

Biventricular Pacing (Cardiac Resynchronization Therapy)

An Evidence-Based Analysis

September 2005



Medical Advisory Secretariat
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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and information from practicing medical experts and industry, adds important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to maximize patient outcomes.

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This evidence-based analysis was prepared by the Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care, for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data, and information provided by experts and applicants to the Medical Advisory Secretariat to inform the analysis. While every effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of publication. This analysis may be superceded by an updated publication on the same topic. Please check the Medical Advisory Secretariat Website for a list of all evidence-based analyses: <http://www.health.gov.on.ca/ohtas>

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Abbreviations

BiV	Biventricular
CARE-HF	Cardiac Resynchronization in Heart Failure (trial)
CI	Confidence interval
COMPANION	Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (trial)
CRT	Cardiac resynchronization therapy
EF	Ejection fraction
HF	Heart failure
ICD	Implantable cardioverter defibrillator
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MIRACLE	Multicentre Insync Randomized Clinical Evaluation (trial)
MUSTIC	Multisite Stimulation in Cardiomyopathy (trial)
NYHA	New York Heart Association
QoL	Quality of Life
RCT	Randomized controlled trial
RR	Relative risk
SCD	Sudden cardiac death
SR	Sinus rhythm
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Executive Summary

Issue

In 2002, (before the establishment of the Ontario Health Technology Advisory Committee), the Medical Advisory Secretariat conducted a health technology policy assessment on biventricular (BiV) pacing, also called cardiac resynchronization therapy (CRT). The goal of treatment with BiV pacing is to improve cardiac output for people in heart failure (HF) with conduction defect on ECG (wide QRS interval) by synchronizing ventricular contraction. The Medical Advisory Secretariat concluded that there was evidence of short (6 months) and longer-term (12 months) effectiveness in terms of cardiac function and quality of life (QoL). More recently, a hospital submitted an application to the Ontario Health Technology Advisory Committee to review CRT, and the Medical Advisory Secretariat subsequently updated its health technology assessment.

Background

Chronic HF results from any structural or functional cardiac disorder that impairs the ability of the heart to act as a pump. It is estimated that 1% to 5% of the general population (all ages) in Europe have chronic HF. (1;2) About one-half of the patients with HF are women, and about 40% of men and 60% of women with this condition are aged older than 75 years.

The incidence (i.e., the number of new cases in a specified period) of chronic HF is age dependent: from 1 to 5 per 1,000 people each year in the total population, to as high as 30 to 40 per 1,000 people each year in those aged 75 years and older. Hence, in an aging society, the prevalence (i.e., the number of people with a given disease or condition at any time) of HF is increasing, despite a reduction in cardiovascular mortality.

A recent study revealed 28,702 patients were hospitalized for first-time HF in Ontario between April 1994 and March 1997. (3) Women comprised 51% of the cohort. Eighty-five percent were aged 65 years or older, and 58% were aged 75 years or older.

Patients with chronic HF experience shortness of breath, a limited capacity for exercise, high rates of hospitalization and rehospitalization, and die prematurely. (2;4) The New York Heart Association (NYHA) has provided a commonly used functional classification for the severity of HF (2;5):

- Class I: No limitation of physical activity. No symptoms with ordinary exertion.
- Class II: Slight limitations of physical activity. Ordinary activity causes symptoms.
- Class III: Marked limitation of physical activity. Less than ordinary activity causes symptoms. Asymptomatic at rest.
- Class IV: Inability to carry out any physical activity without discomfort. Symptoms at rest.

The National Heart, Lung, and Blood Institute estimates that 35% of patients with HF are in functional NYHA class I; 35% are in class II; 25%, class III; and 5%, class IV. (5) Surveys (2) suggest that from 5% to 15% of patients with HF have persistent severe symptoms, and that the remainder of patients with HF is evenly divided between those with mild and moderately severe symptoms.

Overall, patients with chronic, stable HF have an annual mortality rate of about 10%. (2) One-third of patients with new-onset HF will die within 6 months of diagnosis. These patients do not survive to enter the pool of those with “chronic” HF. About 60% of patients with incident HF will die within 3 years, and there is limited evidence that the overall prognosis has improved in the last 15 years.

To date, the diagnosis and management of chronic HF has concentrated on patients with the clinical syndrome of HF accompanied by severe left ventricular systolic dysfunction. Major changes in treatment have resulted from a better understanding of the pathophysiology of HF and the results of large clinical trials. Treatment for chronic HF includes lifestyle management, drugs, cardiac surgery, or implantable pacemakers and defibrillators. Despite pharmacologic advances, which include diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, spironolactone, and digoxin, many patients remain symptomatic on maximally tolerated doses.

The Technology

Owing to the limitations of drug therapy, cardiac transplantation and device therapies have been used to try to improve QoL and survival of patients with chronic HF. Ventricular pacing is an emerging treatment option for patients with severe HF that does not respond well to medical therapy. Traditionally, indications for pacing include bradyarrhythmia, sick sinus syndrome, atrioventricular block, and other indications, including combined sick sinus syndrome with atrioventricular block and neurocardiogenic syncope. Recently, BiV pacing as a new, adjuvant therapy for patients with chronic HF and mechanical dyssynchrony has been investigated. Ventricular dysfunction is a sign of HF; and, if associated with severe intraventricular conduction delay, it can cause dyssynchronous ventricular contractions resulting in decreased ventricular filling. The therapeutic intent is to activate both ventricles simultaneously, thereby improving the mechanical efficiency of the ventricles.

About 30% of patients with chronic HF have intraventricular conduction defects. (6) These conduction abnormalities progress over time and lead to discoordinated contraction of an already hemodynamically compromised ventricle. Intraventricular conduction delay has been associated with clinical instability and an increased risk of death in patients with HF. (7) Hence, BiV pacing, which involves pacing left and right ventricles simultaneously, may provide a more coordinated pattern of ventricular contraction and thereby potentially reduce QRS duration, and intraventricular and interventricular asynchrony. People with advanced chronic HF, a wide QRS complex (i.e., the portion of the electrocardiogram comprising the Q, R, and S waves, together representing ventricular depolarization), low left ventricular ejection fraction and contraction dyssynchrony in a viable myocardium and normal sinus rhythm, are the target patients group for BiV pacing. One-half of all deaths in HF patients are sudden, and the mode of death is arrhythmic in most cases. Internal cardioverter defibrillators (ICDs) combined with BiV pacemakers are therefore being increasingly considered for patients with HF who are at high risk of sudden death.

Current Implantation Technique for Cardiac Resynchronization

Conventional dual-chamber pacemakers have only 2 leads: 1 placed in the right atrium and the other in the right ventricle. The technique used for BiV pacemaker implantation also uses right atrial and ventricular pacing leads, in addition to a left ventricle lead advanced through the coronary sinus into a vein that runs along the ventricular free wall. This permits simultaneous pacing of both ventricles to allow resynchronization of the left ventricle septum and free wall.

Mode of Operation

Permanent pacing systems consist of an implantable pulse generator that contains a battery and electronic circuitry, together with 1 (single-chamber pacemaker) or 2 (dual-chamber pacemaker) leads. Leads conduct intrinsic atrial or ventricular signals to the sensing circuitry and deliver the pulse generator charge to the myocardium (muscle of the heart).

Complications of Biventricular Pacemaker Implantation

The complications that may arise when a BiV pacemaker is implanted are similar to those that occur with standard pacemaker implantation, including pneumothorax, perforation of the great vessels or the myocardium, air embolus, infection, bleeding, and arrhythmias. Moreover, left ventricular pacing through the coronary sinus can be associated with rupture of the sinus as another complication.

Conclusion of 2003 Review of Biventricular Pacemakers by the Medical Advisory Secretariat

The randomized controlled trials (RCTs) the Medical Advisory Secretariat retrieved analyzed chronic HF patients that were assessed for up to 6 months. Other studies have been prospective, but nonrandomized, not double-blinded, uncontrolled and/or have had a limited or uncalculated sample size. Short-term studies have focused on acute hemodynamic analyses. The authors of the RCTs reported improved cardiac function and QoL up to 6 months after BiV pacemaker implantation; therefore, there is level 1 evidence that patients in ventricular dyssynchrony who remain symptomatic after medication might benefit from this technology. Based on evidence made available to the Medical Advisory Secretariat by a manufacturer, (8) it appears that these 6-month improvements are maintained at 12-month follow-up.

To date, however, there is insufficient evidence to support the routine use of combined ICD/BiV devices in patients with chronic HF with prolonged QRS intervals.

Summary of Updated Findings Since the 2003 Review

Since the Medical Advisory Secretariat's review in 2003 of biventricular pacemakers, 2 large RCTs have been published: COMPANION (9) and CARE-HF. (10) The characteristics of each trial are shown in Table 1. The COMPANION trial had a number of major methodological limitations compared with the CARE-HF trial.

Table 1: Characteristics of the COMPANION and CARE-HF Trials*

	COMPANION, 2004	CARE-HF, 2005
	Optimal Therapy vs. BiV Pacing vs. BiV Pacing/ICD†	Optimal Therapy vs. BiV Pacing
Population	New York Heart Association class III/IV heart failure	
	EF† ≤ 0.35	
	QRS† ≥ 120 ms	
N	1,520	813
	(optimal therapy, n = 308; BiV pacing, n = 617; BiV pacing/ICD, n = 595)	
Follow-up (months)	Median, 16	Mean, 29
Comment	<ul style="list-style-type: none"> - Definition of "hospitalization" in primary outcome changed 3 times during trial w/o documentation in protocol and FDA† not notified (dominant outcome for composite endpoint). - Dropouts/withdrawals/crossovers not clearly described. - Study terminated early. - No direct comparison between BiV pacing vs. BiV pacing/ICD. - High number of patients withdrew from optimal therapy to device arms. - Not blinded. 	Not blinded

*COMPANION; (9) CARE-HF. (10)

†BiV indicates biventricular; ICD, implantable cardioverter defibrillator; EF, ejection fraction; QRS, the interval representing the Q, R and S waves on an electrocardiogram; FDA, United States Food and Drug Administration.

Overall, CARE-HF showed that BiV pacing significantly improves mortality, QoL, and NYHA class in patients with severe HF and a wide QRS interval (Tables 2 and 3).

Table 2: CARE-HF Results: Primary and Secondary Endpoints*

Outcome	Medical Therapy Alone (N = 404)	Medical Therapy and BiV [†] Pacing [†] (N = 409)	Hazard Ratio (95% CI)	P	NNT [†]
	No. (%) Patients	No. (%) Patients			
Primary (Combined Endpoint)					
Death (any cause) or unplanned hospitalization for major cardiovascular event.	224 (55)	159 (39)	0.63 (0.51–0.77)	< .001	6
Secondary					
Death (any cause) at 29 months	120 (30)	82 (20)	0.64 (0.48–0.85)	< .002	10
(at 36 months – grey literature) (11)	154 (38)	101 (25)	0.60 (0.47–0.77)	< .0001	7
Death from any cause or unplanned hospitalization with worsening HF	191 (47)	118 (29)	0.54 (0.43–0.68)	< .001	6

†BiV indicates biventricular; NNT, number needed to treat.

*Cleland JGF, Daubert J, Erdmann E, Freeman N, Gras D, Kappenberger L et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure (CARE-HF). *New England Journal of Medicine* 2005; 352:1539-1549; Copyright 2003 Massachusetts Medical Society. All rights reserved. (10)

Table 3: CARE H-F Results: NYHA Class and Quality of Life Scores*

Outcome	Medical Therapy Alone (N = 404)	Medical Therapy and BiV Pacing (N = 409)	Difference in Means (95% CI)	P
	Mean (SD) at 90 days	Mean (SD) at 90 days		
NYHA class	2.7 (0.9)	2.1 (1.0)	0.6 (0.4–0.7)	< .001
Minnesota Living with Heart Failure score [†]	40 (22)	31 (22)	-10 (-8 to -12)	< .001
EuroQoL EQ-5D score [‡]	0.63 (0.29)	0.70 (0.28)	0.08 (0.04–0.12)	< .001

†Minnesota Living with Heart Failure scores range from 0 to 105; higher scores reflect poorer QoL.

‡European Quality of Life–5 Dimensions scores range from -0.594 to 1.000; 1.000 indicates fully healthy; 0, dead

*Cleland JGF, Daubert J, Erdmann E, Freeman N, Gras D, Kappenberger L et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure (CARE-HF). *New England Journal of Medicine* 2005; 352:1539-1549; Copyright 2005 Massachusetts Medical Society. All rights reserved. (10)

GRADE Quality of Evidence

The quality of these 3 trials was examined according to the GRADE Working Group criteria, (12) (Table 4).

Quality refers to criteria such as the adequacy of allocation concealment, blinding, and follow-up.

Consistency refers to the similarity of estimates of effect across studies. If there is an important unexplained inconsistency in the results, confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the size of the differences in effect, and the significance of the differences guide the decision about whether important inconsistency exists.

Directness refers to the extent to which the people interventions and outcome measures are similar to those of interest. For example, there may be uncertainty about the directness of the evidence if the people of interest are older, sicker, or have more comorbid conditions than do the people in the studies.

As stated by the GRADE Working Group, (12) the following definitions were used in grading the quality of the evidence:

- High: Further research is very unlikely to change our confidence on the estimate of effect.
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low: Any estimate of effect is very uncertain.

Table 4: Quality of Evidence: CARE-HF and COMPANION

Trial	Design	Quality	Consistency	Directness	Quality Grade
CARE-HF (BiV pacing only vs. medical therapy)	RCT	Not blinded.	No important inconsistency. Consistent with COMPANION in terms of mortality results. Consistent with previous studies regarding QoL and functional status results.	Direct.	Moderate/High
COMPANION (BiV pacing only vs. combined BiV pacing/ICD vs. medical therapy)	RCT	Definition of "hospitalization" in primary outcome changed 3 times during trial without documentation in protocol and FDA not notified (dominant outcome for composite endpoint). Dropouts/withdrawals/crossovers not clearly described.	No important inconsistency for BiV pacing only. No other RCT prospectively examined the combined BiV pacing/ICD device in patients with NYHA III/IV HF and QRS > 120 ms and EF < 0.35 and refractory to drugs. No other RCT prospectively examined	Direct for BiV pacing only. No other RCT examined the prophylactic use of ICDs in patients with NYHA IV HF.	Low

Study terminated early.	the prophylactic use of ICDs in patients with NYHA IV HF.
No direct comparison between BiV pacing vs. BiV pacing/ICD.	
High number of patients withdrew from optimal therapy to device arms.	
Not blinded.	

Conclusions

Overall, there is evidence that BiV pacemakers are effective for improving mortality, QoL, and functional status in patients with NYHA class III/IV HF, an EF less than 0.35, a QRS interval greater than 120 ms, who are refractory to drug therapy.

As per the GRADE Working Group, recommendations considered the following 4 main factors:

- The tradeoffs, taking into account the estimated size of the effect for the main outcome, the confidence limits around those estimates, and the relative value placed on the outcome
- The quality of the evidence (Table 4)
- Translation of the evidence into practice in a specific setting, taking into consideration important factors that could be expected to modify the size of the expected effects such as proximity to a hospital or availability of necessary expertise
- Uncertainty about the baseline risk for the population of interest

The GRADE Working Group also recommends that incremental costs of health care alternatives should be considered explicitly alongside the expected health benefits and harms. Recommendations rely on judgments about the value of the incremental health benefits in relation to the incremental costs. The last column in Table 5 shows the overall trade-off between benefits and harms and incorporates any risk/uncertainty.

- For BiV pacing, the overall GRADE and strength of the recommendation is moderate: the quality of the evidence is moderate/high (because of some uncertainty due to methodological limitations in the study design, e.g., no blinding), but there is also some risk/uncertainty in terms of the estimated prevalence and wide cost-effectiveness estimates (Table 5).
- For the combination BiV pacing/ICD, the overall GRADE and strength of the recommendation is weak—the quality of the evidence is low (because of uncertainty due to methodological limitations in the study design), but there is also some risk/uncertainty in terms of the estimated prevalence, high cost, and high budget impact (Table 5). There are indirect, low-quality comparisons of the effectiveness of BiV pacemakers compared with the combination BiV/ICD devices.

A stronger recommendation can be made for BiV pacing only compared with the combination BiV/ICD device for patients with an EF less than or equal to 0.35, and a QRS interval over or equal to 120 ms, and NYHA III/IV symptoms, and refractory to optimal medical therapy (Table 5).

- There is moderate/high-quality evidence that BiV pacemakers significantly improve mortality, QoL, and functional status.
- There is low-quality evidence that combined BiV/ICD devices significantly improve mortality, QoL, and functional status.

- To date, there are no *direct* comparisons of the effectiveness of BiV pacemakers compared with the combined BiV/ICD devices in terms of mortality, QoL, and functional status.

Table 5: Overall GRADE and Strength of Recommendation

	Quality	Estimated Prevalence, Ontario	NNT* Death (Any Cause)	Cost-Effectiveness	Cost in Ontario \$(Millions)	Overall Grade & Strength of Recommendation (Including Uncertainty)
BiV* Pacing	Moderate/high	~2,560	7	\$7,000 to \$59,000 / QALY*	38–46 ~14–16/year over 4 years	Moderate
BiV Pacing/ICD*	Low Major study limitations	~2,560	14	? Low quality data	74–82 ~27–29/year over 4 years	Weak

*BiV refers to biventricular; ICD, implantable cardioverter defibrillator; NNT, number needed to treat.

Issue

In 2002 (before the establishment of the Ontario Health Technology Advisory Committee), the Medical Advisory Secretariat conducted a health technology policy assessment on biventricular (BiV) pacing, also called cardiac resynchronization therapy (CRT). The goal of treatment with BiV pacing is to improve cardiac output for people in heart failure (HF) with conduction defect on ECG (wide QRS interval) by synchronizing ventricular contraction. The Medical Advisory Secretariat concluded that there was evidence of short (6 months) and longer-term (12 months) effectiveness in terms of cardiac function and quality of life (QoL). More recently a hospital submitted an application to the Ontario Health Technology Advisory Committee to review CRT, and the Medical Advisory Secretariat subsequently updated its health technology assessment.

Background

Clinical Need and Target Population

Chronic HF results from any structural or functional cardiac disorder that impairs the ability of the heart to act as a pump. It is estimated that 1% to 5% of the general population (all ages) in Europe have chronic HF. (1;2) About one-half of the patients with HF are women and about 40% of men and 60% of women with this condition are aged over 75 years.

The incidence (i.e., the number of new cases within a specific period) of chronic HF is age dependent: from 1 to 5 per 1,000 people each year in the total population, to as high as 30 to 40 per 1,000 population each year in people aged 75 years and older. Hence, in an aging society, the prevalence (i.e., the total number of cases of a disease or condition at a specified time) of HF is increasing, despite a reduction in cardiovascular mortality. The Framingham heart study (13) reported that in the 1980s, the annual age-adjusted incidence of HF among people aged over 45 years old was 7.2 per 1,000 for men and 4.7 per 1,000 for women. The age-adjusted prevalence of overt HF was 24 per 1,000 in men and 25 per 1,000 in women, and the 5-year survival rate from the time of diagnosis was less than 40%. Levy et al. (14) examined the long-term trends in the incidence and survival with HF among subjects in the Framingham study. Cases of HF were classified according to the date of onset: 1950 through 1969 (223 cases), 1970 through 1979 (222 cases), 1980 through 1989 (307 cases), and 1990 through 1999 (323 cases). The age-adjusted rates of HF were higher among men than among women in all four time periods. As compared with the rate in the period from 1950 through 1969, there was no significant change in the age-adjusted incidence of HF among men in the 3 subsequent periods. Among women however, the incidence of HF declined by 31% to 40% in the decades following the first time period. Age-adjusted survival rates after onset of HF improved over time. The overall trend across time was a decline in the risk of death of 12% per decade ($P = .01$ for men, and $P = .02$ for women).

A recent study (3) revealed 28,702 patients were hospitalized for HF for the first time in Ontario between April 1994 and March 1997. Fifty-one percent were women. Eighty-five percent were aged 65 years or older, and 58% were aged 75 years or older.

Patients with chronic HF have shortness of breath, limited capacity for exercise, high rates of hospitalization and rehospitalization, and die prematurely. (4) The New York Heart Association (NYHA) has a commonly used functional classification for the severity of HF (5):

- Class I: No limitation of physical activity. No symptoms with ordinary exertion.
- Class II: Slight limitations of physical activity. Ordinary activity causes symptoms.

- Class III: Marked limitation of physical activity. Less than ordinary activity causes symptoms. Asymptomatic at rest.
- Class IV: Inability to carry out any physical activity without discomfort. Symptoms at rest.

The National Heart, Lung, and Blood Institute (5) estimates that 35% of patients with HF are in functional NYHA class I, 35% are in class II, 25% are in class III, and 5% are in class IV. Surveys (2) suggest that from 5% to 15% of patients with HF have persisting severe symptoms and that the remainder of patients with HF is evenly divided between those with mild and moderately severe symptoms.

Overall, patients with chronic, stable HF have an annual mortality of about 10%. (2) One-third of patients with new-onset HF will die within 6 months of diagnosis. These patients do not survive to enter the pool of people with “chronic” HF. About 60% of patients with incident HF will die within 3 years, and there is limited evidence that the overall prognosis has improved in the last 15 years.

To date, the diagnosis and management of chronic HF has concentrated on patients with the clinical syndrome of HF accompanied by severe left ventricular (LV) systolic dysfunction. Major changes in treatment have resulted from a better understanding of the pathophysiology of HF and the results of large clinical trials. Treatment for chronic HF includes lifestyle management, drugs, cardiac surgery, or implantable pacemakers and defibrillators. Despite pharmacologic advances, which include diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, spironolactone, and digoxin, many patients remain symptomatic on maximally tolerated doses. (4)

Owing to the limitations of drug therapy, cardiac transplantation and device therapies have been used to try to improve QoL and survival of patients with chronic HF further. Biventricular pacing is an emerging treatment option for patients with severe HF that does not respond to medical therapy. Traditionally, indications for pacing include bradyarrhythmia, sick sinus syndrome, atrioventricular block, and other indications including combined sick sinus syndrome with atrioventricular block and neurocardiogenic syncope.

More recently, it has also been advocated for conditions such as hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy, long QT syndrome, and after cardiac transplantation. Recently, BiV pacing as a new adjuvant therapy for patients with chronic HF and mechanical dyssynchrony has been investigated. Ventricular dysfunction is a sign of HF, and if associated with severe intraventricular conduction delay, can cause dyssynchronous ventricular contractions resulting in decreased ventricular filling. The therapeutic intent is to activate both ventricles simultaneously, thereby improving the mechanical efficiency of the ventricles.

About 30% of patients with chronic HF have intraventricular conduction defects. (6) These conduction abnormalities progress over time and lead to discoordinated contraction of an already hemodynamically compromised ventricle. Intraventricular conduction delay has been associated with clinical instability and an increased risk of death in patients with HF. (7) Hence, BiV pacing, which involves pacing left and right ventricles, simultaneously may provide a more coordinated pattern of ventricular contraction and potentially reduces QRS duration and intraventricular and interventricular asynchrony. People with advanced chronic HF, a wide QRS complex, low left ventricular ejection fraction (LVEF), and contraction dyssynchrony in viable myocardium and normal sinus rhythm are the target patient group for BiV pacing. One-half of all deaths in HF patients are sudden, and the mode of death is arrhythmic in most cases. Internal cardioverter defibrillators (ICD) combined with BiV pacemakers are therefore being increasingly considered for patients with HF who are at high risk of sudden death.

Farwell et al. (5) examined how many people might benefit from BiV pacing through a retrospective review of all patients with a diagnosis of HF admitted to a large hospital in the United Kingdom. All

patients who were classified with a diagnosis of HF between October 1, 1997 and September 30, 1998 were audited. Inclusion criteria to assess the benefit of BiV pacing consisted of the following: NYHA class III or IV; QRS greater than or equal to 120 ms or bundle branch block pattern; and HF due to a dilated cardiomyopathy. Exclusion criteria were second- or third-degree heart block, HF primarily due to valvular dysfunction, HF due to an acute myocarditis, poorly controlled arrhythmias, and pacemaker in situ. Of 721 patients diagnosed with HF, 10% (n = 72) fulfilled the authors' criteria for BiV pacing.

Because previous studies suggested that patients with a variety of QRS durations might benefit from BiV pacing, Farwell et al. did a sub-analysis based on variations of the QRS interval. If a QRS duration of 150 ms was considered appropriate for pacing, then 19 patients would be eligible. If a QRS duration of 120 ms was acceptable, then 43 patients would be eligible.

Stelbrink et al. (15) retrospectively analyzed how many patients with an ICD indication might be candidates for left or BiV pacing as an adjunct therapy for chronic HF. Data were obtained from 384 patients with regard to NYHA HF class, mean QRS duration, mean PR interval, presence of a QRS duration greater than 120 ms, and incidence of atrial fibrillation at the time of ICD implantation. Twenty-eight (7.3%) patients fulfilled eligibility criteria for BiV pacing if NYHA class III patients were considered candidates, and 48 (12.5%) of patients with NYHA II and an EF less than or equal to 0.30 were included.

Current Implantation Technique for Cardiac Resynchronization

Conventional dual-chamber pacemakers have only 2 leads: 1 placed in the right atrium and the other in the right ventricle. The technique used for BiV pacemaker implantation also uses right atrial and ventricular pacing leads as well as LV lead advanced through the coronary sinus into a vein that runs along the ventricular free wall. This permits simultaneous pacing of both ventricles to allow resynchronization of the LV septum and free wall.

Mode of Operation

Permanent pacing systems consist of an implantable pulse generator that contains a battery and electronic circuitry, together with 1 (single-chamber pacemaker) or 2 (dual-chamber pacemaker) leads. Leads conduct intrinsic atrial or ventricular signals to the sensing circuitry and deliver the pulse generator charge to the myocardium.

Complications of Pacemaker Implantation

Complications are similar to those associated with standard pacemaker implantation, including pneumothorax, perforation of the great vessels or the myocardium, air embolus, infection, bleeding, and arrhythmias. Left ventricular pacing through the coronary sinus can also be associated with the rupture of the sinus as an additional complication.

Summary of the Medical Advisory Secretariat's 2003 Review

In 2003, the Medical Advisory Secretariat reviewed the effectiveness and cost-effectiveness of BiV pacemakers for patients with chronic HF (Appendix 2). The following is the summary of findings from the initial review of BiV pacemaker implantation.

- RCTs assessed chronic HF patients for up to 6 months. Other studies have been prospective, but nonrandomized, not double-blinded, uncontrolled or with a limited or uncalculated sample size. Short-term studies have focused on acute hemodynamic analyses. RCTs reported improved cardiac function

and improved QoL for up to 6 months after BiV pacing; therefore, there is level 1 evidence that patients in ventricular dyssynchrony who are still symptomatic after medication could benefit from this technology. Based on evidence made available to the Medical Advisory Secretariat by a manufacturer, (8) it appears that these 6-month improvements are now maintained at 12-month follow-up.

- Implantation procedure is more complex than either the implantation of traditional pacemakers or ICDs alone. These devices would need to be implanted in select centres to maintain adequate patient volume as well as further to refine the surgical technique as the technology evolves.
- To date, there is insufficient evidence to support the routine use of combined ICD/BiV devices in patients with chronic HF with prolonged QRS intervals.

Regulatory Status

The following BiV pacemakers are licensed by Health Canada as Class 4 devices.

Manufactured by Cardiac Pacemakers Inc., a wholly owned subsidiary of Guidant (St. Paul, Minnesota, United States):

- CONTAK CD congestive HF device (licence 17880)
- CONTAK TR congestive HF device (licence 20759)
- CONTAK RENEWAL 2 HF device (licence 37442)
- CONTAK RENEWAL TR CRT-P (licence 64466)
- CONTAK RENEWAL 4 CRT-D (licence 65260)

Manufactured by Medtronic Inc. (Minneapolis, Minnesota, United States):

- InSync Sentry (licence 65393)
- InSync III Marquis rapid read implantable cardioverter (licence 62649)
- InSync Marquis ICD model 7277 (licence 60560)
- InSync III atrial synchronous biventricular pacing device (licence 29732)

Manufactured by BIOTRONIK GmbH & CO (Berlin, Germany):

- Stratos LV and Stratos LV-T (licence 65053 [both])

Manufactured by St. Jude Medical, Cardiac Rhythm Management Division (Sylmar, California, United States):

- Frontier II implantable pulse generator (licence 69279)
- Atlas + HF (licence 36930)
- Epic + HF (licence 62788)

Updated Literature Review on Effectiveness

Objective

The aim of this literature review was to assess the effectiveness, safety, and cost-effectiveness of BiV pacing to treat patients with severe HF who are refractory to optimal drug therapy and who have ventricular dyssynchrony as defined by a long QRS interval.

Methods

Inclusion criteria

- English-language articles (September 2002–May 2005)
- Journal articles that reported primary data on the effectiveness or cost-effectiveness of BiV pacing obtained in a clinical setting, or analysis of primary data maintained in registries or databases
- Clearly described study design and methods
- Systematic reviews, RCTs, non-RCTs, and/or cohort studies that have more than 20 patients, cost-effectiveness studies

Exclusion criteria

- Studies that were duplicate publications (superseded by another publication by the same investigator group, with the same objective and data)
- Non-English-language articles
- Non-systematic reviews, letters, and editorials
- Animal and in vitro studies
- Case reports
- Studies that do not examine the outcomes of interest

Literature Search

- Cochrane database of systematic reviews
- ACP Journal Club
- DARE
- INAHTA
- EMBASE
- MEDLINE
- Reference section from reviews and extracted articles

Outcomes of Interest

- Mortality
- Improved NYHA class
- Improved LV function
- Adverse effects
- QoL
- Economics analysis data

GRADE Quality of Evidence and Strength of Recommendations

A modification of the GRADE (12) approach was used to make judgments systematically and explicitly about the quality of evidence and strength of recommendations. GRADE provides a framework for structured reflection and can help to ensure that appropriate judgments are made. GRADE takes into account study design, quality, consistency, and directness in judging the quality of evidence for each outcome. The balance between benefits and harms, quality of evidence, applicability, and the certainty of the baseline risks are considered in judgments about the strength of recommendations.

Results of Literature Search

The Cochrane and INAHTA databases yielded 2 health technology assessments on BiV pacing. A search of MEDLINE and EMBASE since the last review was conducted, and this search produced 3 RCTs that met the inclusion criteria. The quality of the included articles is presented in Table 1.

Table 1: Quality of Evidence

Study Design	Level of Evidence	Number of Eligible Studies
Large RCTs*, systematic reviews of RCTs	1	3
Large RCT unpublished but reported to an international scientific meeting	1(g)†	
Small RCT	2	
Small RCT unpublished but reported to an international scientific meeting	2(g)	
Nonrandomized study with contemporaneous controls	3a	
Nonrandomized study with historical controls	3b	
Nonrandomized study presented at international conference	3(g)	
Surveillance (database or register)	4a	
Case series (multisite)	4b	
Case series (single site)	4c	2
Retrospective review, modeling	4d	
Case series presented at international conference	4(g)	

*RCT indicates randomized controlled trial.

†g indicates grey literature.

Updated Summary of Findings: International Health Technology Assessments

Agency for Health Care Research and Quality (AHRQ), November 2004

The objectives of this AHRQ systematic review (16) were to determine the efficacy, safety, and cost-effectiveness of CRT in adults with symptomatic HF.

Studies were selected if they were RCTs (efficacy review) and/or prospective cohort studies (safety review) on patients with symptomatic HF and reduced LVEF that examined active CRT with medical therapy compared with medical therapy alone or nonactive/univentricular pacing

The following outcomes were of interest:

- Mortality
- HF hospitalizations
- 6-minute walk test
- Functional status
- QoL

Efficacy Results

Trials that were included in the systematic review were as follows:

- MIRACLE
- PATH CHF
- COMPANION
- MUSTIC
- CONTAK CD
- MIRACLE ICD
- MUSTIC AF
- RD CHF
- Garrigue et al.

In total, 3,574 patients were enrolled in these trials. Of these, 3,216 (90%) were randomized either to receive CRT (n = 2,063) or to be in a control group (n = 1,153). Most of those who were enrolled but not randomized had failed implant attempts. About 75% were considered NYHA class III (range, 55%–100%) and 10% NYHA class IV (range, 6%–33%). Two trials (CONTAK CD and MIRACLE ICD) included NYHA class II (range, 10%–38%).

In the 3 trials that evaluated CRT with ICDs, most patients' conditions were ischemic (~59%); in the other trials, ischemic etiology ranged from 37% to 55%. Other comorbidities such as diabetes mellitus, renal failure, previous cardiac history, or a history of sudden cardiac death (SCD) were reported in only 1 trial (MIRACLE ICD).

All trials (except PATH CHF) were limited to patients with an EF lower than 0.35 or 0.40. The mean LVEFs were similar in all trials and ranged from 0.21 to 0.30.

QRS width was a criterion for all trials including cut-offs from more than or equal to 120 ms, 130 ms, 140 ms, 150 ms, 180 ms, and 1 trial with 200 ms. Six of the 9 trials had a mean QRS between 159 ms and 175 ms, with the MUSTIC AF trial having a mean QRS of 209 ms.

Five trials were restricted to patients with normal sinus rhythm, but 2 trials were restricted to patients with atrial fibrillation. Overall, about 5% of randomized patients included in the meta-analysis had atrial fibrillation. It is unclear why the atrial fibrillation studies were combined with the sinus rhythm studies.

In the 3 trials where ICDs were tested along with CRT, there was a general requirement that study patients meet indications for ICD placement. Although it was not specified by which ICD criteria patients were evaluated, the indications in MIRACLE ICD and CONTAKCD were consistent with the AHA/ACC/NASPE guidelines for *secondary* prevention. COMPANION indications for ICD treatment were for *primary* prevention.

Nine RCTs were identified (N = 3,216; 85% with NYHA class III or IV HF, and 100% with prolonged QRS duration).

All-Cause Mortality

All-cause mortality was reduced by 25% (relative risk [RR], 0.75; 95% CI, 0.60–0.93), number needed to treat [NNT], 27. The all-cause mortality rate for the patients in the control group with symptomatic HF (NYHA class II–IV) was 14.9%. There was no significant statistical heterogeneity between trials ($P = .88$, $I^2 = 0\%$). The results were identical when the analysis was restricted to patients with NYHA class III or IV symptoms (RR, 0.76; 95% CI, 0.60–0.95). All-cause mortality was reduced mainly due to 40% fewer progressive HF deaths (RR, 0.60; 95% CI, 0.36–1.01).

Time-to-Death Analysis

Trials with longer follow-up periods reported greater survival benefits. When data were used for trials with a follow-up of more than 6 months, all-cause mortality remained significant with a relative risk of 0.70 (95% CI, 0.56–0.89). The 12-month survival rate for the CRT group was 89% (95% CI, 87%–90%). For the non-CRT group, it was 83% (95% CI, 79%–86%). This difference was significant based on the log rank test ($P = .005$).

The risk of death was reduced 41% after the first 3 months (hazard ratio, 0.59; 95% CI, 0.43–0.81).

Cardiac Mortality

Seven trials reported progressive HF mortality in NYHA class II to IV patients ($n = 60$ deaths; 1,647 patients). The relative risk favoured CRT, but was not statistically significant using a random effects model (RR, 0.60; 95% CI, 0.36–1.01). Restricting the analysis to patients with NYHA class III or IV symptoms produced similar results (RR, 0.58; 95% CI, 0.32–1.06).

Sudden Cardiac Death

No significant differences were seen in sudden cardiac deaths.

Pooled data from the 8 trials that reported the cause of death indicated that SCD ($n = 28$; 1,691 patients) was not significantly higher when patients were treated with CRT compared with controls (RR, 1.99; 95% CI, 0.95–4.16). This result was not statistically significant for heterogeneity ($P = .98$; $I^2 = 0\%$) and was similar if only trials longer than 6 months were included, or if only patients with NYHA class III or IV were included (RR, 1.89; 95% CI, 0.76–4.70).

Only 1 trial that included an ICD for all patients reported the cause of death; the risk for SCD was not significant (RR, 1.89; 95% CI, 0.35–10.21).

Noncardiac Death

No significant differences were seen in noncardiac deaths.

Pooled data from 6 trials ($n = 17$; 1,194 patients) did not demonstrate any significant differences in noncardiac deaths between patients with CRT compared with controls (RR, 0.90; 95% CI, 0.35–2.35). This result was not statistically significant for heterogeneity ($P = .46$; $I^2 = 0\%$). Restricting the analysis to patients in NYHA class III or IV HF did not alter this conclusion.

Heart Failure Hospitalizations

HF hospitalizations decreased by 32% (RR, 0.68; 95% CI, 0.41–1.12) in favour of CRT compared with those in the controls. The result was statistically significant for heterogeneity ($P = .01$; $I^2 = 65\%$), but was not significant in the fixed effects analysis (RR, 0.80; 95% CI, 0.64–1.00). Restricting the analysis to patients with NYHA class III/IV symptoms revealed significant reductions (RR, 0.65; 95% CI, 0.48–0.88), NNT = 12 and was not statistically heterogeneous ($P = .31$; $I^2 = 16\%$).

Six-Minute Walk Test

Patients' test scores on the 6-minute walk test distance improved (WMD, 23 metres (m); 95% CI, 9–38 metres) in favour of CRT. This improvement was similar in those patients with NYHA class III or IV symptoms (WMD 26 m; 95% CI, 11–41 m). However, these data were heterogeneous ($P = .06$; $I^2 = 50\%$),

in part due to one trial in which the control group's walk test scores worsened by 24 m; the control groups in all other trials that reported baseline results showed an improvement.

NYHA Class

Data from 3 studies were pooled for NYHA class and showed improvements in NYHA class in 57% of CRT patients and 34% of controls (CRT was associated with a 4.63 times increased chance of improving at least 1 NYHA class (95% CI, 1.05–2.52). This result was statistically significant for heterogeneity ($P = .04$; $I^2 = 70\%$). In patients with NYHA class III or IV symptoms, the RR improved to 1.68 (95% CI, 1.25–2.27). The data from the MIRACLE ICD were not reported in a format that permitted pooling with the other 3 trials; however, the baseline median NYHA class for both groups was III, and the endpoint median was II in the CRT group and III in the control group. This significant difference ($P = .01$) favoured CRT.

In contrast, the authors of PATH CHF (not included because data were not amenable for extraction) did not find a significant difference ($P = 0.36$) between treatment and control groups, although both groups showed significant improvement from baseline.

Quality of Life

QoL was measured by the Minnesota Living with Heart Failure Instrument for 6 of the 8 trials; pooled results showed a significant improvement in favour of CRT (WMD reduction of 5.5 points; 95% CI, 2–9 points on the Minnesota Living with Heart Failure Questionnaire). This result was statistically significant for heterogeneity ($P = .008$; $I^2 = 68\%$); however, the authors stated the results were consistent in direction.

When the analysis was restricted to only those patients with NYHA class III and IV, the difference was increased between the CRT and control groups (WMD -6.4 points; 95% CI, -9.4 to -3.4), but the results remained significantly heterogeneous ($P = .07$; $I^2 = 50\%$).

The differences are clinically significant, because the minimal clinically important difference for the Minnesota Living with Heart Failure Questionnaire has been established to be 5 points.

The use of a different scale prevented pooling with the other trials.

Sensitivity Analysis

The Agency for Healthcare Research and Quality (AHRQ) (16) stated that many a priori subgroup and sensitivity analyses could not be performed owing to the paucity of subgroup data in the trial reports and their inability to obtain individual-patient-level data from each of the trials listed despite requests.

CRT/ICD versus CRT alone

Post hoc, AHRQ examined the impact of ICDs on the efficacy of CRT using meta-regression. When the data were pooled for all-cause mortality from the 2 trials that included an ICD in both the experimental and control arms (i.e., CRT + ICD versus medical therapy + ICD), the RR was 0.84 (95% CI, 0.54–1.28). Pooled data from the other 5 trials comparing CRT with medical therapy yielded a RR of 0.78 (95% CI, 0.56–1.08) with CRT. The difference was not statistically significant ($P = .80$), supporting the assertion that the benefits of CRT on all-cause mortality are not appreciably altered by the addition of an ICD. Using the same meta-regression model, secondary outcomes (including HF hospitalizations, 6-minute walk tests, QoL, and NYHA functional class improvements) were not significantly different in patients with or without an ICD in addition to their BiV pacemaker.

The data from COMPANION could not be used in the meta-regression for ICDs, because none of the arms in COMPANION consisted of ICD alone. The COMPANION data provided the only comparison between CRT plus ICD treatment and CRT treatment alone. AHRQ stated that the analysis did approach statistical significance ($P = .07$) in favour of the CRT/ICD group for all-cause mortality. However, the reductions in HF hospitalizations were similar in CRT-treated patients with or without ICDs. AHRQ stated that until detailed data from the COMPANION subanalyses were made available, the most conservative conclusion that can be made at this stage is that the benefits of CRT are similar with or without ICDs. Of note, COMPANION did not provide statistical analyses for the direct comparison between CRT and ICD treatment and CRT treatment alone, nor was the study designed to make this direct comparison.

Impact of drugs on mortality

Post-hoc, AHRQ examined the relationship between the baseline use of beta-blockers and/or digoxin with the impact of CRT on all-cause mortality. Neither meta-regression was statistically significant ($P = .37$ and $P = .31$, respectively), suggesting that the benefits of CRT are not modified by the use of these drugs. “However, as expected, the linear trends showed improved survival with greater use of beta-blockers.” (16)

Safety Results

AHRQ reviewed 17 studies to examine the safety of CRT.

Peri-implantation risks

Ten studies reported data on deaths of patients during implantation of a BiV pacemaker. There were 13 deaths in 3,113 patients (pooled risk, 0.4%; 95% CI, 0.2%–0.7%). A sensitivity analysis, which assumed that any studies that did not report mortality had zero occurrences, yielded the same estimate.

Immediate deterioration in heart function was noted after 1.3% (95% CI, 0.7%–2.2%) of implantation procedures.

Implants of devices were successful in 89.9% (95% CI, 8.8%–90.9%) of attempts in 3,475 patients from 17 studies; this rate did not vary, but trended toward improvement by year of publication.

Problems with implantation of the LV lead were encountered in 6.0% (95% CI, 4.7%–7.2%) of cases. The assumption of the sensitivity analysis that any studies failing to report any implantation problems had zero occurrences led to a reduced estimate of 3.9% (95% CI, 3.1%–4.8%). The device or battery was problematic in 0.9% (95% CI, 0.6%–1.6%) of cases (0.7%; 95% CI, 0.4%–1.2% with sensitivity analysis). The procedure or equipment used for the procedure was reported to be a problem in 6.4% (95% CI, 5.3%–7.6%) of cases attempted (reduced to 5.6%; 95% CI, 4.7%–6.7% in the sensitivity analysis). Additional information on the type of equipment failure was not uniformly available, so pooling of results was not possible. Some specific problems in this category were lead fracture, loss of capture, inappropriate sensing, and extra cardiac stimulation.

Postimplantation risks

Data from 13 studies were used to assess postimplantation risks with CRT.

Over a median of 6 months follow-up, mechanical malfunction of the CRT device was noted in 6.7% (95% CI, 5.4%–8.2%) of successful implants. On sensitivity analysis, assuming any studies that failed to report this outcome had zero occurrences, this rate fell to 4.4% (95% CI, 3.6%–5.4%). Lead dislodgment

occurred in 8.5% of patients (95% CI, 7.4%–9.9%). There were no differences with the studies that used specially designed LV leads. (This estimate was reduced to 8.3% [95% CI, 7.1%–9.6%] on sensitivity analysis).

Postimplantation infection, most commonly in the device pocket, occurred in 1.4% of patients (95% CI, 0.8%–2.3%). (This was reduced to 0.9% [95% CI, 0.5%–1.4%] with sensitivity analysis).

Arrhythmias attributed to the CRT device occurred in 1.7% (range, 0.8%–3.4%) of patients during follow-up.

Decision Analysis

Using the results from the systematic review, AHRQ calculated annual event rates (median follow-up time was 22.8 weeks in the trials).

Effectiveness of CRT

- Annual event rates were calculated for patients with NYHA class III HF randomized to CRT.
- RR was as follows: all-cause death, 0.75 (95% CI, 0.60–0.93); HF hospitalizations, 0.68 (95% CI, 0.41–1.12).

Cost-effectiveness of CRT (All costs are in American currency.)

- For patients with NYHA class III HF, medical therapy had a median of 2.68 (interquartile range, [IQR] 2.49, 2.85) discounted quality adjusted life years (QALYs) and a median of \$34,700 (IQR, \$31,100–\$38,100) lifetime costs.
- CRT had a median of 3.03 (IQR, 2.82–3.27) discounted QALYs and a median of \$67,600 (IQR, \$62,000–\$73,800) lifetime costs.
- CRT was associated with an incremental cost of a median of \$90,700 (IQR, \$69,500–\$124,900) per additional QALY.
- Data points from the Monte Carlo simulation indicated that compared with medical therapy CRT is consistently associated with a survival gain and an additional cost.
- The cost-effectiveness acceptability curve illustrates that the probability that CRT is cost-effective relative to medical therapy alone is less than 59%, given a maximum willingness to pay for a QALY of \$100,000.

Limitations of the decision analysis

- There is a large degree of uncertainty in the incremental costs per QALY.
 - The results were sensitive to the value of several key variables including the effectiveness of CRT, the probability of cardiovascular death without pacing, and the incidence of device-related adverse effects.
- Results of the analysis should be interpreted with caution.
 - If CRT is as effective and inexpensive as shown in this study, it might be good value for money.
 - The challenge is to ensure CRT is used in patients who meet these trials' inclusion criteria and that CRT devices are inserted by experienced providers who have low complication rates.
 - Uncertainty about the benefits beyond 1 year needs to be acknowledged, and there is insufficient long-term effectiveness and cost data to warrant broad implementation of CRT at this time.
- CRT had a different pooled effect on all-cause mortality compared with that of cardiac mortality.

- The results may reflect the difference in duration of the follow-up period, given that the former analysis was based on longer-term follow-up than was the latter one. Alternatively, the analysis of cardiac death is susceptible to bias because it is difficult to assign cause of death in cardiovascular trials.
 - The use of CRT/ICD might not necessarily decrease mortality. Because patients with HF experience lethal bradyarrhythmia and tachyarrhythmias, a large Canadian RCT is evaluating the effect of devices with ICD and BiV pacing capability.
- The incidence of complications associated with CRT might decrease over time, whereas the AHRQ analysis assumed that they were constant. Long-term follow-up of patients is required.
 - It is unlikely that the relative benefit of CRT will be constant as the severity of HF increases.
 - The model did not consider short or long-term benefits and costs of selected surgical interventions for patients with HF (e.g., cardiac transplantation and ventricular assist devices).

AHRQ Conclusions (16)

Efficacy and Safety

- There is a 24% relative reduction in all-cause mortality (largely driven by a 40% relative reduction in progressive HF deaths) and a 35% relative reduction in HF hospitalizations with CRT in patients with reduced EF, NYHA class III or IV symptoms (despite currently accepted medical management using ACE inhibitors, beta-blockers and in many cases digoxin and or spironolactone) and a prolonged QRS duration on ECG.
 - Successful implantation of CRT in 24 such patients would prevent 1 death and 2 HF hospitalizations.
- There was a statistically and clinically significant improvement in QoL and functional outcome for patients receiving CRT.
- Up to 10% of HF patients have reduced EF, NYHA class III or IV symptoms, and a prolonged QRS duration. One-half of them would also have indications for an ICD. Therefore, AHRQ estimated that about 250,000 Americans might be eligible for a BiV pacemaker and another 250,000 might be eligible for a combined BiV/ICD device.
- Although preliminary data suggest similar benefits (but lower absolute benefits) for patients with NYHA class II symptoms, the role of CRT in lower-risk HF patients with prolonged QRS duration is untested. Further data are required before extending the device indications beyond those authorized by the United States Food and Drug Association (FDA) (NYHA class III or IV).
- The role of CRT in patients with either indications for conventional pacemakers or atrial fibrillation is unknown at this time.
- CRT appears to be safe; however, there is a 10% failure rate for implantation, and another 9% of patients might require the system to be partially or fully changed within 6 months due to malfunctions or lead displacements.
- There are few data for the efficacy and complications rates beyond 1 year.
- None of the trials reported admission rates for CRT revisions; it is possible that much of the benefit in reduced HF hospitalization may be offset by such admissions.
- An issue that remains to be resolved by ongoing studies (and was beyond the scope of the AHRQ review) is the role of ICDs for primary prevention in patients with HF.
- In an analytical framework for treatment options for patients with HF, the following criteria are provided to determine if a CRT candidate is also a candidate for an ICD:
 - Primary prevention:
 - QRS > 0.2
 - Class III

- EF < 0.30
- > 3.5 months after myocardial infarction/revascularization
- Secondary prevention:
 - History of SCD/ventricular tachycardia (VT)/ventricular fibrillation (VF)
 - Inducible VT/VF

Cost-Effectiveness

- Long-term cost-effectiveness is unknown at present. However, the analyses demonstrated that the incremental cost-effectiveness ratio of CRT is similar to that of other interventions, but has wide uncertainty and is sensitive to multiple inputs.
- There is insufficient long-term effectiveness and cost data to determine whether CRT is sufficient value for money to warrant its broad implementation at this time.
 - CRT should be reserved for select HF patients with advanced disease (NYHA class III or IV despite optimal medical therapy, reduced EF, and prolonged QRS duration) and should be implanted only by clinicians competent in the technique. Treatment should include close follow-up for complications.

Limitations to the AHRQ Review

- Randomization occurred after implantation of the device in all but 1 of the trials. This affects the generalizability of the results, because patients who could not tolerate the procedure or in whom implantation was unsuccessful were not included.
- Selected patients and experienced providers participated in the trials. This affects the generalizability of the results.
- Two of the trials that were incorporated into the review were available directly from the FDA and represent over 1,000 patients. One of the trials (N = 227) did not find any differences in survival or hospitalization (but did find “positive” effects on functional outcomes and QoL scores) and remains unpublished more than 2 years since the final data were presented. (CONTAK CD was presented in May 2001 at the North American Society for Pacing and Electrophysiology 2001.) Exclusion of this trial exaggerates the benefit of CRT on all-cause mortality.

Technology Assessment Unit at the McGill University Health Centre, January 2004

The Technology Assessment Unit (TAU) (17) at McGill University Health Centre (MUHC) stated that no study has shown improved survival with isolated BiV pacing or BiV pacing combined with an ICD when compared with the use of BiV pacing alone.

According to TAU, the cost of implantation of the CRT-ICD at MUHC is \$34,677 (Cdn) per patient compared with \$24,704 (Cdn) for an ICD alone. Specifically, in terms of opportunity costs, given the fixed budget of the cardiology department at MUHC, there will be a budget reduction corresponding to about 1 fewer ICDs being available. If there were 6 combined BiV pacemaker/ICD implantations over the next 12 months at MUHC, the additional \$60,000 (Cdn) would likely have to be offset by the installation of 3 fewer ICD devices.

TAU at MUHC made the following recommendation:

“Based on the 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 benefit of this

therapy, and the considerable opportunity costs, the TAU does not recommend routine use of biventricular pacemakers with ICD at the MUHC. (17)

TAU encourages the active participation of the MUHC in the CIHR funded trial that is further examining this technology. At present, TAU does not expect annually that more than a maximum of 5 or 6 exceptional cases would require BiV pacing outside the context of the funded research trial.” (17)

Limitations to the TAU review include the following:

- There is a lack of critical analysis of the included studies, most notably the COMPANION trial.
- There is a lack of any critical analysis of ICD criteria for primary prevention. TAU stated, “As patients qualifying for a BiV also qualify for an ICD (MADIT 2 criteria), it appears illogical to implant a BiV alone as this would address only QoL without addressing potential length of life.”
- Before the COMPANION trial, all the trials that examined the combined BiV/ICD device had patients with conventional ICD indications (1998 ACC/AHA Guidelines), including secondary prevention.

Updated Summary of Findings: Studies Published After the AHRQ Health Technology Review

Cardiac Resynchronization – Heart Failure Trial (Biventricular Pacing Only)

The CARE HF trial (10) was a level 1 multicentre, international RCT (N = 813) that evaluated the effectiveness of standard drug therapy compared with a combination of standard drug therapy plus BiV pacing without a defibrillator on morbidity and mortality of patients with HF.

Inclusion criteria

- NYHA class III or IV HF
- LVEF < 0.35
- QRS interval > 120 ms

Exclusion criteria

- Major cardiac event in the previous 6 weeks
- Conventional indications for a pacemaker or ICD
- HF requiring continuous intravenous therapy
- Atrial arrhythmias

Patients were evaluated at 1, 3, 6, 9, 12, and 18 months and every 6 months thereafter. The protocol required follow-up to continue for 18 months after the last patient had been enrolled.

The primary endpoint was a composite of death from any cause or an unplanned hospitalization for a major cardiovascular event. Secondary outcomes were death from any cause, composite of death from any cause, and unplanned hospitalization with HF, and, at 90 days post-treatment, the patients’ NYHA class, and QoL.

The mean duration of follow-up was 29.4 months (range, 18.0–44.7 months).

Results

By the end of the study, the primary endpoint had been reached in 159 patients in the BiV group, compared with 224 patients who received medical therapy alone (39% vs. 55%; hazard ratio, 0.63; 95% CI, 0.51–0.77; $P < .001$).

In the BiV group, 82 patients had died, compared with 120 patients who had been assigned to pharmacotherapy alone (20% vs. 30%; hazard ratio, 0.64; 95% CI, 0.48–0.85, $P < .002$). The mode of death was classified as sudden in 38 (32%) of 120 patients who died in the medical therapy group and in 29 (35%) of 82 patients who died in the CRT group.

Adverse Events

There was 1 device-related death in each group: 1 patient in the BiV group died of HF aggravated by lead displacement, and 1 patient in the medical therapy group died of septicemia after receiving a device.

The most common adverse device or procedure-related events in the BiV group were as follows:

- Lead displacement (24 patients)
- Coronary sinus dissection (10 patients)
- Pocket erosion (8 patients)
- Pneumothorax (6 patients)
- Device-related infection (3 patients)

Worsening HF was more common in the medical therapy group (affecting 263 patients compared with 191 patients in the BiV group, $P < .001$).

Cleland (11) presented updated results from the CARE-HF trial at the September 7, 2005 meeting of the European Society of Cardiology. The primary outcome of the extension phase was all-cause mortality from the time of randomization to completion of the extension phase. Analysis was conducted using the intention-to-treat principle.

The mean follow-up was 36.4 months (range, 26.1–52.6 months). There were 154 deaths (38.1%) in 404 patients assigned to medical therapy and 101 deaths (24.7%) in 409 patients assigned to BiV; hazard ratio 0.60 (95% CI, 0.47–0.77, $P < .0001$). Reductions in the risk of death due to HF (hazard ratio, 0.55 [95% CI, 0.37–0.82]; $P = .003$) and sudden death (hazard ratio, 0.54 [95% CI, 0.35–0.84], $P = .006$) were observed.

Tables 7 to 9 summarize the results of CARE-HF. Overall, BiV pacing significantly improved mortality, QoL, EF, and NYHA class.

Table 2: CARE-HF Results: Primary and Secondary Endpoints*

Outcome	Medical Therapy Alone (N = 404)	Medical Therapy + BiV† Pacing (N = 409)	Hazard ratio (95% CI)	P	NNT†
	No. (%) of Patients	No. (%) of Patients			
Primary Endpoint (Combined)					

Death (any cause) or unplanned hospitalization for major cardiovascular event.	224 (55)	159 (39)	0.63 (0.51–0.77)	< .001	6
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Secondary Endpoint					
Death (any cause) at 29 months	120 (30)	82 (20)	0.64 (0.48–0.85)	< .002	10
Death at 36 months – grey literature (11)	154 (38)	101 (25)	0.60 (0.47–0.77)	< .0001	7
Death from any cause or unplanned hospitalization with worsening HF	191 (47)	118 (29)	0.54 (0.43–0.68)	< .001	6

†BiV refers to biventricular; NNT, number needed to treat.

*Cleland JGF, Daubert J, Erdmann E, Freemantle N, Gras D, Kappenberger L et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure (CARE-HF). *New England Journal of Medicine* 2005; 352:1539-1549; Copyright 2005 Massachusetts Medical Society. All rights reserved. (10)

Table 3: CARE H-F Results: New York Heart Association Class and Quality of Life*

Outcome	Medical Therapy Alone (n = 404)	Medical Therapy and BiV Pacing (n = 409)	Difference in Means (95% CI)	P
	Mean (SD) at 90 days	Mean (SD) at 90 days		
NYHA class	2.7 (0.9)	2.1 (1.0)	0.6 (0.4–0.7)	< .001
Minnesota Living With Heart Failure score†	40 (22)	31 (22)	-10 (-8 to -12)	< .001
EuroQoL EQ-5D score‡	0.63 (0.29)	0.70 (0.28)	0.08 (0.04–0.12)	< .001

†Minnesota Living with HF scores range from 0 to 105; higher scores reflect a poorer quality of life.

‡European Quality of Life 5-D scores range from -0.594 to 1.000; 1.000 indicates full health, and 0 indicates dead.

*Cleland JGF, Daubert J, Erdmann E, Freemantle N, Gras D, Kappenberger L et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure (CARE-HF). *New England Journal of Medicine* 2005; 352:1539-1549; Copyright 2005 Massachusetts Medical Society. All rights reserved. (10)

Table 4: CARE-HF Results: Hemodynamic Values*

Variable	Difference in Means at 3 Months† (95% CI)	P	Difference in Means at 18 Months (95% CI)	P
Heart rate (beats/min)	+1.1 (-1.2–3.4)	.33	+1.0 (-1.5–3.6)	.43
Systolic blood pressure (mm Hg)	+5.8 (3.5–8.2)	< .001	+6.3 (3.6–8.9)	< .001
Diastolic blood pressure (mm Hg)	+1.5 (0.1–2.9)	.03	+1.3 (-1.8–4.4)	.42
Interventricular mechanical delay (msec)	-21 (-25 to -18)	< .001	-21 (-25 to -17)	< .001
Left ventricular ejection fraction (%)	+3.7 (3.0–4.4)	< .001	+6.9 (5.6–8.1)	< .001
	~4% of patients had EF increase to ≥ 0.35		~20% of patients had EF increase to ≥ 0.35	

Left ventricular end-systolic volume index (mL/m ²)	-18.2 (-21.2 to -15.1)	< .001	-26.0 (-31.5 to -20.4)	< .001
Mitral regurgitation area (cm ²)	-5.1 (-7.3 to -2.8)	< .001	-4.2 (-7.0 to -1.4)	.003

† “+” sign indicates a greater value; “-“ sign, a smaller value in the CRT group than in the medical therapy group.

*Cleland JGF, Daubert J, Erdmann E, Freemantle N, Gras D, Kappenberger L et al. *The effect of cardiac resynchronization on morbidity and mortality in heart failure (CARE-HF)*. *New England Journal of Medicine* 2005; 352:1539-1549; Copyright 2005 Massachusetts Medical Society. All rights reserved. (10)

Comparison of Medical Therapy, Pacing and Defibrillation in HF Trial

The COMPANION trial (9) was a level 1 prospective, multicentre, RCT that randomized patients with moderate-to-severe HF 1:2:2 to optimal pharmacologic therapy (OPT), OPT plus CRT without defibrillation (CRT-P), or OPT plus CRT-P with defibrillation (CRT-D), respectively. A total of 1,638 patients were enrolled, and 1,520 patients (92.8%) were randomized to a treatment group.

The primary endpoint was all-cause mortality plus all-cause hospitalization. Secondary endpoints included total survival, cardiac morbidity, and change in maximal oxygen consumption from baseline to 6 months in an exercise substudy. The hypotheses compared outcomes for both CRT-D and CRT-P arms with the control (OPT) arm.

Inclusion criteria

- NYHA class III or IV HF resulting from either ischemic or non-ischemic cardiomyopathy
- LVEF \leq .035
- QRS \geq 120ms
- PR interval $>$ 150ms
- Sinus rhythm
- No clinical indication for a pacemaker or ICD
- Hospitalization for the treatment of HF or the equivalent in the preceding 12 months

After enrollment of 1,638 patients, the Data and Safety Monitoring Board recommended termination of further enrollment, based on the rationale that the sample ...

“...met the criteria specified in the protocol for success both for the primary endpoint of mortality and hospitalization combined and for mortality alone for CRT-D plus OPT as compared to OPT alone. In addition, the comparison of CRT-P plus OPT to OPT alone nearly crossed the boundary for statistical significance for the primary endpoint of mortality and hospitalization combined and was consistent but not significant for mortality alone.”(18)

The baseline characteristics of enrolled patients were analyzed by treatment group, and appeared to be well-matched overall. (18) The FDA analysis of the results indicated that there was a modestly higher percentage of NYHA class IV patients in the OPT cohort than in the CRT-D group. Because class IV patients had a 47.2% mortality rate during the trial, and class III patients had a 16.1% mortality rate, this baseline imbalance favoured the device arm. In addition, there was a higher percentage of ischemic patients in the OPT arm. Because ischemic patients had a 25.2% mortality rate during the trial, and nonischemic patients had a 15.0% mortality rate, this imbalance also favoured the device arm. The remainder of baseline characteristics appeared to be well matched.

Primary Efficacy Endpoint

The protocol defined the primary efficacy endpoint as "...a combination of all cause mortality and all cause hospitalization where all cause mortality is defined as death from all causes and all cause hospitalization is defined as admission to a hospital for any reason" (Table 5). (18) The protocol excluded the hospitalization associated with the investigational device implant and included emergency department visits or unscheduled office visits resulting in treatment with intravenous inotropic or vasoactive drugs for worsening HF.

However, during the trial, the definition of hospitalization was altered 3 times. These changes were not documented within a protocol revision, and the FDA was not told. The definition was first changed in March 2001 to include only hospitalizations longer than 24 hours. Then, the definition was changed in February 2002 to include only hospitalizations where the discharge date differed from the admission date. The third change was a requirement that the inotropic or vasoactive infusion last more than 4 hours. The timing of the third change was unknown to the FDA when they reviewed the results.

Although the protocol stated that "...the hospitalization associated with the investigational device implant..." would not be considered, this was expanded to include all subsequent additional hospitalizations for reimplantation attempts. (18) In addition, when patients had their implantation/reimplantation hospitalizations prolonged due to adverse events, these episodes were not included as a hospitalization. The FDA critique commented that it could be argued that such patients should have been included as having reached the primary endpoint, as they were no longer in the hospital to receive a device. (18)

The protocol assigned an alpha of .05 to 4 different endpoints. The trial sponsor justified this excessive alpha allocation by stating that they would "...be conservative in the interpretation of the multiple analyses, looking for consistency across variables." (18) No definition was provided for what would constitute consistency; therefore, there was no specific definition for what would constitute statistical success of the trial.

Table 5: COMPANION Results: Primary and Secondary Endpoints*

Endpoint (12-month rate)	Device	Absolute Benefit, %	Hazard ratio (95% CI)	P	NNT†
Primary (Combined) Endpoint					
Death or hospitalization, any cause	BiV†	12	0.81 (0.69–0.96)	.015	8
	BiV & ICD†	12	0.80 (0.68–0.95)	.010	8
Secondary Endpoint					
Death from <i>any</i> cause	BiV	4	0.76 (0.58–1.01)	.06	25
	BiV & ICD	7	0.64 (0.48–0.86)	.004	14
Death from or hospitalization for cardiovascular causes	BiV	15	0.75 (0.63–0.90)	.002	7
	BiV & ICD	16	0.72 (0.60–0.86)	< .001	6
Death from or hospitalization for HF	BiV	14	0.66 (0.53–0.87)	.002	7
	BiV & ICD	16	0.60 (0.49–0.75)	< .001	6

†BiV refers to biventricular pacemaker; ICD, implantable cardioverter defibrillator; NNT, number needed to treat.

*From Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *New England Journal of Medicine* 2004; 350(21):2140-2150 (9)

Withdrawals

There was a higher than anticipated dropout rate during the trial, particularly within the OPT arm. Before November 30, 2002, there were 80 withdrawals from the OPT arm and 39 from the CRT-D arm. In its explanation to the FDA, the sponsor attributed this imbalance as the desire of the OPT patients to receive commercially marketed CRT-P or CRT-D devices. Because neither investigators nor patients were blinded in this trial, the subsequent effect was a disproportionately high rate of withdrawal from the pharmacologic therapy group. (18) This change was particularly common among patients with ischemic cardiomyopathy for whom such treatment had become an option with the publication of MADIT II. Therefore, the sponsor attempted to obtain information on patients beyond the time at which they were withdrawn from the trial. (18)

Crossovers to a different therapy (e.g., switching patients from the OPT arm to CRT-P devices) without consulting the steering committee were considered class I deviations against the investigator. However, to avoid a class I deviation, investigators sometimes withdrew patients from the trial for the purpose of crossing over to a different therapy. However, this is not consistent to principles underlying an intent-to-treat analysis. Patients should have been withdrawn only if further participation was felt to compromise their welfare, they refused further participation, or participation was no longer possible. (18)

For the FDA review, only events from randomization to patient withdrawal, death, or November 30, 2002 (whichever came first) were included in the analysis. It was found that additional follow-up increased the overall mortality rate in the CRT-D arm from 15.8% (94/595) to 17.6% (105/595), and in the OPT arm from 21.1% (65/308) to 25.0% (77/308). This change favoured the device arm; however, the FDA stated that the difference was not expected to change the overall conclusions of this review with respect to mortality. However, issues regarding informed consent and type I error remain. (18)

Overall, dropouts and withdrawals were not clearly described in the COMPANION trial. (16)

Mortality

There was a 7.4% absolute reduction in all-cause mortality associated with CRT-D therapy in the COMPANION trial. Table 6 shows the mortality rates for the CRT-D, CRT-P, and OPT groups.

Table 6: Mortality Rates From: FDA Clinical Review*

	CRT-D† Number (%) N = 595	CRT-P† Number (%) N = 617	OPT† Number (%) N = 308
Total deaths	105 (17.6)	131 (21.2)	77 (25.0)
Cardiac deaths	76 (12.8)	109 (17.7)	58 (18.8)
Pump failure deaths	52 (8.7)	53 (8.6)	34 (11.0)
Sudden cardiac deaths	17 (2.9)	48 (7.8)	18 (5.8)
Ischemic deaths	4 (0.7)	2 (0.3)	4 (1.3)
Implant procedure deaths	2 (0.3)	6 (1.0)	0 (0.0)
Other cardiac procedure deaths	0 (0.0)	0 (0.0)	2 (0.6)
Hyperkalemic deaths	1 (0.2)	0 (0.0)	0 (0.0)
Deaths within 30 days of randomization	7 (1.2)	11 (1.8)	3 (1.0)

†CRT-D indicates cardiac resynchronization therapy with defibrillation; CRT-P, cardiac resynchronization therapy only; OPT, optimal pharmacologic therapy.

*From Food and Drug Administration. Clinical Review. COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure). PMA P030005. June 14, 2004. www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4063b1_07_P010012.S026%20FDA%20clinical%20%20review%20-%20Final.doc (Accessed June 2005) (18)

When mortality was adjusted for duration of observation, the adjustment improved the mortality results for the CRT-D and CRT-P cohorts relative to OPT, owing to the slightly longer periods of observation in these groups. However, the effect was modest and did not change any of the overall conclusions regarding the effect of CRT-D and CRT-P on mortality.

All-Cause Hospitalization

The total number of hospitalizations and the total amount of time spent in the hospital were not endpoints for this trial. Some consider that the index hospitalizations for the device implant procedures, as well as the additional hospitalizations following failed implant attempts, are not recurring events and should therefore be excluded for the purposes of calculation of the rate of “all-cause hospitalization.” (18)

Patients in the CRT-D group were followed-up on average for 1.29 years, and in the OPT group, for 1.01 years (considering only the follow-up that occurred up to the time of withdrawal). In addition, 122 of the original 903 CRT-D and OPT patients had 2 years of follow-up. No patient had 3 years of follow-up. The FDA clinical review stated that this should give some pause to the interpretation of annualized hospitalization rates based on the COMPANION trial, regardless if the implant procedures are included.

The FDA review conducted an analysis that included all hospitalizations (i.e., those for which there was a date change, including elective device hospitalizations, all index hospitalizations, all reimplant attempt hospitalizations, and all outpatient inotropic infusions for worsening HF). All events from randomization to patient withdrawal, death, or November 30, 2002 (whichever came first) were included (Table 7).

Within the CRT-D group, there were 1,548 hospitalizations (mean duration, 5.42 days [SD, 8.82 days]; median, 3.0 days). A total of 314 of these hospitalizations were attributed to HF. Within the OPT group, there were 507 hospitalizations (mean duration, 6.57 days [SD, 7.32 days]; median, 4.0 days). Of these, 216 were attributed to HF.

However, these results did not take into consideration the difference in overall duration of follow-up between the 2 groups. The mean all-cause hospitalization rate in the CRT-D cohort was 2.02 per year; in the OPT cohort, it was 1.62 hospitalizations per year. The mean days spent hospitalized for any cause in the CRT-D cohort was 11.0 days per year; in the OPT cohort, 10.7 days per year.

Table 7: Frequency of Hospitalizations by Cohort in COMPANION*

Number of Hospitalizations	CRT-D†, No. (%) (n = 595)	OPT†, No. (%) (n = 308)
1	199 (33.4)	71 (23.1)
2	160 (26.9)	43 (14.0)
3	96 (16.1)	26 (8.4)
4	56 (9.4)	20 (6.5)
5	37 (6.2)	15 (4.9)
6	19 (3.2)	4 (1.3)
>6	23 (3.9)	10 (3.2)

†CRT-D indicates cardiac resynchronization therapy with defibrillation; OPT, optimal pharmacological therapy.

*From Food and Drug Administration. Clinical Review. COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure). PMA P030005. June 14, 2004. www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4063b1_07_P010012.S026%20FDA%20clinical%20%20review%20-%20Final.doc (Accessed June 2005) (18)

Adverse Events

All adverse events through to November 30, 2002 were included and are presented in Table 8. For example, 202 patients experienced between 1 and 3 adverse events during the trial. A total of 562 of the 595 patients in the CRT-D arm experienced at least 1 adverse event, whereas 247 of 308 patients in the OPT arm experienced at least 1 adverse event.

Table 8: Number of Adverse Events in COMPANION*

Adverse Events, No.	CRT-D† (n = 595) No. (%)	OPT† (n = 308) No. (%)
1–3	202 (33.9)	118 (38.3)
4–6	150 (25.2)	63 (20.5)
7–9	100 (16.8)	32 (10.4)
>9	110 (18.5)	34 (11.0)
Total	562 (94.5)	247 (80.2)

†CRT-D indicates cardiac resynchronization therapy with defibrillation; OPT, optimal pharmacological therapy.

*From Food and Drug Administration. Clinical Review. COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure). PMA P030005. June 14, 2004. www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4063b1_07_P010012.S026%20FDA%20clinical%20%20review%20-%20Final.doc (Accessed June 2005) (18)

The manufacturer and FDA did not indicate in any analyses agreement letter whether the CRT-D and CRT-P data could be compared. The COMPANION protocol stated, “Descriptive statistics will be used to describe any similarity or difference between CONTAK TR and CONTAK CD.” (18) Therefore, the effectiveness of BiV pacing alone versus combined BiV pacing and defibrillation was not examined.

Additional Studies that Examined Cardiac Resynchronization Therapy

Higgins et al. (2003)

Higgins et al. (19) conducted a RCT to examine the safety and effectiveness of BiV pacemakers when combined with an ICD in patients with both symptomatic HF and ventricular tachyarrhythmias.

Inclusion criteria

- NYHA class II–IV
- $EF \leq 0.35$
- QRS interval ≥ 120 ms
- Conventional indications for implant of an ICD

Exclusion criteria

- Atrial tachyarrhythmias
- Conventional indications for a permanent pacemaker

Because of the need for ICD, investigators implanted the system first and then programmed the randomized therapy after a minimum 30-day period with no BiV (BiV, n = 245; no BiV [control group], n = 245) for up to 6 months. During this period, investigators were permitted to optimize pharmacologic therapy before initiating the randomized phase.

The primary endpoint was progression of HF, defined as all-cause mortality, hospitalization for HF, and VT/VF requiring device intervention. Secondary endpoints included peak oxygen consumption, 6-minute walk test, NYHA class, QoL score, and echocardiography analysis.

During the postimplantation recovery period, many patients showed significant symptomatic improvement with medical therapy. Of the 328 patients who presented in NYHA class III/IV, 131 (40%) improved to NYHA class I or II, whereas 30 (19%) of 162 NYHA class II patients worsened to NYHA class III/IV during this period. After investigators had the opportunity to optimize medical therapy, 227 patients were in NYHA class III/IV and 263 were in NYHA class I/II before the office visit in which the randomized therapy was initiated.

Progression of Heart Failure

- Of the 245 patients randomized to BiV, 79 events were observed, comprising 11 deaths, 32 patients with at least 1 HF hospitalization, and 36 patients with at least one VT/VF event.
- In the control group, there were 94 events, comprising 16 deaths, 39 patients with at least 1 HF hospitalization, and 39 patients with at least 1 VT/VF event.
- The overall relative reduction in composite HF progression of 15% with BiV was not statistically significant ($P = .35$).
 - No statistically significant reductions were found when stratified into NYHA class I/II (12% reduction) or NYHA class III/IV (22% reduction) (no P values provided).

Peak oxygen consumption, 6-minute walk test, QoL, and NYHA class

- In the total patient group, BiV improved peak oxygen consumption ($P = .03$) and the 6-minute walk test score ($P = .043$).
- Improvement in NYHA class was not statistically significant ($P = .10$).
- QoL improved more in those patients randomized to BiV than in patients randomized to the control group, but this change was not statistically different. ($P = .39$).
- Patients with NYHA class III/IV demonstrated statistically significant improvement in peak V_{O_2} ($P = .003$), the 6-minute walk test ($P = .029$), NYHA class ($P = .006$) and QoL ($P = .017$).
- Patients with NYHA class I/II showed no significant improvement in any of these parameters.

All-cause mortality

A total of 109 deaths were reported throughout the study:

- 47 (43%) pump failure
- 21 (19%) noncardiac
- 9 (8%) arrhythmic
- 2 (2%) ischemic
- 2 (2%) cardiac unknown
- 28 (26%) insufficient documentation

Limitations to the study by Higgins et al. (19) included the following:

- The study was not adequately powered to detect a statistically significant difference because the actual event rate observed was about half that expected in the original study design.
- The authors suggested that “the widespread adoption of HF medications such as β blockers and spironolactone after the publication of positive clinical trial results and an evolution in HF management that focused on increased outpatient surveillance may have contributed to the reduction

in expected events...This improvement in status made it more difficult to show benefit in healthier patients while reducing the statistical power to show improvement in those who remained in NYHA class III/IV despite optimizing HF medications.” (19)

- The study was for a short term (6 months).
- The study included patients with NYHA II HF.

Ermis et al. (2004)

Ermis et al. (20) prospectively examined mortality outcome in 126 consecutive patients with LV dysfunction and HF who received a BiV pacemaker alone (n = 64) or a BiV/ICD device (n = 62). A minimum 12 months follow-up was obtained in all surviving patients. Device selection was based on conventionally accepted indications at the time. Patients who did not meet conventional ICD indications at the time of referral received a BiV pacing system.

Among 158 patients initially referred for BiV devices, successful implants were obtained in 126 people. The mean follow-up period was 13.5 months (SD, 12.0 months; range, 0.5–60 months). All patients except those with previously documented ICD indications were screened for nonsustained asymptomatic ventricular arrhythmias by ambulatory ECG recording (24- or 48-hour Holter recordings), implantable loop recorders, or continuous full disclosure in hospital ECG monitoring. Patients who had nonsustained ventricular tachycardia with nonischemic cardiomyopathy or with ischemic heart disease but an EF over 0.30 and under 0.40 underwent electrophysiologic testing to assess susceptibility to inducible sustained tachyarrhythmia.

ICD indications were as follows:

- Sustained VT (n = 26)
- VF (n = 4)
- NSVT with an inducible sustained VT in the setting of diminished LV function (n = 20)
- EF \leq 0.30 with ischemic heart disease (n = 12)

Twenty-five ICD-treated patients also had an indication for pacing (sinus node dysfunction [n = 19]; and Mobitz II or high-grade atrioventricular block [n = 6]).

Indications for patients receiving BiV pacing were as follows:

- Sick sinus syndrome (n = 17)
- Complete atrioventricular block (n = 8)
- Sinus bradycardia (n = 6)
- Chronotropic incompetence (n = 1)
- Part of the overall HF management strategy (n = 32)

In all patients, the native QRS duration (left branch bundle block) or the conventional right ventricle apex paced QRS duration was greater than or equal to 150ms.

Baseline clinical and demographic features were comparable in the 2 patient groups. Drug therapies were similar in both groups. Among ICD patients, antiarrhythmic therapy was initiated for ventricular arrhythmia suppression in all cases, whereas among pacemaker patients, drugs were used for atrial fibrillation suppression.

Hospitalizations for HF were comparable in the pacemaker (mean, 1.8 [SD, 3.2]) and ICD (mean, 1.2 [SD, 1.2]) patient groups during follow-up. This suggests that patients' clinical symptom status did not differ

substantially between the 2 groups in that period. Total mortality was significantly lower in the ICD group (13%; 8 deaths) compared with pacemaker group (41%; 26 deaths; $P = .01$). The principal survival difference occurred after the first 12 months of follow-up. Using an intention-to-treat analysis, survival rates through the 36 months of follow-up indicated a statistically significant difference in survival for the ICD group ($P = .01$).

The mode of death could not be ascertained with certainty in this population. Noncardiac deaths occurred in 2 patients who received a BiV/ICD device and 2 patients who underwent BiV pacing.

Arrhythmic death was documented in 1 patient who received an ICD and by inference based on postmortem device examination in 2 patients who received a BiV pacemaker. The cause of death in the remaining cases could not be determined.

The frequency of device-recorded tachyarrhythmias was examined in the ICD group. Nineteen (31%) patients with ICDs received appropriate shocks and/or antitachycardia pacing therapy. Based on ICD programming, a total of 49 VT and 12 VF episodes were appropriately treated in these 19 patients. According to the authors, "Counting deaths (8 patients) and ICD treated arrhythmias, (but only counting one such death per event per patients), such "events" occurred in 27 (44%) ICD patients."

Limitations to the study by Ermis et al. (20) included the following:

- This study used an observational study design.
- Patients with AF were included.
- Both primary and secondary prevention were included.
- The study provided no sample size calculation or discussion.

Pappone et al. (2003)

Pappone et al. (21) conducted a prospective observational study on 135 consecutive patients with HF.

Inclusion criteria

- Patients had no myocardial infarction, unstable angina, coronary angioplasty, or bypass grafting within the last 3 months.
- Patients were NYHA class III or IV despite optimized pharmacologic therapy.
- Patients had QRS interval > 130 ms.
- Patients had LVEF < 0.35.

Electrophysiologic testing was performed at the discretion of the patients' attending physicians or during device implantation.

In the first year (control phase), only the BiV pacemaker was implanted. After that, BiV pacing with ICD as backup was used. Follow-up time averaged 840 days. The first 47 patients received BiV pacing alone. During follow-up study, 19% of these patients died suddenly and 11% died of worsening HF. The BiV pacing/ICD group consisted of 88 patients (18% with VT/VF inducibility on electrophysiologic testing). During the follow-up study, 32% of these patients (18% with positive electrophysiologic testing) had VT/VF episodes successfully treated by ICD; 5% received inappropriate discharges on atrial fibrillation; and 6% died of HF with 1 SCD. For BiV pacing/ICD compared with BiV pacing alone, the hazard ratio for all-cause mortality was 0.76 (95% CI, 0.58–0.96; $P = 0.01$) and for SCD was 0.08 (95% CI, 0.05–0.42; $P < .01$); after adjusting for baseline characteristics and follow-up duration.

The limitations to the study by Pappone et al. included the following:

- This study used an observational study design.
- The study offered no sample size calculation or discussion.
- By their own definition, the study used “preliminary data.”
- The study concluded, “Long-term randomized studies are needed to show whether we can prolong survival in the BVP population, thereby providing good reason for higher costs.”

Studies of Cardiac Resynchronization Therapy (With or Without ICD) in Progress

Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE)

The REVERSE trial is seeking to determine whether CRT can help limit the worsening of HF in people who have mild or even no symptoms, but poor heart pumping function.

In a press release dated July 6, 2004, a manufacturer’s Web site stated that the REVERSE investigators will implant BiV pacemakers and BiV pacemakers/ICDs in more than 500 patients at about 100 centres in Europe, the United States, and Canada. (22) The investigators will select the appropriate device to be implanted based on the patient’s specific indications. Two-thirds of patients will have CRT turned on, and the other one-third will have CRT turned off to serve as a control group. All patients in the study will receive optimal drug therapy and be followed-up for at least 1 year. At the end of the follow-up, patients in the control group will begin receiving CRT.

All the patients in the trial have a broad range of underlying causes for their HF, including those with and without a previous heart attack or coronary heart disease.

BLOCK HF

In a press release dated January 22, 2004, a manufacturer’s Web site stated that BLOCK HF is designed to determine if BIV pacing can slow the progression of HF in people who have mild-to-moderate HF symptoms (NYHA class I, II, and III) and the need for a pacemaker. (23) The study will compare the use of BiV pacing delivered to both lower chambers of the heart with traditional pacing delivered to the lower right chamber of the heart. It is anticipated that up to 1,200 HF patients in 65 centres in the United States and Canada will participate in the trial.

Along with mild-to-moderate HF, patients in the trial will also have evidence of damage to cells that carry electrical signals from the upper to lower chambers of the heart, blocking the signal on one side of the heart (atrioventricular block).

All patients will be initially programmed to traditional right ventricular pacing. They then will be randomized to either continue that therapy or have the device reset to pace both ventricles of the heart. The study’s main outcome is a composite endpoint that measures HF progression.

Summary of Cardiac Resynchronization Therapy Trials

Two large trials examined the effectiveness of BiV pacing in patients with severe HF and a wide QRS. The COMPANION trial had a number of major methodological limitations (Table 9).

Table 9: Summary of the Characteristics of the Key Trials: CARE-HF and COMPANION*

	COMPANION (2004)	CARE-HF (2005)
	Optimal Therapy vs. BiV Pacing vs. BiV Pacing/ICD†	Optimal Therapy vs. BiV Pacing
Population		NYHA III/IV HF EF < 0.35 QRS > 120ms
N	(optimal therapy, n = 308; BiV pacing, n = 617; BiV pacing/ICD, n = 595)	1,520 813
Follow-up (months)		Median, 16 Mean, 29
Comment	1. Definition of "hospitalization" in primary outcome changed 3 times during trial without documentation in protocol and FDA not notified (dominant outcome for composite endpoint). 2. Dropouts/withdrawals/crossovers not clearly described. 3. Study terminated early. 4. No direct comparison between BiV pacing vs. BiV pacing/ICD. 5. High number of patients withdrew from optimal therapy to device arms. 6. Not blinded.	Not blinded

*Cleland et al. (10) and Bristow et al. (9)

†BiV refers to biventricular; ICD, implantable cardioverter defibrillator.

Overall, CARE-HF showed that BiV pacing significantly improved mortality, QoL, and NYHA class in patients with severe HF and a wide QRS (Tables 2 and 3).

GRADE Quality of Evidence

The quality of these 2 trials was examined according to the GRADE Working Group criteria (Table 10). (12) Quality refers to the criteria such as the adequacy of allocation concealment, blinding, and follow-up.

Consistency refers to the similarity of estimates of effect across studies. If there is important unexplained inconsistency in the results, confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the size of the differences in effect, and the significance of the differences, guide the decision about whether important inconsistency exists.

Directness refers to the extent to which the people interventions and outcome measures are similar to those of interest. For example, there may be uncertainty about the directness of the evidence if the people of interest are older, sicker, or have more comorbid conditions than those in the studies.

As stated by the GRADE Working Group, the following definitions were used in grading the quality of the evidence:

- High: Further research is very unlikely to change our confidence on the estimate of effect.
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

- Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low: Any estimate of effect is very uncertain.

Table 10: Quality of Evidence: CARE-HF and COMPANION

Trial	Design	Quality	Consistency	Directness	Quality Grade
CARE-HF (BiV* pacing only vs. medical therapy)	RCT*	Not blinded.	No important inconsistency. Consistent with COMPANION in terms of mortality results. Consistent with previous studies regarding QoL* and functional status results.	Direct	Moderate/high
COMPANION (BiV pacing only vs. combined BiV pacing/ICD vs. medical therapy)	RCT	Definition of "hospitalization" in primary outcome changed 3 times during trial without documentation in protocol and FDA not notified (dominant outcome for composite endpoint). Dropouts/withdrawals/crossovers not clearly described. Study terminated early. No direct comparison between BiV pacing vs. BiV pacing/ICD.* High number of patients withdrew from optimal therapy to device arms. Not blinded.	No important inconsistency for BiV pacing only. No other RCT prospectively examined the combined BiV pacing/ICD device in patients with NYHA* III/IV heart failure and QRS > 120 ms and EF* < 0.35 and refractory to drugs. No other RCT prospectively examined the prophylactic use of ICDs in patients with NYHA IV heart failure.	Direct for BiV pacing only. No other RCT examined the prophylactic use of ICDs in patients with NYHA IV heart failure.	Low

*BiV indicates biventricular; RCT, randomized controlled trial; QoL, quality of life; ICD, implantable cardioverter defibrillator; EF, ejection fraction; NYHA, New York Heart Association.

Economic Analysis

Literature Review

Cleland et al. (11) presented updated results from the CARE-HF trial at the September 7, 2005 meeting of the European Society of Cardiology. The primary outcome of the extension phase was all-cause mortality from the time of randomization to completion of the extension phase. Analysis was conducted using the intention-to-treat principle.

The mean follow-up was 36.4 months (range, 26.1–52.6 months). There were 154 (38.1%) deaths in 404 patients assigned to medical therapy and 101 (24.7%) deaths in 409 patients assigned to CRT (hazard ratio, 0.60 [95% CI, 0.47–0.77]; $P < .0001$). Reductions in the risk of death due to HF were observed (hazard ratio, 0.55 [95% CI, 0.37–0.82], $P = .003$) and as were reductions in death due to sudden death (hazard ratio, 0.54 [95% CI, 0.35–0.84]; $P = .006$).

A health economic analysis suggested a within-trial cost per QALY gained of 19,367 euros (95% CI, 5,494 euros–45,507 euros).

Banz et al. (24) described a European model developed to assess clinical and economic outcomes of CRT compared with OPT alone in patients with HF. The analysis for Germany indicated that CRT was cost-effective. Although CRT was associated with average direct medical net costs of 5,880 euros per patient, this finding means that 22% of its upfront implantation cost is recouped within 1 year due to decreased hospitalizations.

With 36,600 euros, the incremental cost per QALY gained is below the euro equivalent (41,300 euros; 1 euro = \$1.21 [US]) of the commonly used threshold level of \$50,000 (US) considered to represent cost-effectiveness. The sensitivity analysis showed these preliminary results to be fairly robust towards changes in key assumptions.

Nichol et al. (25) examined the cost-effectiveness of CRT in patients with symptomatic HF. The following summarizes the key characteristics of this study:

- The study used the Markov model with Monte Carlo simulation. Future costs and effects were discounted at 3%.
- Effects data were obtained from a concurrent systematic review. Health-related QoL and cost data were obtained from publicly available data or from surveys.
- Time horizon: lifetime.
- The study took place in the context of the American health care system and currency.
- The interventions studied were CRT compared with medical therapy.
- The outcome measures were QALYs, costs, and incremental cost-effectiveness.
- The results of base case analysis were that medical therapy yielded a median of 2.64 (IQR, 2.47–2.82) discounted QALYs and a median discounted lifetime cost of \$34,400 (IQR, \$31,100–\$37,700). CRT was associated with a median incremental cost of \$107,800 (IQR, \$79,800–\$156,500) per additional QALY.
- The sensitivity analysis showed that the results were sensitive to changes in several variables including the relative risk for death or hospitalization.

The limitations to the study by Nichol et al. (25) included the following:

- The effectiveness of resynchronization was not adjusted for comorbid conditions

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- Cost-effectiveness is extremely sensitive to variations in clinical efficacy. If clinicians could prospectively identify patients whose QoL would be greatly improved by CRT, use of BiV pacemakers in such patients would be more economically attractive. (26) Routine use of CRT is not cost-effective, but properly targeted use may well be. (26)
- The cost-effectiveness of combined CRT/ICD devices was not examined. “More data are needed on the clinical and economic outcomes of combined CRT/ICD devices to develop evidence based recommendations for their appropriate use in patients with HF.” (26)

In a small (N = 16), uncontrolled Swedish study, Braunschweig et al. (27) assessed whether BiV pacing affected the number of total and HF-related hospital days in severe HF patients who were eligible for BiV pacing. In Sweden, health care expenditures for HF account for nearly 2% of the health care budget, of which 65% to 75% are related to hospital care.

Inclusion criteria consisted of patients recruited from a HF clinic:

- NYHA class III–IV despite optimal drug treatment
- Clinically stable at implantation and no change of drug treatment allowed for at least 1 month prior to operation
- LVEF < 0.40
- QRS interval > 150 ms; for patients who had been previously paced the QRS interval had to be >200 ms

No further description was provided regarding previously paced patients (e.g., type of pacemaker, indication for pacing).

Exclusion criteria:

- Unstable angina
- Need for revascularization
- Coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty performed within the last 6 months
- Myocardial infarction within last 3 months
- Traditional indication for a pacemaker or ICD

Medication for HF was maintained unchanged over the study period except for diuretics, which were adjusted as clinically needed. Patients were followed up at the outpatient clinic after 1, 6, and 12 months.

The need for hospitalizations, all-cause and HF-related, were monitored and comparisons were based on a follow-up period up to a maximum of 1 year. The hospital records were reviewed to determine the cause and duration of the hospital stays. Pacemaker-related hospitalizations and hospital days following the primary implantation of the BiV pacemaker were monitored separately. When a patient was hospitalized due to HF as the primary diagnosis, with a concomitant pacemaker-related problem, an estimate was made that of the duration of hospitalization that related to each of these 2 reasons. The estimation of all costs was made in collaboration with hospital administration.

Sixteen patients were enrolled and received successful implantations. The mean follow-up time was 291 days (SD, 76 days). No patients were lost to follow-up. Two patients died at 120 days and 224 days, respectively, after implantation due to pneumonia following a hip fracture and progression of HF. The mean duration of HF prior to inclusion in the study was 3.1 years (SD, 2.8 years). Patients were hospitalized a mean of 2.5 days (SD, 0.7 days) for implantation.

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There were 40 and 9 hospital days related to pacemaker implantation and pacemaker-related complications, respectively. Complications occurred in 3 patients: LV lead dislodgement in 2 people, and hematoma in the pacemaker pocket in 1 person. Table 11 shows the reported number of total and HF-related hospital days and hospitalizations (combined for all patients):

Table 11: Total and Heart Failure-Related Hospital Days and Hospitalizations

Type of Hospital Care	Hospital Days Before BiV Pacing,* No. (Median)	Hospital Days After BiV Pacing, No. (Median)	Hospitalizations Before BiV Pacing, No. (Median)	Hospitalizations After BiV Pacing, No. (Median)
Total	253 (10.0)	45 (0)	42 (1.5)	8 (0)
Heart failure - related	183 (9.5)	39 (0)	31 (1.5)	7 (0)

*BiV refers to biventricular.

Table 12 shows the estimated costs for hospital care, pacemaker implantation, follow-up, and complications.

Table 12: Estimated Costs for Hospital Care, Pacemaker Implantation, Follow-up, and Complications**

	Costs (Euros)	Costs/Patient (Euros)
Hospital days (number)		
Before BiV Pacing (253)	148,823	9,301
After BiV Pacing (45)	26,471	1,654
Difference	122,353	7,647
Pacemaker-related costs		
Implantation procedure	7,721	483
Pacemakers	62,447	3,903
Standard leads	9,176	574
Coronary sinus leads	14,118	882
Hospital days for implantation (n = 40)	20,004	1,250
Pacemaker follow-up (n = 16)	7,354	460
Pacemaker-related complications		
Reoperation (n = 4)	2,000	NA*
Hospital days (n = 9)	4,501	NA
Coronary sinus lead (n = 1)	882	NA
Total costs for pacing	128,295	8,019

*NA refers to not applicable.

**Reprinted from the *European Journal of Heart Failure*, v. 2, Braunschweig F, Linde C, Gadler F, Ryden L. Reduction of hospital days by biventricular pacing, p.p. 399-406, Copyright 2000, with permission from the European Society of Cardiology.

Braunschweig et al. (27) state that the calculation was based on a daily cost estimation of 588 euros per hospital day for heart failure. The authors did not provide an explanation as to why information on costs per patient for pacemaker-related complications was “not applicable.” Any interpretation of this study is severely limited due to lack of a control group with a small, uncalculated sample size, a very wide QRS interval, and an extremely limited discussion of any economic analysis.

Eligible Population

The prevalence of HF is 1%. This increases to 10% in people aged over 80 years. (5) Farwell et al. (5) report the incidence is 5 cases per 1,000 people per year. Recently, Cowie et al. (1) reported the incidence of CHF to be 0.02 cases per 1,000 population per year for those aged 25 to 34 years, rising to 11.6 cases per 1,000 people per year in those aged 85 years or older. In the United States, about 5 million people have HF, and between 400,000 and 700,000 new cases are diagnosed annually. (28)

A conference abstract by Moller et al. (29) evaluated how many patients with severe HF (NYHA III/IV) were eligible for BiV pacing. Based on the size of the referral population, and the assumption that the findings were representative for all 2,531 patients with an EF less than or equal to 0.35, it was calculated that a maximum of 145 patients per million inhabitants per year fulfilled the criterion of NYHA III/IV, an EF of up to 0.35, and a QRS of at least 120 ms. This number was reduced to 51 patients if the QRS interval was set to at least 150 ms.

The National Horizon Scanning Centre (30) reported the BiV pacemaker with the associated leads and delivery systems costs between £3,000 and £6,000. Follow-up of these patients was stated as being not much more time-consuming than that need for patients who had conventional pacing devices. Currently, it is not known how long the BiV pulse generator and leads will last. Some estimates are about 5 to 6 years; however, this needs to be considered with the remaining life expectancy of this particular patient group. Even though there are several trials with mortality as the primary endpoint, severe HF causes major health care costs and reduced QoL; therefore, benefit may be sufficient without demonstrable effects on mortality. However, this would depend on accurate and restrictive selection of patients.

The National Horizon Scanning Centre (30) has estimated that implantation and follow-up costs for 20 patients are about £100,000 to £150,000, and costs for each 1,000 patients are about £5 million to £7.5 million. Using prevalence figures for people in the United Kingdom aged 65 years and older, (men 40/1,000; women 30/1,000), and assuming 30% are in NYHA class III/IV, they estimated that 4,200 to 8,400 people in the United Kingdom could be eligible for BiV pacing.

Prospective data in large patient cohorts with sufficient follow-up duration are needed to determine the true number of patients that may benefit from the combined BiV/ICD device. Most studies of HF have described the major cause of sudden death as arrhythmic. (31) This has led to interest in the potential effect of ICDs in the primary prevention of sudden cardiac death in HF. (31) Stelbrink et al. (15) speculated that a combined BiV/ICD device may lead to a reduction in sudden death (VT) in HF patients. The retrospective analysis by Stelbrink et al. (15) indicated that 28 (7.3%) of 384 patients who were implanted with an ICD fulfilled eligibility criteria for BiV pacing if NYHA class III patients with a QRS higher than 120 ms were considered candidates. NYHA IV patients were not considered in the analysis. Several studies are underway to evaluate the efficacy of BiV pacing/ICD in chronic HF and whether this therapy improves mortality.

Cleland et al. (2) estimate that about 1% of the population will have HF (10,000/million), assume 20% with HF would remain moderately/severely symptomatic, and that 20% would have a QRS greater than 120 ms, and 10% have a QRS greater than 150 ms. Therefore, according to Cleland et al., 200 to 400 people per 1 million population may be candidates for intervention. Farwell (5) estimated 3% to 10% of patients (100–300 patients per 1 million population per year) hospitalized for HF would be candidates.

About 13,000 patients per year are hospitalized in Ontario with HF. (32) Using the estimation of Cleland et al. (2) for Ontario, 20% of HF patients would still be moderately/severely symptomatic (n = 2,600); 20% of moderate-to-severe HF patients will have a QRS greater than 120 ms (n = 520); and 10% of

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moderate-to-severe HF patients will have a QRS greater than 150 ms (n = 260); therefore, 260 to 520 patients per year may be candidates for BiV pacing in Ontario.

Ontario-Based Economic Analysis

Disclaimer: This economic analysis represents an estimate only, based on assumptions and costing methodologies that have been explicitly stated. These estimates will change if different assumptions and costing methodologies are applied for the purpose of developing implementation plans for the technology.

Prevalence (All costs are in Canadian currency.)

0.67	= added life years expected (CARE-HF conference data)(11)
\$15,000	= minimum estimated cost per case for BiV pacing
\$18,000	= maximum estimated cost per case for BiV pacing
\$22,388.06	= minimum cost-effectiveness estimate per life year
\$26,865.67	= maximum cost-effectiveness estimate per life year
23,700	= prevalence of HF (SCD-HeFT criteria) in Ontario
30%	= % in SCD-Heft with wide QRS
30%	= % of subjects in SCD-HeFT with NYHA class III HF

- Assume that the breakdown of class III and class II is the same regardless of wide QRS status (i.e., 30%/70% split)

According to SCD-HeFT, wide QRS was 30% of the sample (7,100) and 30% of this comprised class III HF, ($30\% * 30\% * 23,700 = 2,133$ = class III HF with wide QRS).

2133 = prevalence of NYHA class III HF with wide QRS in Ontario

Breakdown percentages (5)

Class I:	35%	
Class II:	35%	
Class III:	25%	2,133 = prevalence of class III HF with wide QRS in Ontario
Class IV:	5%	427 = prevalence of class IV HF with wide QRS in Ontario
<hr/>		
N = 8,532 (estimated prevalence of HF in Ontario)		

Therefore, the estimated prevalence of either class III or class IV HF and wide QRS in Ontario is 2,560 (2,133 + 427).

Incidence

0.67	= added life years expected (CARE-HF conference data)(11)
\$15,000	= minimum estimated cost per case for BiV pacing
\$18,000	= maximum estimated cost per case for BiV pacing
\$22,388.06	= minimum cost-effectiveness estimate per life year
\$26,865.67	= maximum cost-effectiveness estimate per life year
2,521	= incidence of HF (SCD-Heft criteria) in Ontario

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30% = % in SCD-Heft with Wide QRS)
 30% = % of subjects in SCD-HeFT with class III HF

- Assume that breakdown of class III and class II is the same regardless of wide QRS status (i.e., 30%, 70% split)

According to SCD-HeFT, wide QRS was 30% of the sample (7,100) and 30% of this comprised class III HF, (30%*30%*23,700 = 2,133 = class III HF with wide QRS).

227 = incidence of class III HF with wide QRS in Ontario

Breakdown percentages (5)

Class I 35%
 Class II 35%
 Class III 25% 227 = incidence of class III HF with wide QRS in Ontario
 Class IV 5% 45 = incidence of class IV HF with wide QRS in Ontario
 N = 908 (estimated incidence of HF in Ontario)

Therefore, the estimated incidence of either class III or class IV HF with wide QRS in Ontario is 272 (227 + 45).

Table 13 shows the budget impact of BiV pacing over a 4-year period.

Table 13: Cost of BiV Pacing Over 4-Year Period for NYHA III/IV, EF < 0.35, + Wide QRS*

	Year 1	Year 2	Year 3	Year 4
	\$ Million (Cdn)	\$ Million (Cdn)	\$ Million (Cdn)	\$ Million (Cdn)
BiV Pacing Only (100%)				
Prevalence	9.6–11.5	9.6–11.5	9.6–11.5	9.6–11.5
Incidence	4.1–4.9	4.1–4.9	4.1–4.9	4.1–4.9
Total each year	13.7–16.4	13.7–16.4	13.7–16.4	13.7–16.4
BiV Pacing/ICD* Combined (100%)				
Prevalence	18.6–20.5	18.6–20.5	18.6–20.5	18.6–20.5
Incidence	7.9–8.7	7.9–8.7	7.9–8.7	7.9–8.7
Total each year	26.5–29.2	26.5–29.2	26.5–29.2	26.5–29.2

*BiV indicates biventricular; NYHA, New York Heart Association; EF, ejection fraction; ICD, implantable cardioverter defibrillator.

BiV Pacing Only Prevalence Costs

2560 * \$15,000 = \$38.4 million
 2560 * \$18,000 = \$46.1 million
 2560 / 4 = 640 patients/year
 \$38.4 million / 4 years = \$9.6 million
 \$46.1 million / 4 years = \$11.5 million

BiV Pacing Only Incidence Costs

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$272 * \$15,000 = \4.1 million

$272 * \$18,000 = \4.9 million

BiV Pacing/ICD Combination Prevalence Costs

$2560 * \$29,000 = \74.2 million

$2560 * \$32,000 = \81.9 million

$2560 / 4 = 640$ patients/year

$\$74.2$ million / 4 years = $\$18.6$ million

$\$81.9$ million / 4 years = $\$20.5$ million

BiV Pacing/ICD Combination Incidence Costs

$272 * \$29,000 = \7.9 million

$272 * \$32,000 = \8.7 million

Existing Guidelines Regarding the Use of the Technology

Canadian Cardiovascular Society/Canadian Heart Rhythm Society Position Paper

The following is derived from the 2005 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Position Paper (33):

- Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective
- Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
- Class IIa: Weight of evidence/opinion is in favour of usefulness/efficacy
- Class IIb: Usefulness/efficacy is less well established by evidence/opinion

Class IIa Recommendation

A BiV pacemaker should be considered for patients with ischemic or nonischemic LV dysfunction in sinus rhythm, with NYHA class III to IV HF symptoms, despite optimal medical therapy, with a LV end diastolic dimension greater than 60 mm, with an EF less than or equal to 0.35, and with a QRS greater than or equal to 130ms.

In patients with ICD and CRT indications, a combined ICD/CRT device should be considered.

Canadian Cardiovascular Society Consensus Conference Recommendations on Heart Failure 2006

The following are the levels of evidence used by the Canadian Cardiovascular Society Consensus Conference Recommendations on HF (34) :

Classes of recommendations:

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- Class I: Evidence and/or general agreement that a given diagnostic procedure/procedure or treatment is beneficial, useful, and effective.
- Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/ and efficacy of the treatment.
- Class IIa: Weight of evidence/ or opinion is in favour of usefulness and /efficacy.
- Class IIb: Usefulness/Usefulness and efficacy is less well established by evidence or /opinion.
- Class III: Evidence or general agreement that the treatment is not useful/ and effective, and in some cases may be harmful.

Levels of evidence:

- Level of Evidence A: Data derived from multiple RCTs or meta-analyses
- Level of Evidence B: Data derived from a single RCT or large nonrandomized studies.
- Level of Evidence C: Consensus of opinion of the experts and/or small studies.

Cardiac Resynchronization Therapy:

Patients with symptomatic (NYHA III to IV HF despite optimal medical therapy who are in normal sinus rhythm with a QRS duration of 120 ms or longer and an LVEF of 35% or less should be considered for cardiac resynchronization therapy (class I, level A).

The addition of ICD therapy should be considered for patients being referred for cardiac resynchronization therapy who meet the requirements for ICD (class IIa, level B).

American College of Cardiology/American Heart Association 2005 Guideline Update

The following is derived from the American College of Cardiology/American Heart Association 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (35):

Class I recommendation, level of evidence A:

- “Procedure/treatment should be performed/administered.”
- Recommendation that procedure or treatment is useful/effective.
- Sufficient evidence from multiple RCTs or meta-analyses.

“Patients with LVEF less than or equal to 35%, sinus rhythm and NYHA functional class III or ambulatory class IV symptoms despite recommended, optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration greater than 0.12 ms, should receive cardiac resynchronization therapy unless contraindicated.” (35)

European Society of Cardiology Guidelines for the Diagnosis and Treatment of Chronic HF: Update 2005

Task force for the diagnosis and treatment of HF of the European Society of Cardiology (36):

Classes of recommendations:

- Class I: Evidence and/or general agreement that a given diagnostic procedure/procedure or treatment is beneficial, useful, and effective.

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- Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/ and efficacy of the treatment.
- Class IIa: Weight of evidence/ or opinion is in favour of usefulness and /efficacy.
- Class IIb: Usefulness/Usefulness and efficacy is less well established by evidence or /opinion.
- Class III*: Evidence or general agreement that the treatment is not useful/ and effective, and in some cases may be harmful. (*Note, the use of this class is discouraged by the European Society of Cardiology.)

Levels of evidence:

- Level of Evidence A: Data derived from multiple RCTs or meta-analyses
 - Level of Evidence B: Data derived from a single RCT or large nonrandomized studies.
 - Level of Evidence C: Consensus of opinion of the experts and/or small studies, retrospective studies, registries.
-
- Resynchronization therapy using BiV pacing can be considered in patients with reduced EF and ventricular dyssynchrony (QRS width ≥ 120 ms) who remain symptomatic (NYHA II–IV) despite optimal medical therapy to improve symptoms (class of recommendation 1, level of evidence A), hospitalizations (class of recommendation 1, level of evidence A) and mortality (class of recommendation 1, level of evidence B).
 - Implantation of an ICD in combination with BiV pacing can be considered in patients who remain symptomatic with severe HF NYHA class III–IV, with a LVEF of 0.35, and QRS duration greater than 120 ms to improve morbidity or mortality (class of recommendation IIa, level of evidence B).

Appraisal

Experts in the field note that surgeon experience is required. CRT is a time-intensive procedure that can easily take up to 3 hours to thread the leads through the coronary sinus. Slow diffusion is anticipated.(37)

Individuals with advanced chronic HF, a wide QRS interval, low LVEF, and who are refractory to optimal medical therapy represent the target patient group for BiV pacing. In Ontario, the estimated incidence and prevalence of patients who may be eligible for a BiV pacemaker is about 280 and 3,000 per year, respectively.

According to Gillis,

“...a very important randomized clinical trial, Resynchronization /Defibrillation for Advanced Heart Failure Trial (RAFT) comparing BiV pacing/ICD therapy with ICD therapy in patients with symptomatic heart failure is presently underway in Canada The study commenced in 2003 and there are presently 21 electrophysiology/heart function clinics across Canada actively enrolling patients... We wish to encourage physicians to refer eligible patients for consideration of participation in RAFT....” (38)

The MADIT-CRT trial (39) started in December 2004 and is designed to determine if combined ICD/BiV pacing will reduce the risk of mortality and HF events by about 25% in patients who are in NYHA class II with nonischemic or ischemic cardiomyopathy, and patients in NYHA class I with ischemic cardiomyopathy, an EF less than 0.35, and a prolonged QRS interval (≥ 130 ms).

The primary outcome of MADIT-CRT is to determine whether implanting combined ICD/BiV devices in high-risk coronary patients will significantly reduce the combined endpoint of all cause mortality or HF events when compared with ICD-only therapy.

Conclusions

Overall, there is evidence that BiV pacemakers are effective for improving mortality, QoL, and functional status in patients with NYHA III–IV HF, and an EF less than or equal to 0.35, and a QRS greater than 120 ms, and who are refractory to drug therapy.

As per the GRADE Working Group (12), recommendations considered the following 4 main factors:

- The tradeoffs, taking into account the estimated size of the effect for the main outcome, the confidence limits around those estimates, and the relative value placed on the outcome
- The quality of the evidence (Table 10)
- Translation of the evidence into practice in a specific setting, taking into consideration important factors that could be expected to modify the size of the expected effects such as proximity to a hospital or availability of necessary expertise
- Uncertainty about the baseline risk for the population of interest

The GRADE Working Group also recommends that incremental costs of health care alternatives be considered explicitly with the expected health benefits and harms. Recommendations rely on judgments about the value of the incremental health benefits in relation to the incremental costs. The last column in Table 14 is the overall trade-off between benefits and harms and incorporates any risk/uncertainty.

- For BiV pacing, the overall GRADE and strength of the recommendation is moderate—the quality of the evidence is moderate-to-high (some uncertainty due to methodological limitations in the study design— no blinding), but there is also some risk/uncertainty in terms of the estimated prevalence and wide cost-effectiveness estimates (Table 14).
- For the combination BiV/ICD device, the overall GRADE and strength of the recommendation is weak – the quality of the evidence is low (uncertainty due to methodological limitations in the study design) but there is also some risk/uncertainty in terms of the estimated prevalence, high cost and high budget impact. There are indirect, low-quality comparisons of the effectiveness of BiV pacemakers compared with the combination BiV/ICD devices.

A stronger recommendation can be made for BiV pacing only compared with the combination BiV/ICD device for patients with an EF less than or equal to 0.35 and a QRS greater than or equal to 120 ms, who have NYHA III/IV symptoms and are refractory to optimal medical therapy (Table 14).

- There is moderate/high quality evidence that BiV pacemakers significantly improve mortality, QoL, and functional status.
- There is low quality evidence that combined BiV/ICD devices significantly improve mortality, QoL, and functional status.
- There are no *direct* comparisons of the effectiveness of BiV pacemakers compared with combined BiV/ICD devices in terms of mortality, QoL, and functional status.

Table 14: Overall GRADE and Strength of Recommendation

Quality	Estimated Prevalence in Ontario	NNT* Death (Any)	Cost-Effectiveness	Cost in Ontario \$ Millions	Overall Grade and Strength of Recommendation (Including
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		Cause)			(Cdn)	Uncertainty)
BiV pacing*	Moderate/ high	~2,560	7	\$7,000– \$59,000 / QALY	38–46	Moderate
					~14–16/year over 4 years	
BiV/ICD device*	Low	~2,560	14	?	74–82	Weak
	Major study limitations			Low quality data	~27–29/year over 4 years	

*BiV refers to biventricular; ICD, implantable cardioverter defibrillator; NNT, number needed to treat.

Glossary

Biventricular pacemaker	A pacemaker with 3 leads that are implanted through a vein into the right atrium, right ventricle and into the coronary sinus vein to sense and pace the left ventricle.
Implantable cardioverter defibrillator	An implantable device that detects sustained ventricular tachycardia or fibrillation and terminates it by a shock or shocks delivered directly to the muscle of the heart.
QRS complex	The deflections in the tracing of the electrocardiogram comprising the Q, R, and S waves that represent the ventricular activity of the heart (depolarization of the ventricles).
QRS interval	The interval from the beginning of the Q wave to the termination of the S wave, representing the time for ventricular depolarization.
Ventricular dyssynchrony	Discoordinated contraction of the ventricles.

Appendices

Appendix 1: Randomized Controlled Trials in Previous Literature Review

Completed Randomized Controlled Trials with Permanent Cardiac Biventricular Pacing Included in the 2003 Health Technology Policy Assessment by the Medical Advisory Secretariat

Study	N	Years	Randomized?	Controlled?	NYHA Functional Class*	Follow-up, Months	Results
MIRACLE Abraham et al., 2002 (40)	453	1998–2002	Yes/parallel Pace/no pace	Yes	III–IV	6	Improved 6-min walk test ($P < .005$) Improved QoL* ($P < .001$) Improved NYHA class ($P < .001$) Largest study to date. Mortality $< 10\%$ in both treatment arms at 6 months. Hospitalization significantly lower in active treatment group.
PATH-CHF Auricchio et al., 2002 (41)	41	1995–1998	Yes/crossover 4 wks active pacing (LV or BiV)*, then 4 weeks no pacing 2 nd 4 week active pacing period Continued for 12 months after crossover period Single blind	Yes	III–IV	3	No significant difference between BiV and univentricular (mostly LV) stimulation found for clinical effects: 6-min walk test, $P = .345$ QoL, $P = .069$ NYHA class, $P = .360$ Oxygen uptake at peak exercise, $P = .324$ Oxygen uptake at anaerobic threshold, $P = .290$
MUSTIC SR Cazeau et al., 2001 (42)	67	1998–1999	Yes/single blind crossover 3 months stimulation on or off; mode then switched for the 2 nd 3 month period	Yes	III	3/3	Improved 6-min walk test, $P < .001$ Improved QoL, $P < .001$ Improved peak oxygen uptake, $P < .03$ Decreased hospitalization, $P < .05$ Mortality 5% during 6-month crossover phase

*NYHA indicates New York Heart Association; QoL, quality of life; LV, left ventricular; BiV, biventricular.

Non-Randomized Controlled Trials with Permanent Cardiac BiV Pacing Included in the 2003 Health Technology Policy Assessment by the Medical Advisory Secretariat

Study	N	Randomized?	Controlled?	NYHA Class*	Follow-up, Months	Results
InSync Italian Registry (Zardini et al., 2000) (43)	151	No	No Registry	II–IV	Mean, 10 (SD, 5)	Improved QoL* ($P < .0001$) Improved NYHA class ($P < .0001$) Improved 6-min walk ($P < .0001$)

*NYHA indicates New York Heart Association; QoL, quality of life.

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