end systolic volume, EF, LV mass, Severity of mitral regurgitation (MR), peak transmitral velocities during early (E wave) and late (A wave) diastolic filling, myocardial performance index (MPI).<br><br>Secondary outcomes: | Effectiveness<br>Difference from baseline<br>3 mths (Ctrl v CRT):<br>LVEDV 2.8 v –22.6 (P<0.05)<br>LVESV 0.6 v –21.8 (P<0.05)<br>LV EF (%) 0.6 v 2.3 (P<0.05)<br>LV mass (g) –2.3 v –10.2 (P<0.05)<br>MR severity index 0.00 v –0.08 (P<0.05)<br>LV E wave velocity 0.0 v –5.0 (P<0.05)<br>LV A wave velocity 1.0 v 1.0 (NSD)<br>LV filling time (ms) –7.0 v 59.0 (P<0.05)<br>MPI 0.01 v –0.16 (P<0.05)<br><br>6 mths (Ctrl v CRT):<br>LVEDV 4.7 v –27.2 (P<0.05)<br>LVESV 0.3 v –25.6 (P<0.05)<br>LV EF (%) 0.4 v 3.6 (P<0.05)<br>LV mass (g) 10.6 v –12.0 (P<0.05)<br>MR severity index -0.03 v –0.09 (P<0.05)<br>LV E wave velocity –1.5 v –5.0 (P<0.05)<br>LV A wave velocity –4.0 v -1.5 (NSD)<br>LV filling time (ms) 9.0 v 47.0 (P<0.05)<br>MPI 0.02 v –0.23 (P<0.05) | Double blind (though investigators may be able to break blinding by reference to ECG ventricular pacing pulses).<br>ITT analysis<br>Industry supported (authorship and financially)<br>Doppler echo analysed by a single sonographer who was blinded to treatment group<br>Good description of measurement methods<br>Baseline results presented for 323 of 453 patients with a device implanted (71%) – 67% in controls and 75% in CRT group. Selected based on analysable echo results for all three time points.<br>Method of randomisation unclear – presumably not block randomisation given unequal groups<br>Authors conclusions: CRT in patients with moderate to severe HF is associated with reverse LV remodelling, as evidenced by reduction in LV volumes, improved systolic and diastolic function, and decreased severity of MR. These changes occur by 3 mths and are sustained at 6 mths. This remodelling occurs in patients on maximal medical therapy. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample, Inclusion criteria | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Woo et al 2005)<br><br>MIRACLE study<br><br>Level II | Subgroup analysis of MIRACLE study for 8 baseline character-istics that were prospect-ively identified. MIRACLE study random-ised 453 patients with a successful CRT implant-ation to CRT on or CRT off.<br><br>Double blind. | 45 centres in the US and Canada.<br><br>November 1998 to December 2000.<br><br>Multicentre InSync Randomised Clinical Evaluation (MIRACLE) Study.<br><br>Reports on 6-month follow-up. | All 453 patients in the MIRACLE study were included in the time- to-event analysis and 416 were followed to the 6-month visit.<br><br>Controls (n=225), Intervention (n=228)<br><br>Age ≥ 65 years: Controls 52.9%, Intervention 47.4%<br><br>% Male: Controls 68.0%, Intervention 68.4%<br><br>% ischaemic aetiology: Controls 58.2%, Intervention 50.4%<br><br>NYHA Class III: Controls 91.1%, intervention 90.4%<br><br>LVEF ≥ 20%: controls 67.6%, intervention 69.7%<br><br>MR average jet area ≥ 6 $cm^2$: Controls 48.8%, intervention 49.4%<br><br>% lateral LV lead location: controls 72.3%, intervention 76.8%.<br><br>Inclusion criteria:<br><br>Severe heart failure (NYHA heart failure III or IV) due to idiopathic or ischaemic cause, EF<35%, EDD >55mm. QRS > 130 ms, 6-minute walk >450 m, receiving optimal therapy (diuretics, ACE inhibitor at max doses stable for >1 month). | Transvenous implantation of cardiac resynchronisation device (Insync Model 8040, Medtronic) with three pacing leads.<br><br>After randomisation patients were assigned to active or inactive pacing for a period of six months by an electrophysiologist not otherwise involved with patient care. Baseline variables were assessed at one, three and six months of follow-up.<br><br>Crossover was prohibited.<br><br>Prospective sub-group analyses examining age (<65 years versus >65 years), male versus female, ischaemia versus non-ischaemia. | Primary endpoints at 6 months:<br><br>NYHA class, Minnesota Living with Heart Failure quality of life score, and the distance walked in six minutes.<br><br>Secondary outcomes were: peak oxygen consumption, time on treadmill, electrophysiological and haemodynamic outcomes and death or number of days spent in hospital. | No significant subgroup differences in response among treatment groups based on NYHA class, EF, lead position or Beta blocker use.<br><br>Benefit of CRT over control was similar in all subgroups for clinical end points.<br><br>Significant difference between intervention and controls for the following (by subgroup):<br><br>Ejection fraction: non-ischaemic patients (P<0.001)<br><br>Ejection fraction: Ischaemic patients (P=0.007)<br><br>Ejection fraction: MR jet area <6cm (P<0.001)<br><br>Ejection fraction: MR jet area ≥6cm (P=0.03)<br><br>LVEDV: Non-ischaemic patients (P<0.001)<br><br>LVEDV: Ischaemic patients (P=0.01)<br><br>Time to first heart failure admission: women (P=0.002)<br><br>Time to first heart failure admission or death: women (P<0.001) | Follow-up period was limited – only six months.<br><br>Study did not have adequate power to assess mortality.<br><br>Groups were comparable at baseline.<br><br>Data was missing for some patients.<br><br>Intention-to-treat analysis.<br><br>6-month follow-up limited to 416 of 453 patients (dropouts included missed follow-up, patient deaths and other study withdrawals)<br><br>Sub-group analysis with consequential limitations<br><br>Authors' conclusions:<br><br>'Results suggest there are sub-group differences in response to CRT as shown in improvements in LV function and reverse remodelling. Although most patients benefit from CRT, non-ischaemic heart failure patients and women may derive more benefit. There is a need for further large-scale studies of sub-groups based on heart failure aetiology and gender.<br><br>'Women may also derive more benefit than men with respect to occurrence of heart failure hospitalisation or death.' |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample, Inclusion criteria | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Aranda et al 2004)<br><br>MIRACLE study<br><br>Level II | Retro-spective analysis of MIRACLE study based on three sub-groups: LBBB, RBBB and non-specific inter-ventricular conduct-ion delay. | 45 centres in the US and Canada.<br>November 1998 to December 2000.<br>Multicentre InSync Randomised Clinical Evaluation (MIRACLE) Study.<br><br>Reports on 6-month follow-up. | Sample (LBBB v RBBB v IVCD)<br>Age 63.5 v 66.3 v 66.8<br>% Male 63.9 v 79.1 v 74.3<br>% ischaemic aetiology 49.5 v 74.4 v 74.3 (P<0.001)<br>NYHA class III 92.0 v 86.0 v 94.3<br>QRS 168.5 v 161.7 v 153 (P<0.001)<br>LV EF 21.5 v 24.0 v 22.4 (P=0.04)<br>LVEDD 69.5 v 65.1 v 69.3 (P=0.02)<br>6 minute walk 305 v 304 v 317<br><br>Inclusion criteria:<br>Severe heart failure (NYHA heart failure III or IV) due to idiopathic or ischaemic cause, EF<35%, EDD >55mm. QRS > 130 ms, 6 minute walk >450m, receiving optimal therapy (diuretics, ACE inhibitor at max doses stable for >1 month) | Transvenous implantation of cardiac resynchronisation device (Insync Model 8040, Medtronic) with three pacing leads.<br>After randomisation patients were assigned to active or inactive pacing for a period of six months by an electrophysiologist not otherwise involved with patient care. Baseline variables were assessed at one, three and six months of follow-up.<br>Crossover was prohibited.<br><br>Retrospective analysis of whether patients with heart failure who have conduction abnormalities other than LBBB also respond favourably to CRT at 6 months. | Primary endpoints:<br>NYHA class, Minnesota Living with Heart Failure quality of life score, and the distance walked in six minutes.<br>Secondary outcomes were: peak oxygen consumption, time on treadmill and exercise time. | CRT on versus off<br>NYHA class<br>LBBB P<0.001, RBBB p=0.001, IVCD p=0.08<br>When they received CRT there was a significant improvement in quality of life (p=0.038) by patients with interventricular conduction delay. Patients in RBBB and interventricular conduction delay groups showed improvement in exercise after CRT.<br><br>QoL<br>No significant improvement in LBBB and RBBB. IVCD (p=0.04)<br><br>6-minute walk<br>LBBB P<0.001, RBBB p=0.46, IVCD P=0.14<br><br>Exercise time<br>LBBB P=0.007, RBBB P=0.84, IVCD P=0.47 | Follow-up period was limited – only six months.<br>Study did not have adequate power to assess mortality.<br>Groups were comparable at baseline.<br>Intention–to-treat analysis.<br>6 month follow-up limited to 391 patients (453 eligible).<br>Small groups.<br>Sub-group analysis with consequential limitations (small sample in RBBB and IVCD sub-groups)<br>Blinded assessment of ECG.<br><br>Authors' conclusions:<br>Demonstrates that patients with CHF and conduction abnormalities other than LBBB obtain some of the benefits from CRT. This improvement may be associated with RBBB producing interventricular and intraventricular dyssynchrony. Further sub-group analyses of other CRT trials will be necessary to increase sample size and validate these hypothesis-generating results. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Cazeau et al 2001)<br><br>MUSTIC<br><br>Level II | RCT<br><br>Crossover (active vs inactive)<br><br>Single (patient)-blinded | 15 centres in six European countries during 1998-9 as part of ongoing Multisite Stimulation in Cardio-myopathies (MUSTIC) Trial. | 58 patients with heart failure, average age 63 years, all NYHA III, randomised block–stratified by study site included at baseline.<br><br>No significant difference between the groups in age, weight, gender, distance walked in 6 minutes, peak oxygen uptake, QoL heart rate or QRS interval at baseline.<br><br>Inclusion criteria:<br><br>Severe heart failure due to idiopathic or ischaemic cause, EF<35%, EDD >60mm. Sinus rhythm, QRS interval>150msec, no standard indication for pacemaker, receiving optimal therapy (diuretics, ACE inhibitor at max doses for >1 month). | Transvenous implantation of biventricular Medtronic or ELA Medical system, optimised using venogram and echocardiography. The pacemakers were triple-output devices with standard dual-chamber technology and built-in adapters.<br><br>Two weeks after implantation, patients were randomly assigned to active pacing (atriobiventricular) or inactive pacing (ventricular, inhibited at a rate of 40bpm) in a crossover design with three month periods in each phase. | Primary outcome: Distance walked in six minutes<br><br>Secondary outcomes: quality of life (Minnesota Questionnaire Living with Heart Failure), hospital admissions due to decompensated heart failure, peak oxygen uptake, patient preferences at the end of the crossover phase and death. | Effectiveness<br><br>Main outcome: walking distance increased 23% in active versus inactive period (399 versus 325 p<0.001) and 13% in the per-protocol analysis (424 versus 375, p<0.004).<br><br>Secondary outcomes:<br><br>QoL: Minnesota score decreased by 32% (p<0.001) with active pacing.<br><br>Peak oxygen uptake increased by a mean of 8% (p<0.03).<br><br>Three hospitalisations occurred during active pacing compared with nine during inactive pacing (p<0.05) (RRR=67%, ARR=21%, NNT=4.8).<br><br>At the end of the crossover phase 85% (p<0.001) per cent of patients preferred active-pacing. | Drop-outs: nine prior to randomisation, and10 patients did not complete the study 3 of whom died.<br><br>Sample size: 22 patients needed for walk test, QoL assessment required 40 patients.<br><br>Optimal medical therapy: patients received ACE inhibitor (96%), diuretic therapy (94%), digoxin (48%), amiodorone (31%), beta-blockers (28%), spironolactone (22%).<br><br>An intention–to-treat analysis was employed.<br><br>Minnesota QoL scale has been validated in other studies.<br><br>Compliance checks were undertaken (follow-up interviews, script checks) but results were not presented. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Cazeau et al 2001)<br><br>Level II<br>*Continued* | | | Exclusion criteria:<br>Hypertrophic or restrictive cardiomyopathy, acute myocarditis, correctable valvulopathy, acute coronary syndrome lasting <3 months, coronary revascularisation within the last three months, treatment resistant hypertension, severe COAD, inability to walk, reduced life expectancy not associated with cardiovascular disease or an indication for implantation of cardioverter/defibrillator. | No modification in medication other than adjustment of the dose of diuretic was permitted during the study.<br>A one-month observation period preceded implantation during which time the stability of heart failure was verified. | Other outcomes:<br>NYHA classification, need for medication, electrocardiography and cardiopulmonary exercise testing, safety. | Safety:<br>Implantation was not possible in five patients. Early lead dislodgement occurred in eight patients, and in three of these it could not be corrected. Two patients subsequently had uncorrectable loss of left ventricular pacing. Three patients died (one during active pacing). One patient's heart failure decompensated during active pacing and three decompensated during inactive pacing. | No carry-over or period effects were detected.<br>Methods of randomisation and allocation to study groups were not described.<br>Follow-up in relation to study groups and all outcomes were not described.<br>Small study with limited follow-up: a larger parallel trial would be needed to assess long-term mortality and morbidity.<br><br>Authors' conclusions:<br>Atrioventricular pacing significantly improves exercise tolerance and quality of life in patients with chronic heart failure and intraventricular conduction delay. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Cazeau et al 2001, Varma et al 2003b)<br><br>MUSTIC<br><br>Level II | RCT<br><br>Crossover (active vs inactive). Evaluations were conducted at enrolment, randomisat-ion (2 weeks after implant), after phase 1 (12 weeks) and after phase 2 (24 weeks). | 15 Centres in six European countries during 1998-9 as part of ongoing Multisite Stimulation in Cardio-Myopathies (MUSTIC) Trial. | 58 patients with heart failure, average age 63 years, all NYHA III, randomised block–stratified by study site included at baseline.<br><br>No significant difference between the groups in age, weight, gender, distance walked in 6 minutes, peak oxygen uptake, QoL heart rate or QRS interval at baseline.<br><br>Inclusion criteria:<br><br>Severe heart failure due to idiopathic or ischaemic cause, EF<35%, EDD >60mm. Sinus rhythm, QRS interval> 150msec, receiving optimal therapy (diuretics, ACE inhibitor at max doses for >1 month). NYHA Class III for ≥1 mth before inclusion while receiving optimal treatment.<br><br>6-minute walk test < 450m | Transvenous implantation of biventricular InSync 8040 (Medtronic) or Chorum MSP ELA Medical system, optimised using venogram and echocardiography. The pacemakers were triple-output devices with standard dual-chamber technology and built-in adapters.<br><br>LV lead 2187 or 2188 (Medtronic) and RV and RA leads inserted via cephalic or subclavian veins. Optimal LV lead placement was mid-lateral in a wedged position (antero-lateral and posterior were also acceptable).<br><br>Pacemaker programmed to a basic rate of 40 beats/min and upper limit 85% of the age-gender maximum predicted. | Primary outcome: Distance walked in six minutes<br><br>Secondary outcomes: quality of life (Minnesota Questionnaire Living with Heart Failure), hospital admissions due to decompensated heart failure, peak oxygen uptake, patient preferences at the end of the crossover phase and death. | Effectiveness<br><br>Main outcome:<br><br>6-min walk test 414 v 359, P=0.001<br><br>Secondary outcomes:<br><br>Active vs inactive:<br><br>$VO_2$ 15.8 v 14.4, P=0.02<br><br>Maximum $O_2$ pulse 9.3 v 8.1, P=0.002<br><br>Exercise test 501s v 437s (P<0.001)<br><br>Anaerobic threshold 11.2 v 9.5, P=0.01<br><br>$VE/VCO_2$ slope 32 v 36, P=0.03 (indicating improved ventilatory efficiency)<br><br>QoL 27 v 39, P=0.002 Minnesota score decreased by 32% with active pacing.<br><br>Three hospitalisations occurred during active pacing compared to nine during inactive pacing (p<0.05) (RRR=67%, ARR=21%, NNT=4.8).<br><br>At the end of the crossover phase 85% (p <0.001) per cent of patients preferred active-pacing. | Drop-outs: nine prior to randomisation, and10 patients did not complete the study, 3 of whom died. 67 included in clinical efficacy study, 48 completed crossover phase, complete exercise sets/inadequate studies performed in 13 patients and a further 5 did not achieve a respiratory quotient >1 (indicating satisfactory effort). Therefore, 30 of 67 participated (45%).<br><br>Sample size: 22 patients needed for walk test, QoL assessment required 40 patients.<br><br>Optimal medical therapy: patients received ACE inhibitor (96%), diuretic therapy (94%), digoxin (48%), amiodorone (31%), beta-blockers (28%), spironolactone (22%).<br><br>An intention-to-treat analysis was employed.<br><br>Minnesota QoL scale has been validated in other studies.<br><br>Compliance checks were undertaken (follow-up interviews, script checks) but results were not presented.<br><br>Single blind.<br><br>Industry supported.<br><br>Data analysed centrally to avoid bias and standardise interpretation<br><br>Randomisation: block design with stratification by centre |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Cazeau et al 2001, Varma et al 2003b)<br>*(continued)*<br>MUSTIC | | | No acute myocarditis, hypertrophic or restrictive cardiomyopathy, systolic BP >160, diastolic BP >95 despite treatment, symptomatic/sustained ventricular tachycardia, unstable coronary symptoms within 3 mths or a planned revascularisation, correctable valve disease, inability to walk, or a conventional pacemaker indication. | Two weeks after implantation, patients were randomly assigned to active pacing (atriobiventricular) or inactive pacing (ventricular, inhibited at a rate of 40bpm) in a crossover design with three-month periods in each phase. | | | Changes in diuretic therapy permitted during crossover phases<br>More patients received active pacing in the 1st CO period. If there was carryover, this would underestimate the true difference between active and inactive pacing<br>Single blinding – subjective or effort based measures susceptible to bias potentially overestimating the active phase effectiveness.<br>Authors' conclusions: BVP can significantly improve both maximal and submaximal measures of exercise, which may better reflect exercise capacity during normal daily activities. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Alonso et al 2003)<br><br>MUSTIC<br><br>Level II | RCT (single blind) – crossover: 3 mths in each phase (random order).<br>Followed by 6 mths program-ming according to patient choice. | 15 Centres in six European countries during 1998-nine as part of ongoing Multisite Stimulation in Cardio-myopathies (MUSTIC) Trial. | 22 patients were presented (14 men, mean age = 62 years, all NYHA = III, Ischaemic heart failure: 27%,<br>LV EF 22%, QRS 175 ms, 6-minute walking distance 321 metres).<br><br>Inclusion criteria:<br>Severe heart failure due to idiopathic or ischaemic cause, EF <35%, EDD >60mm. Sinus rhythm, QRS interval >150msec, receiving optimal therapy (diuretics, ACE inhibitor at max doses for >1 month). NYHA Class III for ≥ 1 mth before inclusion while receiving optimal treatment. No acute myocarditis, hypertrophic or restrictive cardiomyopathy, systolic BP >160, diastolic BP >95 despite treatment, symptomatic/sustained ventricular tachycardia, unstable coronary symptoms within 3 mths or a planned revascularisation, correctable valve disease, inability to walk, or a conventional pacemaker indication. | Transvenous implantation of biventricular InSync 8040 (Medtronic) or Chorum MSP ELA Medical system, optimised using venogram and echocardiography. The pacemakers were triple-output devices with standard dual-chamber technology and built-in adapters.<br>Two weeks after implantation, patients were randomly assigned to active pacing (atriobiventricular) or inactive pacing (ventricular, inhibited at a rate of 40bpm) in a crossover design with three month periods in each phase. Twenty-four hour ambulatory electrocardiograms were obtained at the end of each crossover phase and at 9 and 12 months. | Primary outcome: Distance walked in six minutes<br><br>Secondary outcomes: heart rate variability measures | Effectiveness<br>Distance walked crossover phase: active versus inhibited pacing (392 v 326m, P=0.02)<br><br>Secondary outcomes:<br>HRV improved during crossover phase (active v inhibited):<br>SD normal to normal interval over recording duration: 102 v 88, P=0.04<br>SD 5 min normal to normal interval over entire recording: 90 v 78, P=0.07<br>Square root of mean squared successive differences between adjacent RR intervals over entire recording: 38 v 32, P=0.07<br>Proportion of successive interval differences >50ms over the entire recording: 12.6 v 6.8, P=0.03.<br><br>No significant correlation between 6-min walk test and HRV improvement. | 67 patients with heart failure were included in the clinical efficacy study. 48 completed the crossover phase. 46 underwent the additional 6-month period programmed to active pacing. 42 completed 1 year of follow-up. 20 of the 42 were excluded from the heart rate variability sub-study because of incomplete or unsuitable data Therefore, 22 of 67 participated (33%).<br>Patients were randomised, block-stratified by study site included at baseline.<br>Single blind<br>ITT analysis<br>Industry supported<br>Walking distance is a subjective outcome measure – susceptible to increased effort which may have biased results since study was only single blind (investigators aware of status)<br>Heart rate variability measures are an intermediate outcome.<br>Authors' conclusions:<br>'In patients with severe heart failure, CRT improves HRV. Improvement is preserved beyond 1 year of follow-up. The benefit provided by CRT was all the more important because baseline ventricular asynchrony was severe.' |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample, Inclusion criteria | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Duncan 2003)<br><br>MUSTIC<br><br>Level II | RCT (single blind) – crossover: 3 mths in each phase (random order).<br>Followed by 6 mths program-ming according to patient choice. | France, Germany, Italy, Sweden, Switzerland, United Kingdom | Inclusion criteria:<br>LV EF < 35%<br>EDD > 60mm<br>QRS > 150 ms<br>NYHA Class III for ≥ 1 mth before inclusion while receiving optimal treatment.<br>No acute myocarditis, hypertrophic or restrictive cardiomyopathy, systolic BP >160, diastolic BP >95 despite treatment, symptomatic/sustained ventricular tachycardia, unstable coronary symptoms within 3 mths or a planned revascularisation, correctable valve disease, inability to walk, or a conventional pacemaker indication.<br><br>Sample:<br>N=34<br>QRS 172 msec<br>??NYHA Class 2.8 | Atriobiventricular pacing active versus inhibited.<br>All inserted transvenously. LV lead 2187 or 2188 (Medtronic) and RV and RA leads inserted via cephalic or subclavian veins. Optimal LV lead placement was mid-lateral in a wedged position (antero-lateral and posterior were also acceptable).<br>Pacemaker programmed to a basic rate of 40 beats/min and upper limit 85% of the age-gender maximum predicted. | Primary outcome:<br>6-min walk<br><br>Secondary outcomes:<br>Total isovolumic time (IVT)<br>End diastolic dimension (EDD)<br>End systolic dimension (ESD)<br>Peak $VO_2$ | Effectiveness<br>6-min walk: 401 v 336 m (P<0.001)<br><br>Secondary outcomes:<br>EDD (cm): 6.8 v 7.3 (P<0.05)<br>ESD (cm): 5.9 v 6.2 (NSD)<br>Peak $VO_2$ (ml/kg/min) 16.0 v 14.8 (P<0.05)<br><br>NOTE: all comparisons at end of crossover (active v inactive) | Single blind<br>ITT analysis<br>Industry supported<br>Randomisation: block design with stratification by centre<br>67 included in clinical efficacy study, 64 underwent implantation and 58 were randomised, 48 completed crossover phase, 3 died between 6 and 12 months and 11 had incomplete ECHO recordings leaving a sample of 34. Therefore, 34 of 67 participated (51%).<br>NOTE: some discrepancy with Alonso study where 2 were excluded in the post-crossover phase due to patient preference for inactive phase.<br>Estimated 80% power to detect a significant difference in filling time at the 5% level with a sample size of 26.<br>Carryover effects were evaluated in those randomly assigned to the intervention in the first crossover period. Carryover was a possibility with longer filling time and shorter IVT at the end of the inactive phase, when it followed active pacing. This would dilute the difference between active and inactive phases. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample, Inclusion criteria | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Duncan 2003)<br>*(continued)*<br>MUSTIC | | | | | | | How can mean NYHA class be 2.8 if entry criteria requires class III?<br>Limited comparisons between groups after cross over phase.<br>Walking distance is a subjective outcome measure – susceptible to increased effort which may have biased results since study was only single blind (investigators aware of status).<br>Possibly best to ignore walking distance results because they are a subset of patients presumably reported more fully elsewhere. |

**Table 48 Studies included under effectiveness (continued)**

| Source | Study design | Setting | Sample, Inclusion criteria | Interventions | Outcomes | Results | Comments |
|---|---|---|---|---|---|---|---|
| (Linde 2003)<br><br>MUSTIC<br><br>Level II | RCT (single blind) – crossover: 3 mths in each phase (random order).<br>Followed by 6 mths program-ming according to patient choice | France, Germany, Italy, Sweden, Switzerland, United Kingdom | Inclusion criteria:<br>LV EF < 35%<br>EDD > 60mm<br>QRS > 150 ms<br>NYHA Class III for ≥1 mth before inclusion while receiving optimal treatment.<br>No acute myocarditis, hypertrophic or restrictive cardiomyopathy, systolic BP >160, diastolic BP >95 despite treatment, symptomatic/sustained ventricular tachycardia, unstable coronary symptoms within 3 mths or a planned revascularisation, correctable valve disease, inability to walk, or a conventional pacemaker indication.<br><br>Sample (SR group):<br>Age 63<br>Male 50/67 (67%)<br>NYHA class III: 67 (100%)<br>LV EF 22%<br>6-min walking distance 320 m<br>QRS duration 176 msec | Atriobiventricular pacing active versus inhibited.<br>All inserted transvenously. LV lead 2187 or 2188 (Medtronic) and RV and RA leads inserted via cephalic or subclavian veins. Optimal LV lead placement was mid-lateral in a wedged position (antero-lateral and posterior were also acceptable).<br>Pacemaker programmed to a basic rate of 40 beats/min and upper limit 85% of the age-gender maximum predicted. | Primary outcome:<br>Quality of Life (QoL): Minnesota Living with Heart Failure Questionnaire and Karolinska Questionnaire. | Effectiveness<br>Total Minnesota score (SR group)<br>Active phase during 1st CO: NSD between end of CO1 and pre CO.<br>Active phase during 2nd CO: P<0.001 between end of CO2 and pre CO. Also significantly reduced self perceived restriction in health (P<0.001), dyspnoea (P<0.001) and quality of sleep (P<0.01).<br>NSD in cognitive functioning (either phase first) or (for active phase first): self perceived restriction in health, dyspnoea and quality of sleep. | Single blind<br>ITT analysis<br>Industry supported<br>Randomisation: block design with stratification by centre<br>131 patients in the MUSTIC trial (how does this compare with the 67 included in clinical efficacy study for the two previous MUSTIC papers?), and 76 fulfilled the 12-month QoL questionnaire. Therefore, 76 of 131 participated (58%).<br>SR and AF patients included<br>Demographic details based on all 131 patients rather than the 76 who took part.<br>No comparison between intervention and control groups – analysed more as a before and after study<br>QoL is somewhat subjective – may have biased results since study was only single blind. |

# Appendix D Pacemaker coding system

The North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG) have developed and recently updated the NBG code to describe different pacing modes (Bernstein et al 2002).

The first letter of the revised code signifies the chamber being paced:

0=none, A=atrium, V=ventricle, D=dual (A + V).

The second letter signifies the chamber being sensed:

0=none, A=atrium, V=ventricle, D=dual (A + V).

The third letter signifies the response to sensing:

0=none, I=inhibited, T=triggered, D=dual (T + I).

The fourth letter signifies rate modulation:

0=none, R=rate modulation.

The fifth letter signifies multi-site pacing:

0=none, A=atrium, V=ventricle, D=dual (A + V).

# Appendix E Excluded papers

| Paper | Not systematic review, RCT or X-over trial | <20 human subjects | Letter/ comment/ abstract only | Background/no primary data[1]/ expert opinion | All non-sinus rhythm | All non-trans-venous lead placement | All ICD |
|---|---|---|---|---|---|---|---|
| (Adachi et al 2003) | X | X | | | | | |
| (Abraham 2000) | X | | | X | | | |
| (Abraham 2003b) | X | | | X | | | |
| (Abraham 2003c) | X | | | X | | | |
| (Abraham and Hayes 2003) | X | | | X | | | |
| (Abraham 2003a) | X | | | X | | | |
| (Adams and Zannad 1998) | X | | | X | | | |
| (Adamson et al 2003) | | | | X | | | |
| (Adamson et al 2004) | X | | | X | | | |
| (Ali et al 2000) | X | X | | X | | | |
| (Alonso et al 2002) | | | X | | | | |
| (Alonso et al 2001) | X | | | | | | |
| (Alonso et al 2001) | X | | | | | | |
| (Alonso et al 2003) | | | | X | | | |
| (Anonymous 2001) | X | | X | | | | |
| (Ansalone et al 2003) | X | | X | | | | |
| (American College of Cardiology Foundation 2001) | X | | X | | | | |
| (MERIT-HF Triallists Group 1999) | | | | X | | | |
| (CIBIS-II Investigators 1999) | | | | X | | | |
| (Digitalis Investigation Group 1997) | | | | X | | | |
| (Ansalone et al 2002) | X | | | | | | |
| (Ansalone et al 2001) | X | | | X | | | |
| (Ansalone et al 1999) | X | | | X | | | |
| (Araki et al 2003) | X | X | | | | | |
| (Aranda et al 2005) | X | | | X | | | |
| (Arya et al 2003) | X | | | X | | | |
| (Auricchio and Abraham 2004) | X | | | X | | | |
| (Auricchio 2004) | X | | | X | | | |
| (Auricchio et al 2002a) | X | | | | | | |
| (Auricchio et al 2002b) | | | X | | | | |
| (Auricchio and Klein 2001) | X | | | X | | | |

[1] Includes papers only presenting electrophysiological and/or haemodynamic information.

| Paper | Not systematic review, RCT or X-over trial | <20 human subjects | Letter/ comment/ abstract only | Background/no primary data[1]/ expert opinion | All non-sinus rhythm | All non-trans-venous lead placement | All ICD |
|---|---|---|---|---|---|---|---|
| (Auricchio et al 2003) | | | | X | | | |
| (Auricchio and Spinnelli 2003) | X | | | X | | | |
| (Auricchio and Spinelli 2000) | X | | | X | | | |
| (Auricchio et al 1999a) | X | | | X | | | |
| (Auricchio et al 1999b) | | | | | | X | |
| (Auricchio et al 1999c) | X | | | X | | | |
| (Auricchio and Salo 1997) | X | X | | | | X | |
| (Bakker et al 2000) | X | X | | | | X | |
| (Baller et al 2004) | X | | | X | | | |
| (Barold and Stroobandt 2003) | X | | | X | | | |
| (Barold and Byrd 2001) | | X | | | | X | |
| (Barold et al 2001) | | X | | X | | | |
| (Barold and Levine 2001) | X | | | X | | | |
| (Barold 2001) | X | | | X | | | |
| (Barold 2000) | X | | | X | | | |
| (Bax et al 2003a) | | | | X | | | |
| (Berger et al 2004) | X | | X | | | | |
| (Berruezo et al 2004) | X | X | | X | | | |
| (Betts et al 2001) | X | X | | | | | X |
| (Bhatta et al 2004) | | | | X | | | |
| (Birnie et al 2001) | X | X | X | | | | |
| (Bittner et al 1993) | X | | | X | | | |
| (Blanc and Fatemi 2001) | X | X | X | X | | | |
| (Blanc et al 1997) | | | | | | X | |
| (Bocchiardo et al 2000a) | X | | | | | | X |
| (Bocchiardo et al 2000b) | | | | X | | | X |
| (Boehmer 2003) | X | | | X | | | |
| (Bonanno et al 2004) | X | | | X | | | |
| (Bordachar et al 2003) | X | | | | | | |
| (Bordachar et al 2000) | X | X | | | X | | |
| (Boriani et al 2003) | X | | | X | | | X |
| (Boriani et al 2005) | X | X | | X | | | |
| (Botvinick 2003) | X | | | X | | | |
| (Braunschweig et al 2003) | X | X | | | | | |
| (Braunschweig et al 2000) | X | X | | | | | |
| (Brecker et al 1992) | X | X | | X | | | |

| Paper | Not systematic review, RCT or X-over trial | <20 human subjects | Letter/ comment/ abstract only | Background/no primary data[1]/ expert opinion | All non-sinus rhythm | All non-trans-venous lead placement | All ICD |
|---|---|---|---|---|---|---|---|
| (Breithardt and Stellbrink 2004) | X | | | X | | | |
| (Breithardt et al 2003b) | | X | | X | | | |
| (Breithardt et al 2003a) | | | | X | | | |
| (Breithardt et al 2002a) | X | X | | | | | |
| (Breithardt et al 2002b) | X | | | X | | | |
| (Breithardt et al 2000) | X | | | X | | | |
| (Brignole 2002) | X | | | X | | | |
| (Bristow et al 2000) | X | | | X | | | |
| (Bryce et al 2001) | X | | | X | | | |
| (Bulava et al 2005) | X | X | | X | | | |
| (Butter et al 2001a) | | | | X | | | |
| (Butter et al 2001b) | X | | | | | | X |
| (Butter et al 2004) | X | | | X | | | |
| (Cahalin et al 1996) | X | | | X | | | |
| (Calvert et al 2005) | | | X | | | | |
| (Capasso et al 2004) | X | X | | X | | | |
| (Casey and Knight 2004) | X | | | X | | | |
| (Castellanos and Aranda 2001) | | | X | | | | |
| (Catalan Agency for Health Technology Assessment (CAHTA) 1996) | X | | | X | | | |
| (Cazeau et al 2003a) | X | | | | | | |
| (Cazeau et al 2003b) | X | | | X | | | |
| (Cazeau et al 1996) | X | X | | | | X | |
| (Cazeau et al 1994) | X | X | | | | X | |
| (Chamoun et al 2001) | X | X | | | | | |
| (Chan et al 2003a) | X | | | | | | |
| (Chan et al 2004) | | | X | | | | |
| (Chang et al 2004) | X | X | | X | | | |
| (Chierchia et al 2005) | X | X | | X | | | |
| (Chiladakis et al 2004) | X | | | X | | | |
| (Cholewinski et al 2002) | X | X | | | | | |
| (Clark et al 2004) | X | | | X | | | |
| (Clarke et al 1998) | | | | X | | | |
| (Claus et al 2003) | X | | | X | | | |
| (Cleland et al 2003b) | X | | | X | | | |
| (Cleland et al 2003c) | X | | | X | | | |
| (Cleland et al 2003a) | X | | | X | | | |
| (Cleland et al 2002) | X | | | X | | | |
| (Cleland et al 2001a) | | | X | | | | |
| Cleland, (2001) | X | | | X | | | |

| Paper | Not systematic review, RCT or X-over trial | <20 human subjects | Letter/ comment/ abstract only | Background/no primary data[1]/ expert opinion | All non-sinus rhythm | All non-trans-venous lead placement | All ICD |
|---|---|---|---|---|---|---|---|
| (Cleland and Clark 1999) | X | | | X | | | |
| (Cleland et al 2005a) | | | | X | | | |
| (Cleland et al 2004) | | | | X | | | |
| (Cohen and Klein 2002) | X | | | X | | | |
| (Cohn and Rector 1988) | X | | | X | | | |
| (Coletta et al 2003) | X | | | X | | | |
| (Coletta et al 2004) | X | | | X | | | |
| (Conaway et al 2004) | X | X | | | | | |
| (Conseil d' Evaluation des Technologies de la Sante (CETS) 2000) | X | | | X | | | |
| (Conti 2001) | X | | | X | | | |
| (Cowburn et al 1998) | X | | | X | | | |
| (Cowburn et al 2005) | X | X | | X | | | |
| (Cowie and Zaphirou 2002) | X | | | X | | | |
| (Cowie et al 1997) | X | | | X | | | |
| (Curnis et al 2000) | X | | | X | | | |
| (Curtis et al 2004) | X | | | X | | | |
| (Curtis 2005) | X | | X | | | | |
| (Cuzin et al 1999) | X | | | X | | | |
| (D'Andrea et al 2001) | X | X | | X | | | |
| (Daubert et al 1998) | X | | | | | | |
| (de Cock et al 2001) | X | | | X | | | |
| (De Marco et al 2003) | | | X | | | | |
| (De Sutter et al 2000) | X | | | X | | | |
| (Debrunner et al 2000) | X | X | | X | | | |
| (Diotallevi et al 2005) | X | | | X | | | |
| (Dizon et al 2004) | X | X | | | | | |
| (Doi et al 2004) | X | X | X | | | | |
| (Dresing and Natale 2001) | X | | | X | | | |
| (Dretzke et al 2004) | | | | X | | | |
| (Dubin et al 2003) | X | X | | | | | |
| (Dunselman et al 1988) | X | | | X | | | |
| (Eichhorn 2001) | | | | X | | | |
| (Eidelman et al 2004) | X | X | | X | | | |
| (Ellenbogen et al 2003) | X | | | X | | | |
| (Ellery and Paul 2004) | X | | | X | | | |
| (Engelstein 2003) | X | | | X | | | |
| (Erdogan et al 2003) | X | | | | | | |
| (Etienne et al 2001) | X | | | | | | |
| (Etienne et al 1999) | X | | | | | X | |
| (Faris et al 2003) | X | | | | | | |

| Paper | Not systematic review, RCT or X-over trial | <20 human subjects | Letter/ comment/ abstract only | Background/no primary data[1]/ expert opinion | All non-sinus rhythm | All non-trans-venous lead placement | All ICD |
|---|---|---|---|---|---|---|---|
| (Farwell et al 2000) | X | | | X | | | |
| (Foster et al 1995) | X | X | | | | X | |
| (Franciosa et al 1983) | X | | | X | | | |
| (Fauchier et al 2003) | X | | | | | | |
| (Fauchier et al 2002) | X | | | | | | |
| (Freudenberger et al 2004) | X | | | | | | |
| (Fukuoka et al 2000) | X | X | | X | | | |
| (Funck et al 2005) | X | | | X | | | |
| (Gaita et al 2000) | X | | | | | | |
| (Galizio et al 2003) | X | | | X | | | |
| (Galvao et al 2002) | X | | | | | | |
| (Garcia-Moran et al 2002) | X | X | | | | | X |
| (Garrigue et al 2001a) | X | | | | | X | |
| (Garrigue et al 2001b) | X | X | | | | | |
| (Garrigue et al 2000) | X | X | | | | | X |
| (Gasparini et al 2003a) | X | | | | | | X |
| (Gasparini et al 2003c) | X | X | | | | | |
| (Geist et al 2003) | X | X | | | X | | |
| (Gerber et al 2001) | X | | | X | | | |
| (Gibelin 2001) | | | | X | | | |
| (Gold et al 1995) | | X | | X | | | |
| (Gorcsan et al 2004) | X | | | X | | | |
| (Gottipaty et al 1999) | | | X | | | | |
| (Gradaus et al 2002) | | | | | | | X |
| (Gras et al 2003) | X | | | X | | | |
| (Gras et al 2002a) | X | | | X | | | |
| (Gras et al 2002b) | X | | | | | | |
| (Gras et al 1998) | X superseded | | | | | | |
| (Grassi et al 2004) | X | | | X | | | |
| (Gregoratos 1999) | | | | X | | | |
| (Greenberg et al 2003b) | X | | | | X | | |
| (Greenberg et al 2003a) | X subgroup of other studies | | | | | | |
| (Guo et al 2005) | X | X | | X | | | |
| (Guerra et al 2003) | X | X | | | | | X |
| (Gurevitz et al 2003) | | | | X | | | |
| (Gururaj 2004) | X | | | X | | | |
| (Guyatt et al 1985) | | | | X | | | |
| (Hamdan et al 2000) | X | X | | | | | |
| (Hampton et al 1997) | | | | X | | | |
| (Hansky et al 2002) | X | | | | | | |
| (Hare 2002) | X | | | X | | | |

| Paper | Not systematic review, RCT or X-over trial | <20 human subjects | Letter/ comment/ abstract only | Background/no primary data[1]/ expert opinion | All non-sinus rhythm | All non-trans-venous lead placement | All ICD |
|---|---|---|---|---|---|---|---|
| (Haywood 2001) | X | | | X | | | |
| (Hansky et al 2002) | X | | | | | | |
| (Herweg and Barold 2003) | X | | | X | | | |
| (Higgins et al 2003) | X | | | | | | X |
| (Higgins et al 2000) | X | | | | | X | X |
| (Hiraoka and Hong 2004) | X | | | X | | | |
| (Ho et al 1993) | X | | | X | | | |
| (Horwich et al 2004) | X | X | | X | | | |
| (Hua et al 2003) | | | X | | | | |
| (Huang et al 2003) | X | | | | | | |
| (Huang et al 2004) | | | | X | | | |
| (Hugl et al 2003) | | | X | | | | |
| (Hugl et al 2004) | | | X | | | | |
| (Hussein et al 2004) | X | | | X | | | |
| (Inoue et al 2005) | X | X | | X | | | |
| (Jafri et al 1986) | X | | | X | | | |
| (Jahangir and Shen 2003) | X | | | X | | | |
| (Jais et al 2000) | | X | | | | X | |
| (Jais et al 1998) | | X | | | | | |
| (Jessup 2003) | X | | | X | | | |
| (Jongbloed et al 2005) | X | | | X | | | |
| Joseph, (2002) | X | | | X | | | |
| (Kalinchak and Schoenfeld 2003a) | X | | | X | | | |
| (Kalinchak and Schoenfeld 2003b) | X | | | X | | | |
| (Kanzaki et al 2003) | | X | | X | | | |
| (Kannel and Cupples 1988) | X | | | X | | | |
| (Kanzaki et al 2004) | X | | | X | | | |
| (Kaplinsky et al 2001) | X | X | | | | | X |
| (Kappenberger et al 2000) | X | | | X | | | |
| (Kaprielian and Lefroy 2003) | X | | | X | | | |
| (Kass 2003b) | X | | | X | | | |
| (Kass 2003a) | X | | | X | | | |
| (Kass et al 1999) | X | X | | X | | | |
| (Kay and Bourge 2000) | X | | | X | | | |
| (Kerr et al 2004) | | | | X | | | |
| (Kerwin and Paz 2003) | X | | | X | | | |
| (Kerwin et al 2000) | X | X | | | | | |
| (Khand et al 2000) | X | | | X | | | |

| Paper | Not systematic review, RCT or X-over trial | <20 human subjects | Letter/ comment/ abstract only | Background/no primary data[1]/ expert opinion | All non-sinus rhythm | All non-trans-venous lead placement | All ICD |
|---|---|---|---|---|---|---|---|
| (Klein 2003) | X | | | X | | | |
| (Kim et al 2001) | X | X | | | | | |
| (Knight et al 2004) | | | | X | | | X |
| (Knuuti et al 2004) | X | X | | X | | | |
| (Komura et al 2004) | X | | | X | | | |
| (Kong et al 2004) | | | | X | | | |
| (Kowal et al 2004) | X | X | | X | | | |
| (Kowalsky et al 2001) | X | X | | X | | | |
| (Kramm et al 2003) | | | X | | | | |
| (Kranidis et al 2004) | X | X | | X | | | |
| (Krenning et al 2004) | X | | | X | | | |
| (Kuhlkamp et al 2003) | X | | | X | | | |
| (Kuhlkamp 2002) | X | | | | | | X |
| (Lafitte et al 2004) | X | X | | | | | |
| (Lambiase et al 2004) | X | X | | | | | |
| (Lane et al 2003) | X | | X | X | | | |
| (Lane et al 2002) | | | X | | | | |
| (Lau et al 2000) | X | X | | | | | |
| (Lawo et al 2003) | | | X | | | | |
| (Le Franc et al 1998) | X | X | | | | | X |
| (Le Rest et al 1999) | X | X | | X | | | |
| (Leclercq and Hare 2004) | X | | | X | | | |
| (Leclercq and Daubert 2003) | X | | | X | | | |
| (Leclercq et al 2003) | | | X | | | | |
| (Leclercq and Kass 2002) | X | | | X | | | |
| (Leclercq and Daubert 2000) | X | | | X | | | |
| (Leclercq et al 2000a) | X | | | | | | |
| (Leclercq et al 2000b) | X | | | | | | |
| (Leclercq et al 1998) | | X | | X | | | |
| (Leclercq et al 1995) | | X | | X | | | |
| (Leclercq and Hare 2004) | X | | | X | | | |
| (Lee et al 2004) | X | X | | | | | |
| (Lee and Lau 2001) | | | | X | | | X |
| (Likoff et al 1987) | X | | | X | | | |
| (Linde 2004) | X | | | X | | | |
| (Linde et al 2003) | Results reported as separate study groups | | | | | | |
| (Linde 2003) | | | X | | | | |
| (Linde et al 2002a) | | | X | | | | |

| Paper | Not systematic review, RCT or X-over trial | <20 human subjects | Letter/ comment/ abstract only | Background/no primary data[1]/ expert opinion | All non-sinus rhythm | All non-trans-venous lead placement | All ICD |
|---|---|---|---|---|---|---|---|
| (Linde 2000) | X | | | X | | | |
| (Linde et al 1999) | | | | X | | | |
| (Linde et al 1995) | X | X | | X | | | |
| (Lindner et al 2005) | X | | | X | | | |
| (Lipkin et al 1986) | X | | | X | | | |
| (Liu et al 2003) | X | X | | | | | X |
| (Livanis et al 2003) | | X | | X | | | |
| (Lozano et al 2000) | | | | | | | X |
| (Luck et al 2002) | X | | | X | | | |
| (Lunati et al 2002) | X | | | | | | |
| (Luqman et al 2001) | X | | | X | | | |
| (Makaryus et al 2003) | | | | X | | | |
| (Malinowski 2003) | X | | | | X | | |
| (Mancini et al 1991) | X | | | X | | | |
| (Mansourati et al 2000) | X | | | | | X | |
| (Manolis 2004) | X | | | X | | | |
| (Mardell 2004) | X | | | X | | | |
| (Martinelli Filho et al 2002) | | | | | | X | |
| (Martinelli et al 2005) | | | | X | | | |
| (Mascioli et al 2002a) | | | X | | | | |
| (Matsushita et al 2004) | X | X | | X | | | |
| (McCullough and Abraham 2003) | X | | | X | | | |
| (McMurray and Stewart 2000) | X | | | X | | | |
| (Mele et al 2004) | | | X | | | | |
| (Menardi et al 2003) | | X | X | | | | |
| (Mehta et al 2001) | X | | | X | | | |
| (Meisel et al 2001) | X | | | X | | | X |
| (Meisel et al 2000) | X | | | | | | X |
| (Meluzin et al 2004) | X | X | | | | | |
| (Metra et al 2003) | | | X | | | | |
| (Metra et al 1999) | X | | | X | | | |
| (Molhoek et al 2004b) | X | | | | | | |
| (Molhoek et al 2003) | X | | | | | | X |
| (Molhoek et al 2002) | | | X | | | | |
| (Mond et al 2004) | X | | | X | | | |
| (Morris-Thurgood et al 2000) | X | X | | | | X | |
| (Mosterd et al 1997) | X | | | X | | | |
| (Narang et al 1996) | | | | X | | | |
| (National Heart Foundation of Australia and Cardiac Society of Australia & New | | | | X | | | |

| Paper | Not systematic review, RCT or X-over trial | <20 human subjects | Letter/ comment/ abstract only | Background/no primary data[1]/ expert opinion | All non-sinus rhythm | All non-trans-venous lead placement | All ICD |
|---|---|---|---|---|---|---|---|
| Zealand 2002) | | | | | | | |
| (Nelson et al 2000) | X | X | | | | | |
| (Neri et al 2003) | | X | | X | | | |
| (Neri et al 2002) | X | | | | | | |
| (Neri et al 2001) | X | X | | X | | | |
| (Nielsen et al 2003) | X | X | | | | | |
| (Nishimura et al 1997) | | | | X | | | |
| (Nishimura et al 1995) | X | X | | X | | | |
| (Notabartolo et al 2004) | X | | | X | | | |
| (Nowak et al 2004) | | X | | X | | | |
| (Nowak et al 2003) | | X | | X | | | |
| (Nurnberg et al 2005) | X | X | | X | | | |
| (O'Cochlain et al 2001a) | X | X | | X | | | |
| (O'Cochlain et al 2001b) | X | | | | | | |
| (Oguz et al 2002b) | X | X | | | | | |
| (Opasich et al 1998) | X | | | X | | | |
| (Ovsyshcher and Auricchio 2003) | X | | | X | | | |
| (Packer et al 2001) | | | | X | | | |
| (Packer 2001) | | | | X | | | |
| (Packer et al 1996) | | | | X | | | |
| (Packer et al 1993) | | | | X | | | |
| (Panidis et al 1986) | X | X | | X | | | |
| (Pappone et al 2003) | X | | | X | | | |
| (Pappone et al 2001) | X | X | | | | | |
| (Pappone et al 2000) | X | X | | X | | | |
| (Paulussen and van Gelder 2004) | X | X | | X | | | |
| (Pavia and Wilkoff 2001) | X | | | X | | | |
| (Pedrosa et al 2001) | X | X | X | X | | | |
| (Peichl et al 2004) | X | | | X | | | |
| (Perego et al 2003) | X | | | | | | |
| (Peters and Gold 2000) | X | | | X | | | |
| (Pflugfelder et al 1993) | | | | X | | | |
| (Pires et al 2001) | X | X | | | | | |
| (Pitt et al 2000) | | | | X | | | |
| (Pitt et al 1999) | | | | X | | | |
| (Pitt et al 1997) | | | | X | | | |
| (Pitzalis et al 2002) | | | | X | | | |
| (Poole-Wilson 2000) | X | | | X | | | |
| (Popovic et al 2002) | X | | | | | | |
| (Porciani et al 2000) | X | | | | | | |
| (Prech et al 2001) | X | | | X | | | |

| Paper | Not systematic review, RCT or X-over trial | <20 human subjects | Letter/ comment/ abstract only | Background/no primary data[1]/ expert opinion | All non-sinus rhythm | All non-trans-venous lead placement | All ICD |
|---|---|---|---|---|---|---|---|
| (Prenner et al 2004) | X | | | X | | | |
| (Purerfellner et al 2000) | X | | | | | | |
| (Pyatt et al 2003) | X | | | | | | X |
| (Ramahi and Lee 1995) | X | | | X | | | |
| (Raman et al 2000) | X | X | | X | | | |
| (Rector and Cohn 1994) | X | | | X | | | |
| (Rector and Cohn 1992) | | | | X | | | |
| (Rector et al 1987) | X | | | X | | | |
| (Reuter et al 2002) | X | | | X | | | |
| (Reuter et al 2000) | X superseded | | | | | | |
| (Richardson et al 2005) | X | X | | X | | | |
| (Ricci et al 2000) | X | | | | | | |
| (Riedlbauchova et al 2004) | | | | X | | | |
| (Riedlbauchova et al 2005) | X | X | | X | | | |
| (Roka et al 2004) | X | X | | X | | | |
| (Rose et al 2001) | | | | X | | | |
| (Rostagno et al 2000) | X | | | X | | | |
| (Sackner-Bernstein 2002) | | | X | | | | |
| (St John Sutton et al 2003) | | | | X | | | |
| (Salukhe et al 2004) | X | | | X | | | |
| (Salukhe et al 2003a) | X | | | X | | | |
| (Salukhe et al 2003b) | X | | | X | | | |
| (Sassara et al 2004) | X | X | | X | | | |
| (Saxon and De Marco 2001) | | | X | | | | |
| (Saxon and Ellenbogen 2003) | X | | | X | | | |
| (Saxon et al 2000) | X | | | X | | | |
| (Saxon et al 1999) | X | | | X | | | |
| (Schoeller et al 1993) | X | | | X | | | |
| (Schreieck et al 2001) | X | X | | | | | X |
| (Schuchert et al 2005) | X | | | X | | | |
| (Schuster et al 2003) | | X | | X | | | |
| (Schuster et al 2004a) | X | | | X | | | |
| (Schuster et al 2004b) | X | X | | X | | | |
| (Seidl et al 2002) | X | | | X | | | |
| (Senzaki et al 2004) | X | | | | | X | |
| (Shalaby et al 2005) | X | X | | X | | | |
| (Shamim et al 1999) | X | | | X | | | |
| (Shen et al 2004) | X | | | X | | | |
| (Sindone et al 1997) | X | | | X | | | |

| Paper | Not systematic review, RCT or X-over trial | <20 human subjects | Letter/ comment/ abstract only | Background/no primary data[1]/ expert opinion | All non-sinus rhythm | All non-trans-venous lead placement | All ICD |
|---|---|---|---|---|---|---|---|
| (Sinha et al 2004) | X | | | X | | | |
| (Sitges et al 2003) | | | X | | | | |
| (Sogaard et al 2001) | X | | | | | | |
| (Sperzel et al 2001) | X | | | X | | | |
| (Sra 2003) | X | | | X | | | |
| (Steinberg et al 2004) | X | | | X | | | |
| (Stelken et al 1996) | X | | | X | | | |
| (Stellbrink et al 2001) | X | | | | | X | |
| (Stellbrink et al 2000) | X | | | X | | | |
| (Stellbrink et al 1999) | X | | | | | | X |
| (Sterlinski et al 2004) | | X | X | | | | |
| (Strohmer et al 2004) | X | | | X | | | |
| (Sun et al 2004) | X | | | X | X | | |
| (Sundell et al 2004) | | X | | X | | | |
| (Sutton and Bourgeois 1996) | | | | X | | | |
| (Sweeney 2002) | X | X | | | | | X |
| (Sweeney et al 2003) | X | | | | | | |
| (Swygman et al 2002) | X | | | X | | | |
| (Szlachcic et al 1985) | X | | | X | | | |
| (Tada et al 2005) | X | | | X | | | |
| (Taieb et al 2002) | | X | | X | | | |
| (Tang 2001) | X | | | X | | | |
| (Tavazzi 2000) | X | | | X | | | |
| (Thaman et al 2003) | | | X | | | | |
| (Toussaint et al 2000) | X | | | X | | | |
| (Touiza et al 2001) | X | | | | | | |
| (Turner et al 2004) | X | | | X | | | |
| (Tyers et al 2005) | | | | X | | | |
| (Ukkonen et al 2003) | X | | | | | | |
| (UK National Horizon Scanning Centre 2001) | X | | | X | | | |
| (van den Broek et al 1992) | X | | | X | | | |
| (Van Gelder et al 2003) | X | X | | | | | |
| (van Gelder et al 2001a) | X | X | | | X | | |
| (van Gelder et al 2001b) | X | X | | X | | | |
| (van Gelder et al 2004) | X | | | X | | | |
| (Vardas 2003) | X | | | X | | | |
| (Vardas and Simantirakis 2003) | X | | | X | | | |
| (Varma et al 2003a) | | X | | X | | | |
| (Vinereanu et al 2004) | X | | | X | | | |
| (Vural et al 2004) | | | | X | | | |
| (Vogt et al 2000) | | | | | | X | |

| Paper | Not systematic review, RCT or X-over trial | <20 human subjects | Letter/ comment/ abstract only | Background/no primary data[1]/ expert opinion | All non-sinus rhythm | All non-trans-venous lead placement | All ICD |
|---|---|---|---|---|---|---|---|
| (Vogt et al 2004a) | X | | | X | | | |
| (Waggoner et al 2005) | X | | | X | | | |
| (Walker et al 2000b) | X | | | | | | |
| (Walker et al 2000d) | X | X | | | | | |
| (Walker et al 2000a) | X | | | X | | | |
| (Walker et al 2000e) | X | | | X | | | |
| (Walker et al 2000c) | X | X | | | | | X |
| (Walker et al 2000f) | X | | | | | | |
| (Walker et al 1999) | X | | | | X | | |
| (Walsh and Cecchin 2004) | X | | | X | | | |
| (Wang et al 2002) | X | | | X | | | |
| (Weber et al 1982) | X | | | X | | | |
| (Wiegand et al 2001) | | | | X | | | |
| (Wiegand et al 2001) | X | | | X | | | |
| (Wiegand et al 1999) | X | | | X | | | |
| (Wilensky et al 1988) | X | | | X | | | |
| (Willenheimer and Erhardt 2000) | | | X | X | | | |
| (Willens et al 1987) | X | | | X | | | |
| (Willerson and Kereiakes 2004) | X | | | X | | | |
| (Wilson et al 1983) | X | | | X | | | |
| (Witte et al 2000) | X | | | X | | | |
| (Wolbrette and Naccarelli 2000) | X | | | X | | | |
| (Wong et al 2001) | X | | | X | | | |
| (Wyman et al 2002) | X | X | | X | | X | |
| (Xiao et al 1996) | X | | | X | | | |
| (Xiao et al 1993) | X | | | X | | | |
| (Xiao et al 1992) | X | | | X | | | |
| (Xiao et al 1991) | X | | | X | | | |
| (Yap and Camm 1998) | X | | | X | | | |
| (Young et al 2003) | | | | | | | X |
| (Yong and Duby 2000) | X | | | X | | | X |
| (Yu et al 2003c) | | | | X | | | |
| (Yu et al 2003b) | | | X | | | | |
| (Yu et al 2004b) | X | | | X | | | |
| (Yu et al 2005) | X | | | X | | | |
| (Yu et al 2002) | X | | | | | | |
| (Zanon et al 2004) | X | | | X | | | |
| (Zagrodzky et al 2001) | X | X | | | | | |
| (Zardini et al 2000) | X | | | | | | |
| (Zhang et al 2005) | | X | | X | | | |
| (Zhi et al 2004) | X | X | | X | | | |

| Paper | Not systematic review, RCT or X-over trial | <20 human subjects | Letter/ comment/ abstract only | Background/no primary data[1]/ expert opinion | All non-sinus rhythm | All non-trans-venous lead placement | All ICD |
|---|---|---|---|---|---|---|---|
| (Zugck et al 2000) | X | | | X | | | |

# Appendix F Other sources of information

**Website sources of information**

| Health Technology Assessment organisations | Website URL |
|---|---|
| Agence d'Evaluation des Technologies et des Modes d'Intervention (AETMIS) | http://www.aetmis.gouv.qc.ca/ |
| Agencia de Evaluacion de Tecnologias Sanitarias (AETS) | http://www.isciii.es/unidad/aet/caet.html |
| Agencia de Evaluacion de Tecnologias Sanitarias de Andalucia (AETSA) | http://www.csalud.junta-andalucia.es/orgdep/AETSA/ |
| Alberta Heritage Foundation for Medical Research (AHFMR) | http://www.ahfmr.ab.ca/ |
| Agency for Health Research Quality (AHRQ) | http://www.ahrq.gov |
| L'Agence nationale d'Accréditation et d'Evaluation en Santé | http://www.anaes.fr |
| L'Agence Nationale pour le Developpement de l'Evaluation Medicale (ANDEM) | http://www.upml.fr/andem/andem.htm |
| British Columbia Office of Health Technology Assessment (BCOHTA) | http://www.chspr.ubc.edu.ca/bcohta |
| Catalan Agency for Health Technology Assessment (CAHTA) | http://www.aatm.es/ |
| Canadian Coordinating Office for Health Technology Assessment (CCOHTA) | http://www.ccohta.ca |
| Centre for Clinical Effectiveness, Monash University | http://www.med.monash.edu.au/healthservices/cce/ |
| Center for Medical Technology Assessment (CMT) | http://ghan.imt.liu.se/cmt/ |
| College voor Zorgverzekeringen (CVZ) | |
| German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information (DIMDI) | http://www.dahta.dimdi.de/ |
| Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) | http://www.dihta.dk/ |
| Danish Institute for Health Services Research (DSI) | http://www.dsi.dk/ |
| ECRI (USA) | http://www.ecri.org |
| Unidad de Tecnologias de Salud (ETESA) | http://www.minisal.cl |
| EUROSCAN | http://www.ad.bham.ac.uk/euroscan/index.asp |
| Finnish Office for Health Care Technology Assessment (FinOHTA) | http://www.stakes.fi/finohta/ |
| Health Council of the Netherlands (GR) | http://www.gr.nl/ |
| Health Technology Board for Scotland | http://www.htbs.org.uk/ |
| Minnesota Health Technology Advisory Committee (HTAC) | http://www.health.state.mn.us/htac/ |
| Institute for Clinical Systems Improvement (ICSI) | http://www.icsi.org |
| Institute of Technology Assessment of the Austrian Academy of Science (ITA) | http://www.oeaw.ac.at/ita/hta/ |
| International Network of Agencies for Health Technology Assessment (INAHTA) | http://www.inahta.org |
| International Society of Technology Assessment in Health Care | http://www.istahc.org |
| Medical Technology Assessment Group (M-TAG) | http://www.m-tag.net/ |
| Medical Technology and Practice Patterns Institute | http://www.mtppi.org/ |

| | |
|---|---|
| National Coordinating Centre for Health Technology Assessment (NCCHTA) | http://www.soton.ac.uk/~hta |
| National Horizon Scanning Centre (NHSC) | http://www.bham.ac.uk/PublicHealth/horizon |
| National Institute for Clinical Excellence (NICE) | http://www.nice.org.uk/ |
| New Zealand Health Technology Assessment (NZHTA) | http://nzhta.chmeds.ac.nz |
| Medical and Health Research Council (MW-NWO) | http://www.nwo.nl |
| Basque Office for Health Technology Assessment (OSTEBA) | http://www.euskadi.net/sanidad/ |
| Swedish Council on Technology Assessment in Health Care (SBU) | http://www.sbu.se |
| Norwegian Centre for Health Technology Assessment (SMM) | http://www.oslo.sintef.no/smm/ |
| Swiss Science Council/Technology Assessment (SWISS/TA) | http://www.ta-swiss.ch/ |
| TNO Prevention and Health (TNO) | http://www.tno.nl/homepage.html |
| University Health Consortium Technology Assessment Monitor | http://www.uhc.edu |
| Veterans' Affairs Technology Assessment Program (VATAP) | http://www.va.gov/vatap/ |
| WHO Health Technology Assessment Programme (Collaborating Centres) | http://www.who.int/pht/technology_assessment/index.html |
| **Other organisations** | |
| Australian Institute of Health & Welfare (AIHW) | http://www.aihw.gov.au |
| Australian National Health & Medical Research Council | http://www.health.gov.au/nhmrc/index.htm |
| Commonwealth Department of Health and Aged Care | http://www.health.gov.au |
| Centres for Medicare and Medicaid Services (US Health Care Financing Administration) | http://www.hcfa.gov |
| Health Economics Research Group (Brunel University) | http:// www.brunel.ac.uk/depts/herg |
| US Federal Drug Administration | http://www.fda.gov |
| Health Canada | http://www.hc-sc.gc.ca/ |
| UK Department of Health publications | http://www.doh.gov.uk/publications/index.html |
| US Centers for Disease Control | http://www.cdc.gov |
| **Professional Associations/Societies** | |
| American College of Cardiology | http://www.acc.org |
| British Cardiac Society | http://www.bcs.com |
| National Heart Foundation of Australia | http://www.heartfoundation.com.au |
| Cardiac Society of Australia and New Zealand | http://www.csanz.edu.au |
| North American Society of Pacing and Electrophysiology | http://www.naspe.org |
| **Controlled trials databases** | |
| Controlled Clinical Trials | http://www.controlled-trials.com/ |
| Clinicaltrials.gov | http://www.clinicaltrials.gov |

# Appendix G A reader's guide to decision analysis

Decision analysis is a tool that allows the analyst to compare a number (typically two) of possible decisions in terms of what the outcomes are most likely to be. It is most useful when a particular decision can result in different outcomes with different probabilities attached to them so that at the outset it is not always clear which decision would be most likely to deliver the best outcome.

The basic tool in decision analysis is the decision tree. The decision tree typically depicts the consequences of the decision that needs to be made, according to the known (or estimated) probabilities of obtaining each outcome or of facing each consequence. Usually, a decision tree can also be read from left to right as a series of chronological events that follow the decision that is made with the first set of branches on the tree and that end with a particular outcome that is represented by the end 'nodes' of the tree.

In medical decision-making, the decision tree is typically used to compute and compare total expected costs and expected outcomes of at least two comparable procedures. When these two measures are combined, we obtain an estimate of 'cost-effectiveness'. It is important to note that the definition of effectiveness in this context differs slightly from the definition that is normally assumed. In decision-analysis 'effectiveness' refers to the expected outcome of the *decision* to use the procedure, which can be very different from the effectiveness of the procedure. For example, if a procedure is generally 90 per cent effective at providing a perfect outcome but the remaining 10 per cent can be dealt with using another procedure as a back-up, which is 100 per cent effective at providing a perfect outcome, then the expected outcome of the decision to use the 90 per cent effective procedure will be perfection 100 per cent of the time because all patients who undergo the procedure will eventually obtain a perfect outcome. This 100 per cent perfect outcomes figure would be reported as 'effectiveness' in a decision analysis. The calculation of cost will account for the fact that *two* procedures are used in 10 per cent of cases, so that the calculation of "cost-effectiveness" accounts for all the cost and outcome *implications* of the effectiveness of a procedure and not just the effectiveness of the procedure in question.

Because the implications of a medical decision can have far-ranging implications in that they may be broad or last a long period of time, it is usually necessary to cut off the decision analysis at some appropriate point. This is typically achieved by appropriately defining the outcome measures or by applying a time limit such that the decision tree ends at a point that corresponds to a certain point in time after the initial decision is made. Common non-cost outcomes include the total number of days of hospitalisation, quality of life, the number of life years saved, the number of lives saved, etc. The time duration of a decision tree can be measured in weeks, months, etc. or in cycles of care, eg allowing a maximum of three procedures.

When a decision tree is rolled back for cost-effectiveness, the results show the expected total cost and the expected outcome for each decision in terms of the chosen outcomes within the chosen time frame. So, if the basic assumptions of the tree are accepted by the decision-maker, the results show clearly which decision is best and what, if any, are the trade-offs in terms of cost and expected outcome.

# Appendix H Calculating life years saved

To calculate the number of life years saved, researchers need to know the number of years (on average) that a patient who received the treatment would live from the time of treatment, compared to the average number of years for a patient who did not. This can be calculated from the mortality rate at each point in time from treatment until the point where all patients would have died. An alternative approach is to calculate life years saved up to some imposed cut off-date, say five years. Life years saved over five years is the total number of years lived by patients receiving the treatment in the first five years following treatment, relative to the total number of years they would have lived had they not received the treatment. To calculate this number, one only needs to know the mortality rates at each point of time for those receiving the treatment and those not receiving the treatment for the five years following the treatment.

The available data, however, only reveal how many patients died in the first 12 months and the second 12 months following treatment, and not the mortality rate at each point in time throughout that 24 month period.

To calculate life years saved from these data, we impose in the base case the assumption that there was a constant daily mortality rate for both the treatment and control groups over the 24 months and then further assume that constant daily mortality rate for the two groups would continue unchanged into the future. This is a conservative assumption as it does not allow mortality rates to continue to diverge beyond the average divergence observed in years one and two.

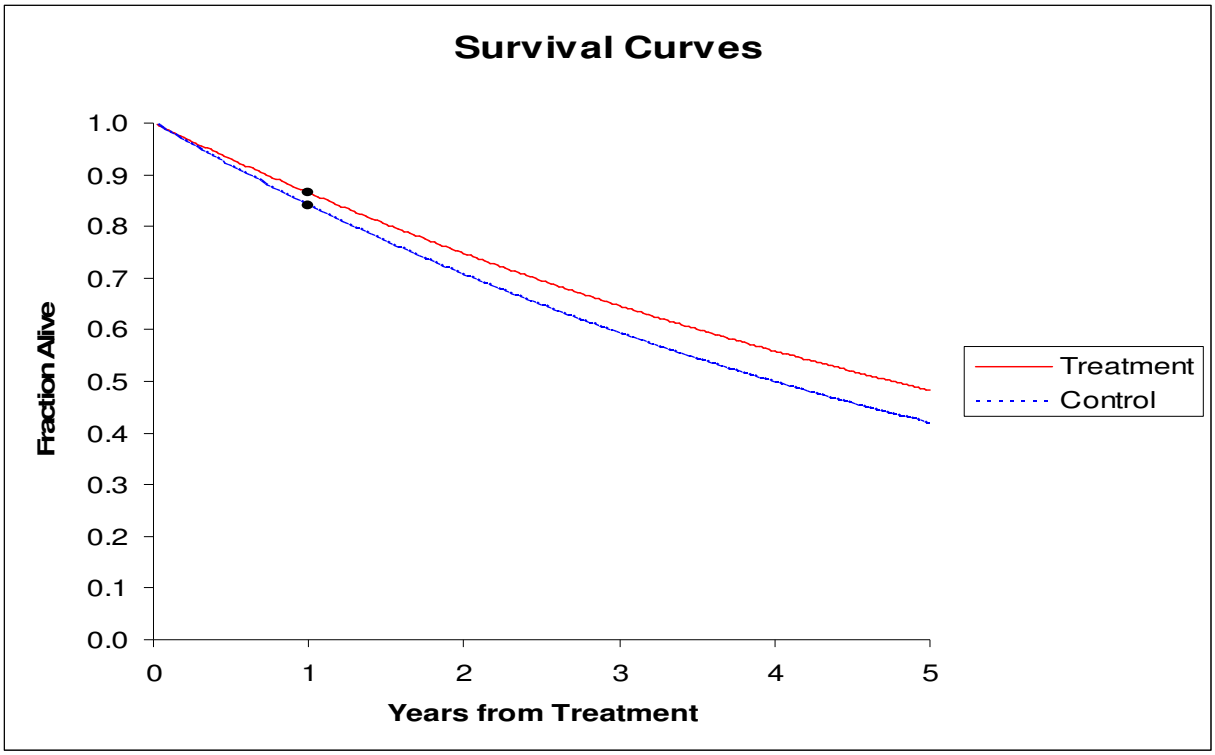
The first step is to calculate the daily death rates that would result in the total number of deaths reported at 24 months for the treatment and control groups.

The second step is to extrapolate this daily death rate into the future to calculate the fraction of patients who would still be alive at any point in time up to five years, under the assumption that the daily death rate remains constant over that time. From this, it is straightforward to calculate the expected number of years alive from the time of treatment to the cut-off date, for both a patient receiving the treatment and a patient in the control group. Total life years saved to that point is the difference in the expected number of years alive between the two groups multiplied by the total number of patients receiving the treatment.

This can best be seen in the graph over. The higher and lower curves show the fraction of patients still alive after a given number of years for those receiving the treatment and those not, respectively. Total expected life years lived up to some number of years after treatment is simply the area under each graph to that point, and so life years saved is the area between the two graphs. The two solid dots at two years represent the known fraction of patients still alive at 24 months. Step 1 above involves calculating the daily death rates so that the two graphs pass through these points. Step 2 involves calculating the area between the two graphs up to five years after treatment. This area is 0.3815, meaning that an extra 0.3815 of a year is saved per patient receiving the treatment.

The base case assumed a constant daily mortality rate through the first 24 months after treatment, even though our data gives us separate mortality rates for the first and second 12-month periods. This is a conservative approach. A less conservative approach that is still grounded in the observed results could have been to assume that only the second

year mortality rate (rather than a combined mortality rate consisting of mortality in years one and two) would remain constant in all subsequent years.



## Formal Calculations

### Formulae when there is a constant mortality rate.

Let $L_t$ be the number of people alive at time t. The assumption that there is a constant mortality rate over time for a particular population (treatment or control) implies that

$$\frac{dL_t / dt}{L_t} = -h,$$

where *h* is the mortality rate. This gives the following expression for $L_t$ :

$$L_t = L_0 e^{-ht}, \tag{1}$$

where $L_0$ is the initial population.

Let $m_t$ be the fraction of the population that has died after *t* years. Then, from Equation (1) we have

$$m_t = \frac{L_0 - L_t}{L_0} = 1 - e^{-ht}. \tag{2}$$

We can then rearrange this to infer *h* when we only know $m_t$ :

$$h = \frac{-\ln(1 - m_t)}{t}.$$

Once we know *h* the number of deaths that would be observed after time *t*, $D_t$ , is

$$D_t = L_0 - L_t = L_0(1 - e^{-ht}).$$

Finally, for a given mortality rate, *h*, the expected total number of years lived from the time of treatment to time *t*, $Y_t$ is

$$Y_t = \int_0^t L_{t'} dt' = L_0 \frac{1 - e^{-ht}}{h}. \tag{3}$$

If future life years are discounted at a rate *r* per year, the expected number of total discounted years lived from the time of treatment to time *t*, $DY_t$ is

$$DY_t = \int_0^t L_{t'} \cdot e^{-rt'} dt' = L_0 \frac{1 - e^{-(h+r)t}}{h + r}. \tag{4}$$

Let $h^T$ be the mortality rate for the treatment group and $h^C$ the mortality rate for the control group. Life years saved to time *t*, $LYS_t$ is just the difference in expected total years lived:

$$LYS_t = L_0\left(\frac{1-e^{-h^T t}}{h^T} - \frac{1-e^{-h^C t}}{h^C}\right)$$

and discounted life-years saved, $DLYS_t$ is

$$DLYS_t = L_0\left(\frac{1-e^{-(h^T+r)t}}{h^T+r} - \frac{1-e^{-(h^C+r)t}}{h^C+r}\right).$$

# Abbreviations

| | |
|---|---|
| ACE | angiotensin converting enzyme |
| AF | atrial fibrillation |
| AII | angiotensin II converting cnzyme |
| AMI | acute myocardial infarction |
| AV | atrio-ventricular |
| BP | blood pressure |
| BPM | beats per minute |
| CRT | cardiac resynchronisation therapy |
| CABG | coronary artery bypass grafting |
| CARE HF | Cardiac Resynchronisation in Heart Failure (trial) |
| CI | confidence interval |
| CM | centimetre |
| CS | coronary sinus |
| CV | coronary vein |
| CVA | cerebrovascular |
| DAVID | Dual chamber and VVI Implantable Defibrillator (study) |
| DL | decilitre |
| ECG | electrocardiograph |
| EF | ejection fraction |
| EPT | elevated pacing threshold |
| f/up | follow-up |
| HF | heart failure |
| ICD | implantable cardiac defibrillator |
| JT interval | calculated by subtracting QRS from QT in individual leads. |
| kg | kilogram |
| LA | local anaesthetic |

| | |
|---|---|
| LBBB | left bundle branch block |
| LPN | left phrenic nerve |
| LV | left ventricle |
| LVEDD | left ventricle end diastolic diameter |
| LVEF | left ventricular ejection fraction |
| m | metre |
| ma | maximum |
| mg | milligram |
| min | minute |
| MIRACLE | Multi-centre InSync Randomized Clinical Evaluation (Trial) |
| MIRACLE –ICD | Multi-centre InSync Randomized Clinical Evaluation in Patients Requiring an ICD (trial) |
| ml | millilitre |
| mm mg | millimetre mercury |
| ms | millisecond |
| MSAC | Medical Services Advisory Committee |
| msec | millisecond |
| mths | months |
| MUSTIC | Multisite Stimulation In Cardiomyopathy (Trial) |
| n | number |
| NHMRC | National Health and Medical Research Centre |
| NNT | number needed to treat |
| ns | numbers |
| NYHA | New York Heart Association |
| OPT | optimal pharmacological treatment |
| PR | odds ratio |
| PACMAN | Pacing for Cardiomyopathy (trial) |
| PE | pulmonary embolus |

| | |
|---|---|
| PERFECT | Pacing Efficiently by Resynchronisation for Efficacy in CHF Therapy (trial) |
| PR | P-R interval |
| QoL | quality of life |
| QRS | quasi-random signal |
| QT interval | beginning of the QRS complex to end of T wave in electrocardiogram |
| RBBB | right bundle branch block |
| RCT | randomised controlled trial |
| ReLeVent | Remodelling of cardiac Cavities by Long-term Left Ventricular–based Pacing in Patients with Severe Heart Failure. (trial) |
| RRR | relative risk reduction |
| RT interval | peak of R wave to peak of T wave in electrocardiogram |
| RV | right ventricle |
| SD | standard deviation |
| SEC | second |
| SR | sinus rhythm |
| UK | United Kingdom |
| US | United States |
| USA | United States of America |
| VF | ventricular fibrillation |
| VT | ventricular tachycardia |
| x | times |

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