



TITLE: Cardiac Resynchronization Therapy for the Treatment of Heart Failure

AUTHOR: Jeffrey A. Tice, MD
Assistant Adjunct Professor of Medicine
Division of General Internal Medicine
Department of Medicine
University of CA, San Francisco

PUBLISHER NAME: California Technology Assessment Forum

DATE OF PUBLICATION: October 20, 2004

PLACE OF PUBLICATION: San Francisco, CA



CARDIAC RESYNCHRONIZATION THERAPY FOR THE TREATMENT OF HEART FAILURE

INTRODUCTION

Traditional pacemakers involve the placement of two leads, one in the atrium and one in the right ventricle. Biventricular (BV) pacing involves the placement of an additional pacemaker lead adjacent to the left ventricle in order to improve synchronization between the right and left ventricles, thus improving cardiac function. This is most commonly referred to in medical literature as cardiac resynchronization therapy (CRT). The California Technology Assessment form is asked to review the scientific evidence for the use of this procedure in patients with congestive heart failure.

Since this topic was last reviewed in 2002, several important randomized clinical trials have been published. The COMPANION trial published data on 1,520 patients with at least 12 months median follow-up (Bristow, 2004). It is the first published study on CRT that was designed with enough power to assess mortality and hospitalization rates. Two other important randomized trials comparing implantable cardioverter defibrillators (ICDs) to ICDs plus CRT were published (Higgins 2003; Young 2003), but they were primarily designed to evaluate quality of life and exercise tolerance.

BACKGROUND

Heart Failure

Heart failure (HF) is a major public health problem in the United States. Nearly five million patients in this country have HF, and nearly 500,000 patients are diagnosed with HF for the first time each year. The disorder is the underlying reason for 12 to 15 million office visits and 6.5 million hospital days each year (O'Connell 2000). During the last ten years, the annual number of hospitalizations has increased from approximately 550,000 to nearly 900,000 for HF as a primary diagnosis and from 1.7 to 2.6 million for HF as a primary or secondary diagnosis (Haldeman, Croft *et al.* 1999). Nearly 300,000 patients die of HF as a primary or contributory cause each year, with the number of deaths steadily increasing, despite advances in treatment.

The approach that is most commonly used to quantify the degree of functional limitation imposed by HF is one first developed by the New York Heart Association (NYHA 1994). This system assigns patients to one of four functional classes, depending on the degree of effort needed to elicit symptoms: patients may have symptoms of HF at rest (Class IV), on less-than-ordinary exertion (Class III), on ordinary exertion (Class II), or only at levels of exertion that would limit normal individuals (Class I).

Medical therapies, such as angiotensin converting enzyme (ACE) inhibitors, beta blockers and spironolactone, have led to improvements in both symptom control and overall survival in patients with heart failure (Stevenson, Stevenson *et al.* 1995). Implanted devices, such as pacemakers and cardioverter-defibrillators (ICDs), may also be beneficial.

Despite recent advances in therapy, longitudinal data from the Framingham study and the Mayo Clinic suggest that there has not been much improvement in the one-year survival of patients with newly diagnosed symptomatic HF (Ho, Anderson *et al.* 1993). In one study of 499 patients with Class III or IV HF, 75% were receiving an ACE inhibitor and 50% were treated with digoxin; the one-year mortality was 35% and the rate of death or hospital readmission was 81% (Zannad, Braincon *et al.* 1999).

Cardiac Resynchronization with Biventricular Pacemakers

Pacing modalities that utilize biventricular stimulation to optimize cardiac pump function through synchronization of ventricular contraction are referred to as cardiac resynchronization therapies (Leclercq and Kass 2002). Resynchronization therapies can be present in a single device, in a device equipped with bradycardia pacemaker support or incorporated into an ICD. The early devices required placement of an epicardial left ventricular (LV) lead using a thoracoscope, a procedure that added the risks associated with general anesthesia in patients at high risk for peri-operative complications. Development of a transvenous system for placement of the LV lead (Daubert, 1998) significantly decreased the risks associated with the use of CRT.

The rationale for resynchronization therapy is based upon several observational studies in patients with heart failure reporting that the presence of an intraventricular conduction delay (IVCD), as manifested by a prolonged QRS interval, was associated with a worsening of NYHA class status and poorer overall outcome when compared to matched patients with normal intraventricular conduction (Xiao, Roy *et al.* 1996). The QRS interval is a measurement on the electrocardiogram that represents the time required for electrical depolarization of the ventricles of the heart.

Resynchronization therapy is currently approved in Europe for symptomatic HF that occurs in the setting of IVCD or bundle branch block (BBB). Since it is estimated that 20 to 30% of patients with symptomatic HF have an IVCD and resultant discoordinate ventricular contraction, there are many patients who may qualify for resynchronization therapy (Saxon, Boehmer *et al.* 1999). It has been estimated that approximately 10% of an unselected group of patients with heart failure would be appropriate candidates for resynchronization therapy (Farwell, Patel *et al.* 2000).

Hemodynamic data acquired in patients with HF and BBB during acute BV stimulation have consistently shown improvements in measures of contractile response, such as force of contraction, cardiac output, left ventricular ejection fraction (EF) and pulmonary artery pressure, when compared to normal sinus rhythm or RV pacing (Cazeau, Ritter *et al.* 1994; Blanc Etienne *et al.* 1997; Leclercq, Cazeau *et al.* 1998; Saxon, Kerwin *et al.* 1998; Auricchio, Klein *et al.* 1999; Kass, Chen *et al.* 1999; Kerwin, Botvinick *et al.* 2000). Interestingly, in contrast to other therapies that

increase myocardial contractility, CRT appears to modestly reduce myocardial energy demands and myocardial oxygen consumption (Nelson, Berger *et al.* 2000).

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate governmental regulatory bodies.

The Medtronic (Medtronic, Inc., Minneapolis, MN) InSync[®] System for cardiac resynchronization therapy received final FDA approval on August 28, 2001, through the pre-market application (PMA) process.

The Guidant CONTAK[®] RENEWAL[™] TR Models H125 and H120 with the Model 2865 Version 1.8 Application Software received final FDA PMA approval on January 26, 2004 with the requirement that a post-market study be conducted to evaluate the long-term safety and effectiveness of the system.

TA criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

Clinical studies of CRT in heart failure include three randomized clinical trials using a parallel design (Abraham, Fisher *et al.* 2002; Higgins *et al.* 2003; Bristow *et al.* 2004), one randomized trial that began as a cross over study and was changed to a parallel design based on FDA recommendations (Young *et al.* 2003) and two small randomized clinical trials using a cross-over design (Cazeau, Leclercq *et al.* 2001; Linde, Leclercq *et al.* 2002; Martinelli Filho, Pedrosa *et al.* 2002). The patient characteristics, heart failure outcomes and complications reported in the clinical trials are summarized in Tables 1 – 3. At least 17 case series have been published (Gras, Mabo *et al.* 1998; Bakker, Meijburg *et al.* 2000; Hamdan, Zagrodzky *et al.* 2000; Jais, Takahashi *et al.* 2000; Lau, Yu *et al.* 2000; Leclercq, Cazeau *et al.* 2000; Lupi, Brignole *et al.* 2000; Reuter, Garrigue *et al.* 2000; Toussaint, Lavergne *et al.* 2000; Walker, Levy *et al.* 2000; Zardini, Tritto *et al.* 2000; Auricchio, Stellbrink *et al.* 2002; Garrigue, Bordochar *et al.* 2002; Gras, Leclercq *et al.* 2002; Kuhlkamp 2002; Lunati, Paolucci *et al.* 2002; Saxon, De Marco *et al.* 2002; Yu, Chan *et al.* 2002). No comparative cohort studies have been published. The inclusion criteria for the studies generally required Class III or IV heart failure, a QRS duration \geq 130-150 msec, a stable medical regimen including diuretics, ACE inhibitors, and more recently beta-blockers and spironolactone. Some trials require an indication for an ICD. Most exclude patients with atrial fibrillation and those with standard indications for a pacemaker such as rate support for bradycardia.

Comparisons of published series are difficult due to the residual variability in the inclusion and exclusion criteria, different proportions of patients on accepted medical treatment for hear failure and short follow-up times. Most studies

have not separated outcomes for patients based on NYHA class or other important prognostic factors. Thus, in order to assess the risks and benefits associated with CRT, most attention should be focused on the randomized clinical trials.

Heart failure is defined primarily by patients' symptoms. Thus, measurements of symptoms, exercise tolerance and quality of life are important outcomes to assess. Overall, symptoms are usually measured from the patient's perspective using the NYHA classification described above (NYHA 1994). Many objective measures of exercise tolerance are used, but the most common is the distance in meters walked during six minutes (Guyatt, Sullivan *et al.* 1985). Finally, the standard measure of quality of life for patients with heart failure is the Minnesota Living with Heart Failure Questionnaire (MLHFQ).(Rector, Kubo *et al.* 1987). The MLHFQ is a validated measure of the patients' perceptions of the effects of congestive heart failure on their lives. It is a 21 item, self-administered questionnaire that covers physical, socioeconomic and psychological impairments that patients often relate to their heart failure. A score, based on how each person ranks each item on a common scale, is used to quantify the extent of impairment and how it is affected by therapeutic intervention. The score ranges from 0 to 105, with higher scores indicating more severe symptoms and lower quality of life.

The most important health outcome of heart failure treatment is survival. Clinical trials large enough to demonstrate an important reduction in overall mortality are feasible because the one-year mortality in patients with Class III and IV heart failure is over 30%. It is important to note that most of the primary therapies used to treat heart failure (beta-blockers, ACE inhibitors and spironolactone) have individually been shown in randomized clinical trials to reduce total mortality (Feldman, Bristow *et al.* 1993; Cohn, Goldstein *et al.* 1998).

Hospitalization rates for patients with Class III and IV heart failure are also very high (Zannad, Braicon *et al.* 1999). Thus, the rate of hospitalization is an important secondary outcome that should also be considered when evaluating the risks and benefits of therapies for heart failure.

TA criterion 2 is met.

Level of Evidence: 1, 2, 5

TA Criterion 3: The technology must improve the net health outcomes.

17 Case Series

The 17 case series report on changes from baseline in 745 patients who successfully received a BV pacemaker

(Gras, Mabo *et al.* 1998; Bakker, Meijburg *et al.* 2000; Hamdan, Zagrodzky *et al.* 2000; Jais, Takahashi *et al.* 2000; Lau, Yu *et al.* 2000; Leclercq, Cazeau *et al.* 2000; Lupi, Brignole *et al.* 2000; Reuter, Garrigue *et al.* 2000; Toussaint, Lavergne *et al.* 2000; Walker, Levy *et al.* 2000; Zardini, Tritto *et al.* 2000; Auricchio, Stellbrink *et al.* 2000; Garrigue, Bordachar *et al.* 2000; Gras, Leclercq *et al.* 2002; Kuhlkamp 2002; Lunati, Paolucci *et al.* 2002; Saxon, De Marco *et al.* 2002; Yu, Chan *et al.* 2002). The majority of these case series follow the participants for three months or less and only the InSync trial (Gras, Mabo *et al.* 1998; Gras, Leclercq *et al.* 2002) and the InSync Italian Registry (Zardini, Tritto *et al.* 2002) report on more than 100 patients. The six-minute walk distance improved significantly in eight of the case series, (Lau, Yu *et al.* 2000; Lupi, Brignole *et al.* 2000; Zardini, Tritto *et al.* 2000; Auricchio, Stellbrink *et al.* 2002; Garrigue, Bordachar *et al.* 2002; Gras, Leclercq *et al.* 2002; Kuhlkamp 2002; Yu, Chan *et al.* 2002). NYHA classification improved in eight of the studies, (Bakker, Meijburg *et al.* 2000; Leclercq, Cazeau *et al.* 2000; Reuter, Garrigue *et al.* 2000; Gras, Leclercq *et al.* 2002; Kuhlkamp 2002; Lunati, Paolucci *et al.* 2002) and quality of life improved in five of the studies. (Lau, Yu *et al.* 2000; Lupi, Brignole *et al.* 2000; Zardini, Tritto *et al.* 2000; Gras, Leclercq *et al.* 2002; Kuhlkamp 2002; Lunati, Paolucci *et al.* 2002; Yu, Chan *et al.* 2002). The remaining studies reported on improved hemodynamics, left ventricular remodeling and safety (Hamden, Zagrodzky *et al.* 2000; Jais, Takhashi *et al.* 2000; Toussaint, Lavergne *et al.* 2000; Walker, Levy *et al.* 2000; Saxon, De Marco *et al.* 2002).

The InSync trial (Gras, Mabo *et al.* 1998; Gras, Leclercq *et al.* 2002) is the highest quality case series evaluating CRT in heart failure that has been published. Participants were required to have stable heart failure (NYHA Class III or IV), left ventricular systolic dysfunction (EF<35%) with normal sinus rhythm and a QRS interval of more than 150 msec. Of 117 attempted implants, 103 (88%) received transvenous BV pacemakers. 88% of the attempted implants were successful. After 12 months follow-up, mean NYHA class declined from 3.3 to 2.2 ($p<0.001$), quality of life improved by 22 points on the MLHFQ ($p<0.001$) and the six-minute walk increased by 75 meters ($p<0.001$). Responders to resynchronization had a consistent shortening of QRS duration, an increase in LVEF, and a reduction in left ventricular end-diastolic diameter. Of note, 22% of the participants died during the one year follow-up period. There were no controls. Complications included one coronary sinus perforation, three leads that lost pacing capture, and three explants (1 infection, 1 pain at generator site, 1 diaphragmatic irritation). Thirteen LV leads had to be replaced or repositioned.

Two Randomized Clinical Trials Using Cross-over Design

In the Multisite Stimulation in Cardiomyopathies (MUSTIC) trial, (Cazeau, Leclercq *et al.* 2001; Linde, Leclercq *et al.* 2002) 67 patients with severe heart failure (NYHA Class III) due to chronic left ventricular systolic dysfunction, with normal sinus rhythm and a duration of the QRS interval of more than 150 msec, received transvenous BV

pacemakers (with leads in one atrium and each ventricle). This single-blind, randomized, controlled crossover study compared the responses of the patients during two periods: a three-month period of inactive pacing (ventricular inhibited pacing at a basic rate of 40 bpm) and a three-month period of active biventricular pacing. The primary end point was the distance walked in six minutes; the secondary end points were the quality of life as measured by the questionnaire, peak oxygen consumption, hospitalizations related to heart failure, the patients' treatment preference (active vs. inactive pacing), and the mortality rate. Nine patients were withdrawn from the study before randomization, and ten failed to complete both study periods. Thus, 48 patients completed both phases of the study. The mean distance walked in six minutes was 22% greater with active pacing (399 \pm 100 m vs. 326 \pm 134 m, $P<0.001$), the quality-of-life score improved by 32% ($P<0.001$), peak oxygen uptake increased by eight% ($P<0.03$), hospitalizations were decreased by two thirds ($P<0.05$), and active pacing was preferred by 85% of the patients ($P<0.001$). The authors conclude that although it is technically complex, CRT significantly improves exercise tolerance and quality of life in patients with chronic heart failure and intraventricular conduction delay. This study was well done, but only randomized 67 patients and followed them for no more than three months, which is not long enough to assess total mortality or long-term pacemaker complications.

Martinelli Filho and colleagues (Martinelli Filho, Pedrosa *et al.* 2002) studied 24 patients with left bundle branch block (LBBB) and NYHA Class III and IV heart failure who underwent pacemaker implantation and were randomized either to conventional or BV pacing. All patients receiving CRT after six months. Sixteen patients were in NYHA Class IV (66.6%) and eight were in Class III (33.4%). After one-year follow-up, 14 patients were in Class II (70%) and five were in Class III (25%). Two sudden cardiac deaths occurred. The EF increased from a mean of 19 % at baseline to 25 % with CRT. Hospital admissions decreased from 60 to 16 admissions per year with CRT ($p<0.05$) compared to the year prior to device implantation. However, no comparisons between participants randomized to CRT and controls were presented in the paper. Furthermore, all three deaths in the study occurred while participants were receiving CRT. The authors concluded that CRT improved NYHA class and reduced hospital admission rates in patients with LBBB and severe heart failure, though the study is very small and they present minimal data to back up their conclusion.

One Study with a Mixed Cross-over and Parallel Design

The VENTAK CHF/ CONTAK CD study was initially designed as a cross-over trial with quality of life and functional status outcomes. Lozano and colleagues (Lozano, Bocchiardo *et al.* 2000) briefly reported on mortality outcomes from the initial cross-over phase. They enrolled 222 participants with NYHA Class II – IV heart failure, an EF \leq 35%, a QRS interval >120 msec, and ventricular tachyarrhythmias. Of note, this is the only large randomized trial that included patients with Class II symptoms. All participants received an implantable cardioverter defibrillator with CRT

capability. Patients were randomized 1:1 to CRT or no pacing, and then crossed over to the alternate mode after three months. All-cause mortality was measured in each arm up to the point of crossover. Fifteen of 222 patients died between implant and crossover. Five patients died while programmed to CRT and ten died while programmed to no pacing. Actuarial survival at six months in the CRT arm was 93 +/- 4% versus 86 +/- 6% in the no pacing arm (P = 0.18). Note, that these six-month estimates are based on only three months of active therapy. In this patient population with symptomatic heart failure and ventricular arrhythmias, CRT does not appear to be associated with excess mortality. The authors conclude that larger and longer studies will be needed to determine if CRT confers a survival benefit.

In the same phase of the study, Higgins and colleagues (Higgins, Yong *et al.* 2000) studied whether CRT decreased the need for ICD termination of tachyarrhythmias. Participants early in the trial received a biventricular ICD with a transvenous right ventricular lead and a left ventricular lead placed via thoracotomy. Of 54 patients enrolled in this portion of the study, 32 completed three blinded months programmed to CRT and a second randomly assigned three-month period of no pacing. Of the 32 patients, 13 (41%) received appropriate therapy for a ventricular tachyarrhythmia at least once in the six-month monitoring period post implant. Five patients (16%) had at least one tachyarrhythmic episode while programmed to CRT, whereas 11 (34%, $p=0.04$) had at least one episode while programmed to no pacing. The authors concluded that CRT does not obviate the need for an ICD, but it does diminish the need for appropriate tachyarrhythmia therapy.

Based on the recommendation of regulatory bodies, the study was redesigned to evaluate parallel groups with longer follow-up (Higgins *et al.* 2003). The larger study assessed the safety and efficacy of CRT when combined with an ICD. The VENTAK CHF/CONTAK CD trial enrolled 581 patients with NYHA Class II - IV HF who had an indication for an ICD, an $EF \leq 35\%$ and a QRS duration > 120 ms. Participants were implanted with a device capable of providing both CRT and ICD therapy and randomized to CRT ($n = 245$) or control (no CRT, $n = 245$) for up to six months. The primary end point was a unique composite variable for progression of HF defined as all-cause mortality, hospitalization for HF or VT/VF requiring device intervention. Secondary end points included peak oxygen consumption (VO₂), six-minute walk (6 MW), New York Heart Association (NYHA) class, quality of life (QOL) and LV ejection fraction (EF). A 15% reduction in the primary endpoint was observed, but this was not statistically significant ($p = 0.35$). There was also no decrease in ventricular tachyarrhythmias in the CRT group compared with the ICD alone. CRT did improve peak VO₂ (0.8 ml/kg/min vs. 0.0 ml/kg/min, $p = 0.030$), the 6 MW (35 m vs. 15 m, $p = 0.043$) and LV EF (5.1% vs. 2.8%, $p = 0.020$). Changes in NYHA class ($p = 0.10$) and QOL ($p = 0.40$) were not significant.

A significant proportion of the participants clinically improved after device implantation, but before randomization (54% were NYHA Class I/II). Furthermore, all other studies of CRT excluded patients with

NYHA Class I or II heart failure. To address this issue, the authors also present their results stratified by NYHA class at randomization (Class I/II vs. III/IV). The baseline characteristics were similar in each arm of the study for the Class III/IV subgroup. Improvements in peak VO₂, 6 MW distance, QOL, NYHA Class and LV EF were all statistically significant for CRT+ICD compared with ICD alone in this subgroup, but none were significant in the subgroup of patients with Class I/II heart failure at randomization. Unfortunately, the authors do not present mortality and hospitalization outcomes for these two subgroups.

Three Clinical Trials using Parallel Group Design

The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial (Abraham 2000; Abraham, Fisher *et al.* 2002) is the only clinical trial using a parallel group design that has been published. Data from this trial formed the basis for the first FDA approval of a device for CRT (2002). Four hundred fifty-three patients with NYHA Class III or IV heart failure, an EF of 35% or less and a QRS interval of 130 msec or more were randomly assigned to CRT (228 patients) or to a control group (225 patients) for six months. Conventional therapy for heart failure was maintained. The primary end points were the NYHA functional class, quality of life and the distance walked in six minutes. As compared with the control group, patients assigned to cardiac resynchronization experienced an improvement in the distance walked in six minutes (+39 vs. +10 m, P=0.005), functional class (P<0.001), quality of life (+0.2% vs. -0.2%, P<0.001). In addition, fewer patients in the group assigned to CRT required hospitalization (8% vs. 15%) or intravenous medications (7% vs. 15%) for the treatment of heart failure (P<0.05 for both comparisons). There was a trend towards improved survival in the CRT group (5% vs. 7%, p=0.4), but the length of follow-up was too short to demonstrate a significant reduction. Implantation of the device was unsuccessful in eight% of patients and was complicated by refractory hypotension, bradycardia or asystole in four patients (two of whom died). Perforation of the coronary sinus required pericardiocentesis in two others. The authors conclude that cardiac resynchronization with CRT results in significant clinical improvement in patients who have moderate-to-severe heart failure and an intraventricular conduction delay.

The MIRACLE trial was the first large, high quality study of biventricular pacing to be published. It clearly demonstrated an improvement in symptoms and exercise capacity as well as reduced hospitalizations during 6 months of follow-up. It has been criticized primarily for the lack of long term outcome data. Dr. Hare, in an editorial published in the same issue of the New England Journal of Medicine⁵¹ (2002), lauded the encouraging results of the study but cautioned: “we do not yet understand whether resynchronization therapy prolongs the lives of patients with heart failure – information that is available for all other therapies for heart failure.” He called for further data to support the sustainability of the clinical improvements reported by the MIRACLE trial investigators.

In 2003, Young *et al.* published the results of the related MIRACLE-ICD study. The study was designed to evaluate the efficacy and safety of combined CRT and ICD therapy in patients with NYHA Class III or IV congestive HF despite appropriate medical management. Patients with LV EF \leq 35%, QRS duration \geq 130 ms, at high risk of life-threatening ventricular arrhythmias (i.e. an indication for an ICD), NYHA class III (n = 328) or IV (n = 41) HF were randomized in a double-blind study. Of those, 182 were controls (ICD activated, CRT off) and 187 were in the CRT group (ICD activated, CRT on). The primary end points were changes between baseline and six months in quality of life, functional class and distance covered during a six-minute walk. Additional outcome measures included changes in exercise capacity, plasma neurohormones, left ventricular function and overall HF status. Survival, incidence of ventricular arrhythmias and rates of hospitalization were also compared. At six months, patients assigned to CRT had a greater improvement in median (95% confidence interval) quality of life score (-17.5 [-21 to -14] vs. -11.0 [-16 to -7], P = .02) and functional class (-1 [-1 to -1] vs. 0 [-1 to 0], P = .007) than controls but were no different in the change in distance walked in six minutes (55 m [44-79] vs. 53 m [43-75], P = .36). Peak oxygen consumption increased by 1.1 mL/kg per minute (0.7-1.6) in the CRT group vs. 0.1 mL/kg per minute (-0.1 to 0.8) in controls (P = .04). No significant differences were observed in changes in left ventricular size or function, overall HF status, survival and rates of hospitalization. No proarrhythmia was observed and arrhythmia termination capabilities were not impaired. The authors concluded that CRT improved quality of life, functional status and exercise capacity in patients with moderate to severe HF, a wide QRS interval and life-threatening arrhythmias. These improvements occurred in the context of underlying appropriate medical management without proarrhythmia or compromised ICD function.

The first large randomized trial with more than six months follow-up to be published was the Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure (COMPANION) trial (Bristow, *et al.* 2004). It was an open-label prospective, multicenter, randomized study that evaluated cardiac resynchronization therapy with and without an ICD compared to standard drug therapies for HF. The goal is to determine whether optimal drug therapy combined with ventricular resynchronization, alone or with an ICD, will decrease mortality and hospitalizations, alleviate HF symptoms and improve function when compared to optimal drug therapy alone. A total of 1,520 patients who had advanced heart failure (New York Heart Association Class III or IV) due to ischemic or non-ischemic cardiomyopathies and a QRS interval of at least 120 msec were randomly assigned in a 1:2:2 ratio to receive optimal pharmacologic therapy (diuretics, angiotensin-converting-enzyme inhibitors, beta-blockers and spironolactone) alone or in combination with CRT or a CRT+ICD. The primary composite end point was the time to death from or hospitalization for any cause. Compared with optimal pharmacologic therapy alone, CRT decreased the risk of the primary end point (hazard ratio, 0.81; P=0.014), as did CRT+ICD (hazard ratio, 0.80; P=0.01). The risk of the combined end point of death from or hospitalization for heart failure was reduced by 34% in the CRT group (P<0.002) and by 40% in the CRT+ICD group (P<0.001 for the comparison with the pharmacologic-therapy group). CRT reduced the risk of the secondary end point of death from any cause by 24% (P=0.059) and CRT+ICD reduced the

risk by 36% ($P=0.003$). The authors concluded that in patients with advanced heart failure and a prolonged QRS interval, cardiac-resynchronization therapy decreases the combined risk of death from any cause or first hospitalization and, when combined with an implantable defibrillator, significantly reduces mortality.

Unfortunately, no comparisons were made between the CRT group and the CRT+ICD group. However, from the data it is clear that the any differences are not statistically significant. The primary outcome, death or any hospitalization occurred in 56% of patients in both groups. Total mortality was slightly lower in the CRT+ICD group (12% vs. 15%). This 3% difference in absolute mortality over 12 months is clinically significant and supports the argument that the combined device, designed to treat ventricular arrhythmias, adds value to CRT in this population of patients at high risk for sudden death. The quality of life and functional outcomes are almost identical in both groups. Since these measure heart failure specific outcomes, it is not surprising that the addition of ICD capacity adds little here.

Ongoing Randomized Clinical Trials

The CARE-HF trial (Cleland, Daubert *et al.* 2001) is designed to evaluate the long-term effects of cardiac resynchronization on the mortality and morbidity of patients with HF due to left ventricular systolic dysfunction already receiving diuretics and optimal medical therapy with ACE inhibitors and beta-blockers (where indicated and tolerated). Over 800 patients were randomized to CRT or medical therapy and are being followed for a minimum of 18 months. The primary end-point is all-cause mortality or unplanned cardiovascular hospitalization. The study completed recruitment in early 2003 and should report results in 2004.

Total Mortality

One meta-analysis was published in 2003 (Bradley *et al.*) that relied on pre-publication data available from the FDA. The meta-analysis included four of the five randomized trials reviewed above. They concluded that cardiac resynchronization therapy reduced mortality from progressive heart failure (OR 0.49, 95% CI 0.25-0.93) and that there was a trend towards lower total mortality (OR 0.77, 95% CI 0.51-1.18). However, the numbers used in the analysis has a number of problems, most likely due to the use of pre-publication data. For instance, the number of deaths that they report for the MIRACLE-ICD study in the no CRT arm is 17, while the actual number in the published data is 15. They also greatly overstate the number of patients randomized in the MIRACLE (532 vs. 443) and MIRACLE-ICD (554 vs. 369) studies. The overstated mortality in the no CRT arm biased the results in favor of CRT and the overstated numbers in the randomized comparisons artificially increased the power of the meta-analysis. However, the addition of new data from the COMPANION trial greatly strengthens the meta-analysis due to the much larger sample size and the longer follow-up. Correcting the errors in the initial meta-analysis and adding the data from the COMPANION trial (CRT alone vs. medical therapy arms) gives a summary estimate for all cause mortality of 0.76 (95% CI 0.61-0.96).

Complications/Harms

Unfortunately, the reporting of complications in the studies has been incomplete and suffers from lack of standardization. Patients who qualify for implantation of biventricular pacemakers are at very high risk for cardiopulmonary complications from any procedure and high complication rates are to be expected. All five of the major randomized clinical trials reported the rate of unsuccessful implantation, ranging from 8% to 13%. Only two of the studies (Abraham 2002; Bristow 2004) reported mortality rates during implantation. These ranged from 0.4% to 0.8%. One study (Higgins 2003) reported 30 day mortality of 2%. Common early complications include coronary sinus dissection or perforation, occurring in approximately 6% of attempted implantations (Abraham 2002; Young 2003). Failure of the LV lead to capture necessitates lead repositioning or replacement in 6% to 11% of patients (Abraham 2002; Linde 2002; Young 2003). In the MIRACLE ICD trial, 28% (120/429) of patients had complications during the hospitalization for device implantation.

These critically ill patients are at very high risk of further complications. Young *et al* (2003) reported that 46% of the participants in the MIRACLE ICD trial had major complications during the 6 months of follow-up after implantation (47% ICD+CRT, 44% control ICD only group, *p* NS). Complications were defined as any medical event that required invasive procedures for treatment or resulted in the death or serious injury to the patient. Similarly, during the one-year follow-up of the COMPANION trial, 61% of patients in the control group, 69% (*p*=0.03 compared with control group) of patients in the CRT+ICD group and 66% (*p*=0.15 compared with control group) of patients in the CRT alone group experienced major complications. Thus, it appears that there may be a 5% to 8% absolute increase in major complications in patients receiving devices compared with patients receiving medical therapy alone.

A recently published systematic review (McAlister *et al*, 2004) obtained additional details on harms from the investigators of the major studies. Using data from ten studies, they estimated the peri-procedural death rate to be 0.4% (95% CI 0.2-0.7%). The pooled estimate of failed implantation was 10% (95% CI 9-11%). Over a median of six months of follow-up, the device malfunctioned in 7% (95% CI 5-8%) and the pacing lead dislodged in 9% (95% CI 7-10%).

Summary

Despite the high rates of complications associated with device implantation, patients reported better quality of life and functional status when randomized to CRT. Additionally, there is a consistent trend towards lower rates of hospitalization and death in patients receiving CRT. Young *et al* (2003) in their meta-analysis of the first four randomized trials reported a 51% reduction in death from progressive heart failure, a 29% reduction in heart failure hospitalization and a trend towards decrease all cause mortality (23% reduction). The recently published COMPANION trial (Bristow *et al*/2004) confirmed these findings. On balance, the benefits of CRT appear to outweigh the substantial risks associated with device implantation and maintenance.

TA Criterion 3 is met

TA Criterion 4: The technology must be as beneficial as any established alternative.

There are no established alternatives to CRT other than optimized medical management of HF with ACE inhibitors, beta-blockers, spironolactone, digoxin and diuretics. The first three medication classes have been demonstrated in randomized clinical trials to improve both symptoms and survival over several years of follow-up. Digoxin and diuretics improve symptoms and reduce hospitalizations without adversely affecting mortality. At least one drug used to treat HF, vesnarinone, improved symptoms and exercise tolerance in clinical trials, but increased total mortality (Cohn, Goldstein *et al.* 1998).

Vesnarinone, a positive inotropic drug used for Class III and IV heart failure, improved quality of life and had a 62% reduction in all cause mortality compared with placebo in a multicenter trial of 577 patients followed for six months, but increased mortality at doses greater than 60 mg. (Feldman, Bristow *et al.* 1993). A larger clinical trial (3,833 participants) with longer follow-up was then performed to assess the long term effects of daily doses of 30 mg. and 60 mg. of vesnarinone compared to placebo (Cohn, Goldstein *et al.* 1998). This study replicated the significant improvement in quality of life with the drug treatment ($p < 0.001$) at two and four months, but found a dose dependant increase in all-cause mortality and decreased survival ($p = 0.02$) (Cohn, Goldstein *et al.* 1998). Vesnarinone is no longer used to treat heart failure. This highlights the need for clinical trials that follow patients with HF long enough to assess the effect of the intervention on total mortality before wide dissemination of the therapy.

Since the last CTAF review of CRT, three additional randomized trials have been published, one of which has median follow-up for key outcomes longer than one year. The data remain consistent: CRT improved patients' quality of life, exercise tolerance and function as measured by the Minnesota Living with Heart Failure Questionnaire, six-minute walking distance and NYHA class. More importantly, hospitalization rates and mortality were reduced. A recent systematic review and meta-analysis (McAlister *et al.*, 2004) also concluded that CRT improves functional status, reduces hospitalizations for heart failure and reduces total mortality. A concurrently published cost-effectiveness analysis (Nichol *et al.*, 2004) concluded that CRT is reasonably cost-effective for patients without another life threatening co-morbidity. There is room for improvement: 8-12% of attempted pacemaker implantations fail and up to 20% of patients appear not to respond to CRT. Investigators have been unable to identify patient factors that predict a poor response to CRT and would allow better selection of candidates for device implantation.

An important question is whether patients with an indication for both CRT and an ICD should receive a device capable of providing both therapies. Two of the trials, MIRACLE ICD and VENTAK CHF/CONTAK CD, address this issue. In both studies, the heart failure symptoms and functional status of patients with NYHA Class III or IV symptoms improved more in patient's receiving a dual device (Higgins *et al.* 2003; Young *et al.* 2003). However,

patients with Class II symptoms did not experience any benefit (Higgins 2003). There was a trend towards a reduction in mortality and hospitalization rates in the VENTAK CHF/CONTAK CD study, but this was not replicated in the MIRACLE ICD study. The summary odds ratio for all cause mortality from the two studies is 0.80 (95% CI 0.48-1.33). Follow-up was relatively short in both studies (six months) and a mortality benefit may have been apparent with longer follow-up. Certainly, the COMPANION trial with much longer follow-up showed a large and significant decrease in total mortality for patients randomized to a dual device compared to medical therapy alone (12% vs. 19%, $p=0.003$), though there was no ICD only group in the study. Mortality at 12 months in the dual device group (12%) was also lower than in the CRT alone group (15%), though no statistical comparison was performed in the study. Taken together, the evidence supports that adding CRT to an ICD in patients with an indication for both devices improves quality of life and function, with no increase in mortality or hospitalization rates and a trend towards decreased mortality long-term.

TA criterion 4 is met.

TA Criterion 5: The improvement must be attainable outside the investigational setting.

The initial chronic clinical trials, which led to approval of cardiac resynchronization in Europe and Canada, utilized an epicardial lead for LV pacing or a transvenous lead that was not specifically designed and tested for long-term LV pacing (Auricchio, Stellbrink *et al.* 1999; Auricchio, Stellbrink *et al.* 1999; Gras, Leclercq *et al.* 2002). Epicardial leads have a greater risk of failure to capture with chronic pacing and placement of an epicardial LV lead requires a limited thoracotomy, which is performed under general anesthesia and associated with a greater operative risk than a completely transvenous system. The development of a completely transvenous coronary sinus lead designed for long-term LV pacing has simplified the implant procedure while markedly reducing operative risk and is now being used in clinical trials. However, implantation of a coronary sinus catheter may result in venous dissection or perforation, and should be done only by experienced operators. In research centers reporting in the large clinical trials 8% to 12% of patients had failed implantation procedures. Less experienced centers may have a lower success rate.

TA criterion 5 is met.

TABLE 1: CHARACTERISTICS OF IMPORTANT CLINICAL STUDIES OF BIVENTRICULAR PACING FOR HEART FAILURE

Reference	Study Manufacturer	Design	N	Median follow-up (months)	Inclusion/ Exclusion	Age (years) Female (%)	Average EF (%)	QRS duration (msec)	MLHFQ Score (points)
PARALLEL									
Abraham 2002 ²² Abraham 2000 ²¹	MIRACLE Medtronic	RCT	453	6	NYHA Class III, IV, EF≤35%, QRS≥130 msec., PR>150 msec, Stable meds	64 32	22	166	59
- CRT			228						
- Control			225						
Higgins 2003	VENTAK CHF / CONTAK CD Guidant	RCT	490	6	NYHA Class II, III, or IV, EF≤35%, QRS≥120 msec., Indications for ICD, Stable meds	66 16	21	158	42
- CRT+ICD			245						
- Control+ICD			245						
Young 2003	MIRACLE ICD aka INSYNC ICD Medtronic			6	NYHA Class III, IV; Indications for ICD, EF≤35%, QRS≥130 msec, LV EDD≥55 mm, Stable meds	67 23	24	164	56
- CRT+ICD			187	6					
- Control+ICD			182						
Bristow 2000 ⁴⁶ Bristow 2004	COMPANION Guidant	RCT SB		18	NYHA Class III, IV; EF≤35%, QRS≥120 msec, PR>150 msec, Stable meds	67 33	21	160	NR
- CRT+ICD			595						
- CRT			617						
- Control			308						
CROSS-OVER									
Linde 2002 ²⁴ Cazeau 2001 ²³	MUSTIC Medtronic	RCT XO	58	3	NYHA Class III EF≤35%, QRS≥150 msec, Stable meds*	64 26	23	174	47
- CRT									
- Control									
Martinelli Filho 2002 ²⁶	- Medtronic	RCT XO	24		NYHA Class III-IV LBBB	55 4	19	181	NR
- CRT			24	6					
- Control			24	6					

TABLE 2: OUTCOMES OF IMPORTANT CLINICAL STUDIES OF BIVENTRICULAR PACING FOR HEART FAILURE

Reference	Study	Mortality (%)	Hosp (%)	HF Hosp (%)	Composite: Hosp or Death (%)	Composite: HF Hosp or death (%)	Composite: HF Hosp, death or VT/VF (%)	NYHA Class Improved 1 or 2 classes (%)	MLHFQ Score (points)	6 minute walk (m)	Ejection Fraction (%)
PARALLEL											
Abraham 2002 ²² Abraham 2000 ²¹	MIRACLE										
- CRT		5	NR	8	NR	12		68	-18	+39 m	+4.6
- Control		7	NR	15, p=0.02	NR	20, p=0.03		38, p<0.001	-9, p=0.001	+10 m, p=0.005	-0.2, p<0.001
Higgins 2003	VENTAK CHF / CONTAK CD										
- CRT+ICD		6				18	32	36	-7	+35	+5.1
- Control+ICD		8				23, NR	38, p=.36	32, p=.10	+5, p=.39	+15, p=.04	+2.8, p=.02
Young 2003	MIRACLE ICD aka INSYNC ICD										
- CRT+ICD		8	46		47	26		66	-17	+55	+2.1
- Control+ICD		8, p=.96	43, p NR		48, p=.88	26, p=.69		49, p=.007	-11, p=.02	+53, p=.36	+1.7, p=.12
Bristow 2000 ⁴⁶ Bristow 2004	COMPANION										
- CRT+ICD		12, p=.003			56, p=.01	29, p<.001		57, p<.001	-26, p<.001	+46, p<.001	NR
- CRT		15, p=.06			56, p=.01	31, p=.002		61, p<.001	-25, p<.001	+40, p<.001	NR
- Control		19			68	45		38	-12	+1	NR
CROSS-OVER											
Linde 2002 ²⁴ Cazeau 2001 ²³	MUSTIC										
- CRT		5	NR	10	NR	NR	NR	NR	30	399	NR
- Control		0, p NR	NR	31, p<0.05	NR	NR	NR	NR	43, p<0.001	326, p<0.001	NR
Martinelli Filho 2002 ²⁶	-		Improved								
- CRT			NR					75			+6.2
- Control			NR					NR			+0.5, p NR

Specified primary outcome for each study is indicated in bold.

TABLE 3: COMPLICATIONS IN IMPORTANT CLINICAL STUDIES OF BIVENTRICULAR PACING FOR HEART FAILURE

Reference	Study	Failed implantation (%)	Early complications (dissection, perforation, etc)	Mortality during implantation procedure (%)	30 day mortality	Hospitalization for lead repositioning or replacement (%)	All major complications (%)	Complications
PARALLEL								
Abraham 2002 ²² Abraham 2000 ²¹	MIRACLE	8	6	0.4				Of 571 attempted implantations: 4 comps w/ 2 deaths: 2 Complete heart block; 1 Hypotension – died; 1 Asystole – died. 23 (4%) coronary sinus dissection. 12 (2%) coronary sinus perforation. 4% LV lead repositioning, 2% replacement LV lead.
- CRT						5		
- Control						1		
Higgins 2003	VENTAK CHF / CONTAK CD	12			2			
- CRT+ICD								
- Control+ICD								
Young 2003	MIRACLE ICD Aka INSYNC ICD	13					46	Of 429 implant attempts: 15 coronary sinus dissections, 4 cardiac perforations, 6 HF decompensation, 5 VT/VF, 3 heart block, 3 hemopneumothorax – chest tube placed. 175/379 (46%) of patients with successful implants experienced 398 complications over the 6 months after hospital discharge: HF decompensation and lead complications were most common.
- CRT+ICD							47	
- Control+ICD							44	
Bristow 2000 ⁴⁶ Bristow 2004	COMPANION	11						
- CRT+ICD			2	0.5			69, p=.03	
- CRT			2	0.8			66, p=.15	
- Control							61	
CROSS-OVER								
Linde 2002 ²⁴ Cazeau 2001 ²³	MUSTIC	8%				12		Before randomization, 8/59 successful implants had early dislodged leads, corrected in 5. Two additional patients had uncorrectable loss of LV pacing during the 1 st crossover period.
- CRT								
- Control								
Martinelli Filho 2002 ²⁶								
- CRT								
- Control								

* Stable medications did not included beta blockers

NYHA: New York Heart Association
QRS: QRS interval
MLHFQ: Minnesota Living with Heart Failure Questionnaire, score 0-105 with higher score indicating worse quality of life
CRT: Cardiac resynchronization therapy
BV: Biventricular pacing
ICD: Implantable cardioverter defibrillator
LV EDD: Left ventricular end diastolic diameter
LBBB: Left bundle branch block
RCT: Randomized clinical trial
XO: Cross-over
Stable meds: Stable medication regimen including a stable dose of a diuretic and an angiotensin converting enzyme inhibitor or angiotensin receptor blocker for at least one month and a beta blocker for at least 3 months.

MIRACLE: Multicenter InSync Randomized Clinical Evaluation trial
MUSTIC: Multisite Stimulation in Cardiomyopathies trial
COMPANION: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure trial
CARE-HF: Cardiac Resynchronization in Heart Failure study

RECOMMENDATIONS OF OTHERS

American College of Cardiology (ACC) (California)

The ACC does not have a position/ opinion statement specific to this procedure. However, the ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult published in 2001 make reference to the use of cardioverter-defibrillators for the treatment of Class III CHF (at the time of printing the level of evidence was "C"). Representatives of the ACC were not able to attend the meeting. The ACC together with the AHA and NASPE (now the Heart Rhythm Society) updated the Guideline for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices in 2002 and assigned a Class IIa indication for the implantation of cardiac resynchronization devices in HF and prolonged QRS.

Blue Cross Blue Shield Association (BCBSA)

The BCBSA TEC Medical Advisory Panel has not reviewed this topic. The BCBSA reference manual position is as follows:

Biventricular pacemakers may be considered medically necessary as a treatment of congestive heart failure in patients who meet all of the following criteria:

- NYHA Class III or IV
- Left ventricular ejection fraction <35%
- QRS duration of => 150 msec
- Patients treated with a stable pharmacological medical regimen prior to implant, including an ACE inhibitor (or an angiotensin receptor blocker: and a beta blocker (or angiotensin receptor blocker), digoxin, and diuretics

Centers for Medicare and Medicaid (CMS)

CMS does not have a national or local coverage policy specific to this technology. Cases are considered on an individual basis.

Heart Rhythm Society (HRS)

In July 2004 the HRS published a Clinical Competency Statement: Training Pathways for Implantation of Cardioverter Defibrillators and Cardiac Resynchronization Devices (available at www.hrsonline.org).

In December 2003 the HRS published an Expert Consensus Statement regarding Resynchronization Therapy for Heart Failure (available at www.hrsonline.org). A HRA representative did attend the meeting and indicated support for the approved recommendation.

CONCLUSION

Many short-term studies have been published demonstrating that CRT in appropriate patients with heart failure improved patient quality of life, increased the distance walked in six minutes and lowered NYHA classification. Four early randomized studies suggest that CRT may reduce hospitalizations from heart failure and total mortality. However, the length of follow-up in these studies was short (three to six months). The recently published COMPANION trial convincingly demonstrates that CRT reduces mortality and hospitalization rates. It is still not clear from current studies whether CRT, in addition to ICD, decreases mortality and hospitalizations in patients with indications for both an ICD and CRT, but symptoms and quality of life are clearly better in patients receiving a dual device. The COMPANION trial suggests that the dual device is as effective as CRT alone at improving symptoms and preventing hospitalizations and there was a trend towards lower all cause mortality in the dual device group compared with CRT alone. Thus, the evidence suggests that adding CRT to ICD therapy does not decrease the effectiveness of the ICD in preventing sudden death and improves patients' quality of life and functional status.

DRAFT RECOMMENDATION

It is recommended that implantation of biventricular pacemakers for patients with a prolonged QRS interval

and Class III or IV heart failure meets California Technology Assessment Forum TA Criteria for treatment of congestive heart failure in patients who fulfill all of the following criteria:

- NYHA Class III or IV
- Left ventricular ejection fraction $\leq 35\%$
- QRS duration of ≥ 120 msec
- PR interval ≥ 150 msec
- Stable pharmacological medical regimen prior to implant including (or having failed) an ACE inhibitor (or an angiotensin receptor blocker), a beta-blocker, spironolactone, digoxin and loop diuretics

Furthermore, it is recommended that implantation of a dual function device (CRT+ICD) for patients with an indication for an ICD, a prolonged QRS interval and Class III or IV heart failure meets California Technology Assessment Forum TA Criteria. Patients must fulfill all of the following criteria:

- Indication for an ICD
- NYHA Class III or IV
- Left ventricular ejection fraction $\leq 35\%$
- QRS duration of ≥ 120 msec
- PR interval ≥ 150 msec
- Stable pharmacological medical regimen prior to implant including (or having failed) an ACE inhibitor (or an angiotensin receptor blocker), a beta-blocker, spironolactone, digoxin and loop diuretics

The California Technology Assessment Forum voted to approve the following recommendation:

It is recommended that implantation of biventricular pacemakers for patients with a prolonged QRS interval and Class III or IV heart failure meets California Technology Assessment Forum TA Criteria for treatment of congestive heart failure in patients who fulfill all of the following criteria:

- NYHA Class III or IV
- Left ventricular ejection fraction $\leq 35\%$
- QRS duration of ≥ 120 msec
- Stable pharmacological medical regimen prior to implant including (or having failed) an ACE inhibitor (or an angiotensin receptor blocker), a beta-blocker, spironolactone, digoxin and loop diuretics

Furthermore, it is recommended that implantation of a dual function device (CRT+ICD) for patients with an indication for an ICD, a prolonged QRS interval and Class III or IV heart failure meets California Technology Assessment Forum TA Criteria. Patients must fulfill all of the following criteria:

- Indication for an ICD
- NYHA Class III or IV
- Left ventricular ejection fraction $\leq 35\%$
- QRS duration of ≥ 120 msec
- Stable pharmacological medical regimen prior to implant including (or having failed) an ACE inhibitor (or an angiotensin receptor blocker), a beta-blocker, spironolactone, digoxin and loop diuretics

October 20, 2004

REFERENCES

1. (2002). FDA Summary of Safety and Effectiveness, Food & Drug Administration.
2. Abraham, W.T. (2002). "Rational and design of a randomized clinical trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with advanced heart failure: the Multicenter InSync Randomized

Clinical Evaluation (MIRACLE)." J Card fail 6(4): 369-80.

3. Abraham, W.T., W.G. Fisher, *et al.* (2002). "Cardiac resynchronization in chronic heart failure." N Engl J Med 346(24): 1845-53.
4. Association, T.C.C. o.t. N.Y.H. (1994). Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. Boston, Little, Brown and Co.
5. Auricchio, A., H. Klein, *et al.* (1999). "Pacing for heart failure: selection of patients, techniques and benefits." Eur J Heart Fail 1(3): 275-9.
6. Auricchio, A., C. Stellbrink, *et al.* (1999). "Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group." Circulation 99(23): 2993-3001.
7. Auricchio, A., C. Stellbrink, *et al.* (2002). "Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay." J Am Coll Cardiol 39(12): 2026-33.
8. Auricchio, A., C. Stellbrink, *et al.* (1999). "The Pacing Therapies for Congestive Heart Failure (PATH-CHF) study: rationale, design, and endpoints of a prospective randomized multicenter study." Am J Cardiol 83(5B): 130D-135D.
9. Bakker, P.F., H.W. Meijburg, *et al.* (2000). "Biventricular pacing in end-stage heart failure improves functional capacity and left ventricular function." J Interv Card Electrophysiol 4(2): 395-404.
10. Blanc, J.J., Y. Etienne, *et al.* (1997). "Evaluation of different ventricular pacing sites in patients with severe heart failure: results of an acute hemodynamic study." Circulation 96(10): 3273-7.
11. Bradley, D. J., E. A. Bradley, K. L. Baughman, *et al.* (2003). "Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials." JAMA 289(6): 730-40.
12. Bristow, M.R., A.M. Feldman, *et al.* (2000). "Heart failure management using implantable, devices for ventricular resynchronization: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial. COMPANION Steering Committee and COMPANION Clinical Investigators." J Card Fail 6(3): 276-85.
13. Bristow, M. R., L. A. Saxon, J. Boehmer, *et al.* (2004). "Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure." N Engl J Med 350(21): 2140-50.
14. Cazeau, S., C. Leclercq, *et al.* (2001). "Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay." N Engl J Med 344(12): 873-80.
15. Cazeau, S., P. Ritter, *et al.* (1994). "Four chamber pacing in dilated cardiomyopathy." Pacing Clin Electrophysiol 17(11 Pt 2): 1974-9.
16. Cleland, J.G., J.C. Daubert, *et al.* (2001). "The CARE-HF study (Cardiac Resynchronization in Heart Failure study): rationale, design and end-points." Eur J Heart Fail 3(4): 481-9.
17. Cohn, J.N., S.O. Goldstein, *et al.* (1998). "A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators." N Engl J Med 339(25): 1810-6
18. Daubert, J. C., P. Ritter, H. Le Breton, *et al.* (1998). "Permanent left ventricular pacing with transvenous leads

inserted into the coronary veins." *Pacing Clin Electrophysiol* 21(1 Pt 2): 239-45.

19. Farwell, D., N.R. Patel, *et al.* (2000). "How many people with heart failure are appropriate for biventricular resynchronization?" *Eur Heart J* 21(15): 1246-50
20. Feldman, A.M., M.R. Bristow, *et al.* (1993). "Effects of vesnarinone on morbidity and mortality in patients with heart failure. Vesnarinone Study Group." *N Engl J Med* 329(3): 149-55.
21. Garrigue, S., P. Bordachar, *et al.* (2002). "Comparison of permanent left ventricular and biventricular pacing in patients with heart failure and chronic atrial fibrillation: prospective haemodynamic study." *Heart* 87(6): 529-34.
22. Gras, D., C. Leclercq, *et al.* (2002). "Cardiac resynchronization therapy in advanced heart failure the multicenter InSync clinical study." *Eur J Heart Fail* 4(3): 311-20.
23. Gras, D., P. Mabo, *et al.* (1998). "Multisite pacing as a supplemental treatment of congestive heart failure: primary results of the Medtronic Inc. InSync Study". *Pacing Clin Electrophysiol* 21(11 Pt 2): 2249-55.
24. Guyatt, G.H., M.J. Sullivan, *et al.* (1985). "The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure." *Can Med Assoc J* 132(8): 919-23.
25. Haldeman, G.A., J.B. Croft, *et al.* (1999). "Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995." *Am Heart J* 137(2): 352-60.
26. Hamdan, M.H., J.D. Zagrodzky, *et al.* (2000). "Biventricular pacing decreases sympathetic activity compared with right ventricular pacing in patients with depressed ejection fraction." *Circulation* 102(9): 1027-32.
27. Higgins, S.L., P. Young, *et al.* (2000). "Biventricular pacing diminishes the need for implantable cardioverter defibrillator therapy. Ventak CHF Investigators." *J Am Coll Cardiol* 36(3): 824-7.
28. Higgins, S. L., J. D. Hummel, I. K. Niazi, *et al.* (2003). "Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias." *J Am Coll Cardiol* 42(8): 1454-9.
29. Ho, K.K., K.M. Anderson, *et al.* (1993). "Survival after the onset of congestive heart failure in Framingham Heart Study subjects." *Circulation* 88(1): 107-15.
30. Jais, P., A. Takahashi, *et al.* (2000). "Mid-term follow-up of endocardial biventricular pacing." *Pacing Clin Electrophysiol* 23(11 Pt 2): 1744-7.
31. Kass, D.S., C.H. Chen, *et al.* (1999). "Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay." *Circulation* 99(12): 1567-73.
32. Kerwin, W.F., E.H. Botvinick, *et al.* (2000). "Ventricular contraction abnormalities in dilated cardiomyopathy: effect of biventricular pacing to correct interventricular dyssynchrony." *J Am Coll Cardiol* 35(5): 1221-7.
33. Kuhlkamp, V. (2002). "Initial experience with an implantable cardioverter-defibrillator incorporating cardiac resynchronization therapy." *J Am Coll Cardiol* 39(5): 790-7.
34. Lau, C.P., C.M. Yu, *et al.* (2000). "Reversal of left ventricular remodeling by synchronous biventricular pacing in heart failure." *Pacing Clin Electrophysiol* 23(11 Pt 2): 1722-5.
35. Leclercq, C., S. Cazeau, *et al.* (1998). "Acute hemodynamic effects of biventricular DDD pacing in patients with

- end-stage heart failure." *J Am Coll Cardiol* 32(7): 1825-31.
36. Leclercq, C., S. Cazeau, *et al.* (2000). "A pilot experience with permanent biventricular pacing to treat advanced heart failure." *Am Heart J* 140(6): 862-70.
 37. Leclercq, C. and D.A. Kass (2002). "Retiming the failing heart: principles and current clinical status of cardiac resynchronization." *J Am Coll Cardiol* 39(2): 194-201.
 38. Linde, C., C. Leclercq, *et al.* (2002). "Long-term benefits of biventricular pacing in congestive heart failure: results from the MULTISITE STimulation in cardiomyopathy (MUSTIC) study." *J Am Coll Cardiol* 40(1): 111-8.
 39. Lozano, I., M. Bocchiardo, *et al.* (2000). "Impact of biventricular pacing on mortality in a randomized crossover study of patients with heart failure and ventricular arrhythmias." *Pacing Clin Electrophysiol* 23(11 Pt 2): 1711-2.
 40. Lunati, M., M. Paolucci, *et al.* (2002). "Patient selection for biventricular pacing." *J Cardiovasc Electrophysiol* 13(1 Suppl): S63-7.
 41. Lupi, G., M. Brignole, *et al.* (2000). "Effects of left ventricular pacing on cardiac performance and on quality of life in patients with drug refractory heart failure." *Am J Cardiol* 86(11): 1267-70, A9.
 42. Martinelli Filho, M., A. A. Pedrosa, *et al.* (2002). "Biventricular pacing improves clinical behavior and reduces prevalence of ventricular arrhythmia in patients with heart failure." *Arq Bras Cardiol* 78(1): 110-3.
 43. McAlister, F. A., J. A. Ezekowitz, N. Wiebe, *et al.* (2004). "Systematic review: cardiac resynchronization in patients with symptomatic heart failure." *Ann Intern Med* 141(5): 381-90.
 44. Nelson, G. S., R. D. Berger, *et al.* (2000). "Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block." *Circulation* 102(25): 3053-9.
 45. Nichol, G., P. Kaul, E. Huszti, *et al.* (2004). "Cost-effectiveness of cardiac resynchronization therapy in patients with symptomatic heart failure." *Ann Intern Med* 141(5): 343-51.
 46. O'Connell, J. B. (2000). "The economic burden of heart failure." *Clin Cardiol* 23(3 Suppl): III6-10.
 47. Rector, R. S., S. H. Kubo, *et al.* (1987). "Patients' self-assessment of their congestive heart failure. II. Content, reliability, and validity of a new measure – the Minnesota Living with Heart Failure Questionnaire." *Heart Fail* 3: 198-209.
 48. Reuter, S., S. Garrigue, *et al.* (2000). "Intermediate-term results of biventricular pacing in heart failure: correlation between clinical and hemodynamic data." *Pacing Clin Electrophysiol* 23(11 Pt 2): 1713-7.
 49. Rodeheffer, R. J., S. J. Jacobsen, *et al.* (1993). "The incidence and prevalence of congestive heart failure in Rochester, Minnesota." *Mayo Clin Proc* 68(12): 1143-50.
 50. Saxon, L. A., J. P. Boehmer, *et al.* (1999). "Biventricular pacing in patients with congestive heart failure: two prospective randomized trials. The VIGOR CHF and VENTAK CHF Investigators." *Am J Cardiol* 83(5B): 120D-123D.
 51. Saxon, L. A., T. De Marco, *et al.* (2002). "Effects of long-term biventricular stimulation for resynchronization on echocardiographic measures of remodeling." *Circulation* 105(11): 1304-10.

52. Saxon, L. A., W. F. Kerwin, *et al.* (1998). "Acute effects of intraoperative multisite ventricular pacing on left ventricular function and activation/contraction sequence in patients with depressed ventricular function." J Cardiovasc Electrophysiol 9(1): 13-21.
53. Shamim, W., D. P. Francis, *et al.* (1999). "Intraventricular conduction delay: a prognostic marker in chronic heart failure." Int J Cardiol 70(2): 171-8.
54. Stevenson, W. G., L. W. Stevenson, *et al.* (1995). "Improving survival for patients with advanced heart failure: a study of 737 consecutive patients." J Am Coll Cardiol 26(6): 1417-23.
55. Toussaint, J. F., T. Lavergne, *et al.* (2000). "Biventricular pacing in severe heart failure patients reverses electromechanical dyssynchronization from apex to base." Pacing Clin Electrophysiol 23(11 Pt 2): 1731-4.)
56. Walker, S., T. M. Levy, *et al.* (2000). "Usefulness of suppression of ventricular arrhythmia by biventricular pacing in severe congestive cardiac failure." Am J Cardiol 86(2): 231-3.
57. Xiao, H. B., C. Roy, *et al.* (1996). "Natural history of abnormal conduction and its relation to prognosis in patients with dilated cardiomyopathy." Int J Cardiol 53(2): 163-70.
58. Young, J.B., W.T. Adraham, A.L. Smith *et al.* (2003). "Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial." *Jama* 289(20):2685-94.
59. Yu, C. M., E. Chau, *et al.* (2002). "Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure." Circulation 105(4): 438-45.
60. Zannad, F., S. Braincon, *et al.* (1999). "Incidence, clinical and etiologic features, and outcomes of advanced chronic heart failure: the EPICAL Study. Epidemiologie de l'Insuffisance Cardiaque Avancee en Lorraine." J Am Coll Cardiol 33(3): 734-42.
61. Zardini, M., M. Tritto, *et al.* (2000). "The InSync Italian Registry: analysis of clinical outcome and considerations on the selection of candidates to left ventricular resynchronization." European Heart Journal Supplements 2: J16-J22.