Cardiac-Resynchronization in Moderate Heart Failure

Christopher Hughes
Pacific University

Recommended Citation
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Cardiac-Resynchronization in Moderate Heart Failure

Abstract

Background: Heart failure affects millions of elderly and is a major cause for hospitalization and death. A large percentage of these patients will present with a prolonged QRS interval. This lag between the firing of the right and left ventricles can make the heart inefficient, causing poor perfusion. Patients with a prolonged QRS generally do not respond well to the current pharmacological treatments available and continue to have worsening symptoms and progression of their disease. Cardiac resynchronization therapy attempts to stimulate both ventricles simultaneously, with an implantable device, and thereby increasing the heart’s output.

Method: An exhaustive search of available medical literature was performed using PubMed, Web of Science, Cochrane, the National Clinical Trials Registry and CINHAL databases looking for studies on mortality and morbidity of cardiac resynchronization therapy compared to pharmacological therapy. Using the key words ‘Heart Failure’, ‘Cardiac Resynchronization’, ‘Moderate’, ‘Mortality’ and ‘Death’, individually and in combination. The search was limited to human subjects, full text availability, the English language and articles from 2000 to 2010.

Results: The search revealed three randomized controlled trials with an extension of one of the three trials. All the studies found a significant decrease of mortality and morbidity with the use of cardiac synchronization therapy. Every one of the three also noted a higher rate of adverse events, secondary to implantation, associated with this therapy.

Conclusion: By performing a systematic review using GRADE to evaluate the quality of evidence, it was determined that cardiac-resynchronization therapy appreciably decreased the rate of death and hospitalizations over optimal pharmacological care and should be considered for patients with a prolonged QRS associated with heart failure.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

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Keywords
Heart Failure, Cardiac Resynchronization, Moderate, Mortality and Death

Subject Categories
Medicine and Health Sciences

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Cardiac-Resynchronization in Moderate Heart Failure

Christopher W. Hughes

A course paper presented to the College of Health Professions
in partial fulfillment of the requirements of the degree of
Master of Science

Pacific University School of Physician Assistant Studies
December, 2010

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Annjanette Sommers MS, PA-C
Biography

[Redacted for privacy]

Acknowledgements

[Redacted for privacy]
ABSTRACT

Background: Heart failure affects millions of elderly and is a major cause for hospitalization and death. A large percentage of these patients will present with a prolonged QRS interval. This lag between the firing of the right and left ventricles can make the heart inefficient, causing poor perfusion. Patients with a prolonged QRS generally do not respond well to the current pharmacological treatments available and continue to have worsening symptoms and progression of their disease. Cardiac resynchronization therapy attempts to stimulate both ventricles simultaneously, with an implantable device, and thereby increasing the heart’s output.

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Keywords: Heart Failure, Cardiac Resynchronization, Moderate, Mortality and Death
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INTRODUCTION

Background

Heart failure (HF) is primarily a disease of the elderly. Approximately 75% of hospital admissions for HF are for persons greater than 65 years old (Golding, J., 2010). It affects approximately 5 million people in the US and more than 20 million people worldwide (Golding, 2010; Mann, D., 2008).

The eventual outcome of most cardiac disease process is HF. Coronary artery disease (CAD) and hypertension contributes 80% of the total cases of HF (Golding, 2010). This situation is likely to worsen as a large cohort, the Baby boomers, moves into the later stages of life. The near epidemic proportions of hypertension, CAD and obesity further exacerbate this situation. The financial burden is staggering. Currently, more Medicare dollars are spent to diagnose and treat heart failure than any other medical condition (Golding, 2010).

Heart failure is considered a progressive disease. It begins when the heart muscle or nerve pathway becomes compromised by either an abrupt event, such as a myocardial infarction or insidiously, by volume overload. No matter how the damage is done, the once efficient pump becomes out of balance and begins to fail, thereby loosing its ability to deliver enough blood to meet the body’s needs. As the heart efficiency decreases, there is correlating increase in the symptoms.

The disease may present with weakness, nocturnal nonproductive cough, orthopnea, paroxysmal nocturnal dyspnea, edema, cyanosis and anxiety. The cardinal symptoms are fatigue and shortness of breath on exertion (Mann, 2008), particularly with left heart failure. These may be the only presenting symptoms. A
comprehensive evaluation will be needed, including a thorough history and physical exam, chest x-ray, a complete serum work up and an Echocardiogram, to measure the ejection fraction (EF). EF is the amount of blood that the ventricles expel with each beat (Normal EF is 55 – 70%).

The New York Heart Association (NYHA) classifies HF, in a four-tiered scale, by the severity of symptoms (Appendix A, Table 1). A patient with moderate HF would have a marked limitation of physical activity. The patient would also be comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. Though, this classification system is very subjective, it has withstood the test of time and continues to be widely applied to patients with HF (Mann, 2008).

There are approximately one-third of Heart Failure patients, with a decreased Ejection Fraction and symptomatic HF (NYHA class III-IV), who will manifest a QRS duration greater than 120 ms (Mann, 2008). This prolonged interval is associated with a poor prognosis (Pires, 2006). These patients respond poorly to conventional therapies and have frequent exacerbations and associated hospitalizations.

A therapy that could be used to reduce hospitalizations and mortality is Cardiac Resynchronization. Over the last decade there have been several randomized controlled studies conducted on Cardiac-Resynchronization therapy (CRT). CRT uses an implanted device that stimulates both ventricles of the heart near-simultaneously. By stimulating it in this manner, there is an improved coordination of contraction and a reduction of the severity of mitral regurgitation.
occurs. CRT has shown promising results.

Purpose of Study

This paper will perform a systematic review using GRADE to evaluate the quality of evidence and answer the question: In a 65 year old patient, with moderate left sided heart failure and a prolonged QRS, does cardiac resynchronization therapy decrease mortality?

METHOD

An extensive literature search was performed using PubMed, Web of science, Cochrane, the National Clinical Trials Registry and CINHAL. These databases were accessed through the Pacific University Library system. The keywords searched included ‘Heart Failure’, ‘Cardiac Resynchronization’, ‘Moderate’, ‘Mortality’ and ‘Death’, individually and in combination. The search was limited to human subjects, full text availability, the English language and articles from 2000 to 2010.

This produced 49 articles. Only randomized controlled trials were reviewed, resulting in five reports addressing the effect of cardiac-resynchronization therapy on patients with heart failure as it relates to mortality and met the inclusion and exclusion criteria for the systematic review. Of the five published articles found, four were randomized controlled trials and one was a follow-up of one of the previously mentioned trials. After a thorough search and review, it was noted that one of the four studies was included in a meta-analysis performed in 2002; therefore this article was excluded from the review.

RESULTS
Bristow, et al. (2004) published a randomized controlled trial titled, the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION). The COMPANION trial looked at 1520 patients who had advanced heart failure, NYHA Class III or IV, a left ventricle ejection fraction of 35% or less, a QRS interval of at least 120 msec., no clinical indication for a pacemaker or implantable defibrillator, and a hospitalization for the treatment of heart failure or the equivalent in the preceding 12 months.

The COMPANION patients were randomly assigned in a 1:2:2 ratio (Bristow et al., 2004). One group received optimal pharmacologic therapy, which included diuretics, angiotensin converting enzyme inhibitors, beta-blockers, and spironolactone. The next group received optimal pharmacologic therapy along with cardiac-resynchronization therapy with the implantation of a pacemaker. The final group received optimal pharmacologic therapy with the implantation of a pacemaker–defibrillator. The follow-up was 11.9 months in the pharmacologic-therapy group, 16.2 months in the pacemaker group and 15.7 months in the pacemaker–defibrillator group (p<0.001 for the comparison with the pharmacologic therapy group).

In the pacemaker or the pacemaker–defibrillator group, commercially available units and leads were used for right atrial pacing and right ventricular pacing or for pacing with defibrillation. An over-the-wire lead was placed into a distal branch of the coronary sinus vein for left ventricular stimulation. A proprietary algorithm was used to program the atrioventricular delay. The final pacing set for both devices settings were chamber paced: ventricle, chamber
sensed: both and, response: both triggering and inhibiting functions exist. The lower rate was set below the patient’s lowest intrinsic heart rate.

The study’s primary outcome was death or hospitalization (Appendix B, Table 2). Bristow et al. (2005) compared optimal pharmacological therapy alone to cardiac-resynchronization therapy with a pacemaker and found a decreased risk of death or hospitalization (hazard ratio, 0.81; \( p = 0.014 \)). The cardiac-resynchronization therapy with a pacemaker–defibrillator also decreased the risk of the primary outcome (hazard ratio, 0.80; \( p=0.01 \)). As far as the risk of the combined end point of death from, or hospitalization for, heart failure, when compared to the pharmacologic-therapy group, there was a reduction of 34\% \( (p<0.002) \) in the CRT group and of 40\% \( (p<0.001) \) in the pacemaker–defibrillator group. Bristow et al. (2004) concluded CRT decreased the risk of death from any cause or first hospitalization and, in combination with an implantable defibrillator, there was a significant reduction in mortality.

In 2005, Cleland et al. (2005) published a report of their randomized controlled trial, The Cardiac Resynchronization - Heart Failure (CARE-HF) involving 813 patients with New York Heart Association Class III or IV heart failure, a left ventricular ejection fraction of less than 35\%, and a QRS interval of at least 120 msec. Additionally, an aortic pre-ejection delay of greater than 140 msec., an interventricular mechanical delay of more than 40 msec., or a delayed activation of the posterolateral left ventricular wall was required for inclusion. The study excluded patients who had had a major cardiovascular event in the previous six weeks, those who had conventional indications for a pacemaker or
an implantable defibrillator, those with heart failure requiring continuous intravenous therapy and patients with atrial arrhythmias.

The randomization was done in a stratified manner according to the patient’s NYHA class by quintiles. One cohort was assigned to have optimal pharmacological therapy. The second cohort was assigned to have optimal pharmacological therapy and to undergo cardiac resynchronization. Follow up was performed at one, three, six, nine, twelve and eighteen months and every six months thereafter, with a mean duration of 29.4 months (range, 18.0 to 44.7).

The devices used in the study were a Medtronic InSync or InSync III. They provided atrial-based, biventricular stimulation with the use of standard right ventricular and Attain (Medtronic) left ventricular leads. The left ventricular lead was positioned to stimulate the lateral or posterolateral, left ventricular wall transvenously. This was then verified radiographically. The device was set with atrial pacing at 60 beats per minute, the interventricular delay at zero, and the atrioventricular delay was optimized via echocardiography.

The study’s primary end point was the time to death from any cause or an unplanned hospitalization for a major cardiovascular event and its secondary end point was death from any cause (Appendix ?, Table 2). Cleland, et al. (2005) found, when compared to optimal pharmacological therapy, the addition of CRT had a reduced incidence of death or hospitalizations (39% vs. 55%; hazard ratio, 0.63; 95% CI, 0.51 to 0.77; p<0.001). When looking at death alone, CRT had a lower incidence than optimal pharmacological therapy (20% vs. 30%; hazard ratio 0.64; 95% confidence interval, 0.48 to 0.85; p<0.002).
In 2006, Cleland et al. (2006) published a report of an extension phase to the CARE-HF study previously described above. The extension lasted approximately 8 months. It was requested and granted because the original study was not powered for mortality and required more time to assess the longer-term effects of CRT and mortality.

The primary outcome was all-cause mortality. This was from the time of randomization of the original study to the completion of the extension phase. The mean follow-up was 37.4 months (median 37.6, IQR 31.5–42.5, range 26.1–52.6 months). This study continued to show a decreased mortality of the patients receiving CRT over that of the optimal pharmacological therapy (hazard ratio 0.60, 95% CI, 0.47–0.77, p=0.0001). Cleland et al. (2005) concluded that CRT reduced complications, reduced the risk of death, and improved symptoms and quality of life.

The secondary outcome that Cleland et al. (2006) considered was mode of death. They found a reduction in the risk of death due to heart failure (64 vs. 38 deaths; hazard ratio 0.55, 95% CI 0.37–0.82, P=0.003) and sudden death (55 vs. 32; hazard ratio 0.54, 95% CI, 0.35–0.84, P= 0.005).

The most recent of the studies, Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT), Tang, et al. (2010) followed 1798 patients with a NYHA Class II or III Heart Failure. The inclusion criteria was continued heart failure symptoms despite optimal pharmacological treatment, a left ventricular EF less than or equal to 30%, an intrinsic QRS duration of 120 msec. or a paced QRS duration of 200 msec. or more, sinus rhythm or permanent atrial
fibrillation or flutter with a controlled ventricular rate (≥60 beats per minute at rest and ≥90 beats per minute during a 6-minute walk test). They excluded patients with a major coexisting illness or a recent cardiovascular event. The mean follow up was 40 months, completed at one month after device implantation and then every six months for a minimum of 18 months.

In this study, Tang, et al. (2010) compared Implantable Cardioverter Defibrillator (ICD) therapy to ICD with CRT. They used commercially available transvenous leads and devices. The implantation was done using a standard technique with an emphasis on placing the left ventricular lead to the lateral or posterolateral wall of the left ventricle. The devices were programmed in a manner to minimize ventricular pacing in the ICD group, maximize ventricular pacing in the ICD–CRT group.

The primary outcome was death from any cause, or hospitalization for HF (Appendix B, Table 2). The study found a decrease in death and hospitalization for the ICD-CRT compared to that of the ICD only group (0.75; 95% CI, 0.64 to 0.87; p<0.001). When just looking at mortality, ICD-CRT again showed a decreased risk (hazard ratio, 0.75; 95% CI, 0.62 to 0.91; P=0.003).

The study did note a higher rate of adverse events, 30 days after surgery, secondary to implantation of ICD-CRT (124 patients in the ICD-CRT group, and 58 in the ICD group (p<0.001)). Despite the high rate of adverse events, Tang et al. (2010) concluded that adding CRT to an ICD reduced the rates of death and hospitalizations for HF.

DISCUSSION
Already a leading cause of hospitalization and deaths in the geriatric population, the rate of heart failure will only rise correspondent to the increasing numbers of cardiac related diseases like hypertension, coronary artery disease and diabetes. Cardiac-Resynchronization Therapy may be a viable option to treat this expanding population. A total of three randomized controlled trials and one extension trial exploring the benefits of CRT, were reviewed.

The combined evidence for the outcome of death, in both CRT vs. IDT with optimal pharmacological therapy and CRT vs. optimal pharmacological therapy is rated ‘Moderate’. To evaluate the strength of evidence for the combination of the study’s outcome, Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Appendix, D, Table 4) was used.

As per the inclusion criteria, each of the studies was randomized. This sets the starting GRADE as High. None of the reviewed trials stated if their randomization was concealed or not. They did include a ‘Table 1’ describing the characteristics of the patients at baseline. After reviewing the tables, it appears the patients were similar in each cohort and surprisingly, between each of the three studies (Appendix C, Table 3) showing ‘Consistency’ between the combined studies.

Evaluating the “Directness” of the studies, revealed all three trials with an outcome of death. Every one of them also included statistics on the effect on hospitalization as an outcome. The earliest of the studies, the COMPANION (Bristow et al., 2004) trial compared CRT, both with, and without, an Implantable Defibrillator, to that of optimal pharmacological care. The CARE-HF and the
CARE-EF Extension Trials compared CRT only to optimal pharmacological care (Cleland et al., 2005, 2006). The latest study, the RAFT (Tang, et al., 2010), compared CRT to standard pacemaker therapy, but primarily looked at patients with mild HF. No matter the comparison or classification of HF, the combined outcome was determined to be ‘Moderate’ in quality and showed a statistically significant decrease in the risk of death and/or hospitalizations from cardiac events with the use of CRT.

Only one of the three studies, the RAFT (Tang et al., 2010), was constructed and performed as a double-blind trial. Whereas the COMPANION trial (Bristow et al., 2004), only blinded the steering committee and its sponsor. Finally, the CARE-HF trial and its extension (Cleland et al., 2005; Cleland et al., 2006) indicated only the endpoint committee was unaware of the patient’s treatment assignment. These latter two studies caused a deduction in the “Study Design” category because of this. The author of the COMPANION (Bristow et al., 2004) trial indicated that this might have caused a larger than expected withdrawal from the study. Though, the CARE-HF and its extension did not suffer from the same fate (Cleland, 2005; Cleland, 2006). Arguably, their design, implantable device vs. none, made blinding impractical and an ethical issue.

Follow-up was complete in all three studies. After review, it was noted that the COMPANION trial (Bristow et al., 2004) had the lowest follow up time and the highest withdrawal rate. Compounding this problem was a difference in the drop out rate between, who left, its three patient groups, with the pharmacological therapy group having nearly four times the loss rate of the other two cohorts.
Though Bristow et al (2004) reported no significant difference between patients, who left, with the exception of the prevalence of ischemic cardiomyopathy, compared to those that remained till completion (Bristow et al., 2004). This high, skewed dropout rate decreased the ‘precision’ of the results in GRADE. The other two trials reported minimal loss to follow up. All of the trials, with the exception of the CARE-HF with its extension (Cleland et al., 2005; Cleland et al., 2006), completed their trials, as scheduled.

While primarily looking at morbidity and mortality, both the COMPANION (Bristow, et al., 2004) and the CARE-HF (Cleland, et al., 2005) evaluated the benefits of CRT on cardiac function also. Bristow et al. (2004) found a decrease in median blood pressure, an increase in distance walked in six minutes and a higher reported quality of life. Cleland et al. (2005) noted an increase in left ejection fraction and improved symptoms with an associated increase in quality of life. These are important findings and should be explored more thoroughly in the future, because an increase in quality of life is probably the most instant and tangible factor for the patient.

A major weakness for all three of the trials was a severe underrepresentation of female patients (Appendix C, Table 3). Almost one in every two women will die from a cardiovascular disease and HF is the number one killer of women (AHRQ, 2009). It would be important to incorporate more women in future trials to assess the effect of CRT on this important population. Please also include a statement about the overall grade and an explanation of what “moderate” means as defined by the GRADE working group.
Each study noted a higher rate of adverse events secondary to the implantation process, but all showed a marked decrease in mortality and morbidity over that of pharmacologically optimal care. Despite the inherent risks with any surgery, let alone a cardiac one, a 65 year old, male patient with moderate heart failure, a prolonged QRS, would be a good candidate for CRT and should be routinely considered for this treatment option.
REFERENCES


### Table 1: NYHA Heart Failure Symptom Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| I (Mild) | • No limitation of physical activity  
|         | • Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea |
| II (Mild) | • Slight limitation of physical activity.  
|         | • Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea |
| III (Moderate) | • Marked limitation of physical activity.  
|         | • Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea, |
| IV (Severe) | • Unable to carry out any physical activity without discomfort.  
|         | • Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased |

(Mann, 2008)
### Table 2

#### Summary of Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAFT</td>
<td>CRT vs. ICD</td>
<td>Death or Hospitalization for HF</td>
<td>↓ Risk of death or hospitalization for HF</td>
</tr>
<tr>
<td>Tang et al., 2010</td>
<td></td>
<td></td>
<td>- Hazard ratio, 0.75; 95% CI, 0.64–0.87; P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Risk of death any cause</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Hazard ratio, 0.75; 95% CI, 0.62–0.91; P= 0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Risk of hospitalization for HF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Hazard ratio, 0.68; 95%; CI, 0.56–0.83; P&lt;0.001</td>
</tr>
<tr>
<td>CARE-HF</td>
<td>CRT vs. Pharmacologic Therapy</td>
<td>Death (All cause) or an unplanned hospitalization for a major cardiovascular event</td>
<td>↓ Risk of death or unplanned hospitalization for a cardiovascular event</td>
</tr>
<tr>
<td>Cleland et al., 2005</td>
<td></td>
<td></td>
<td>- Hazard ratio, 0.63; 95% CI, 0.51 to 0.77; P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Risk of unplanned hospitalization for a cardiovascular event</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Hazard ratio, 0.61; 95% CI, 0.49 to 0.77; P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Risk of death any cause</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Hazard ratio, 0.64; 95% CI, 0.48 to 0.85; P&lt;0.002</td>
</tr>
<tr>
<td>CARE-HF (Extension)</td>
<td>Extension of above trial</td>
<td>As Above</td>
<td>↓ Risk of death any cause</td>
</tr>
<tr>
<td>Cleland et al., 2006</td>
<td></td>
<td></td>
<td>- Hazard ratio, 0.60; 95% CI, 0.47–0.77, P=0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Risk of death due to heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Hazard ratio, 0.55, 95% CI, 0.37–0.82, P=0.003</td>
</tr>
<tr>
<td>COMPANION</td>
<td>CRT vs. ICD vs. Pharmacologic Therapy</td>
<td>Death or Hospitalization for any reason</td>
<td>↓ Risk of death or hospitalization for any cause</td>
</tr>
<tr>
<td>Bristow et al., 2004</td>
<td></td>
<td></td>
<td>- CRT: Hazard ratio, 0.81; 95% CI, 0.69 to 0.96; P = 0.014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- CRT &amp; Defibrillator: Hazard ratio, 0.80; 95% CI, 0.68 to 0.95; P=0.01</td>
</tr>
</tbody>
</table>
## APPENDIX C

### Table 3

<table>
<thead>
<tr>
<th>Study</th>
<th>Size</th>
<th>Age</th>
<th>Sex (% Male)</th>
<th>NYHA Class (%)</th>
<th>Population (Control/Exposed)</th>
<th>Medications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Class II</td>
<td>Class III</td>
<td>Class VI</td>
<td>Median Left EF (%)</td>
<td>Median QRS</td>
</tr>
<tr>
<td>COMPANION (Bristow et al., 2004)</td>
<td>1520</td>
<td>68/67</td>
<td>69/67</td>
<td>~</td>
<td>82/87 1</td>
<td>18/13 2</td>
</tr>
<tr>
<td>CARE-HF and Extension (Cleland et al., 2005; Cleland et al., 2006)</td>
<td>813</td>
<td>66/67</td>
<td>73/74</td>
<td>~</td>
<td>93/94</td>
<td>7/6</td>
</tr>
<tr>
<td>RAFT (Tang et al., 2010)</td>
<td>1798</td>
<td>66/66</td>
<td>81/85</td>
<td>81/79</td>
<td>~</td>
<td>23/23</td>
</tr>
</tbody>
</table>

~ Not reported

1 Optimal pharmacological therapy vs. CRT
2 Optimal pharmacological therapy vs. CRT with implanted deliberator
## Table 4
### Strength of Evidence

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Quantity and Type of Evidence</th>
<th>Findings</th>
<th>Starting GRADE</th>
<th>Decrease in GRADE</th>
<th>Increase in GRADE</th>
<th>GRADE of Evidence for Outcome</th>
<th>Overall GRADE of Evidence Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3 RTC 2, 3, 4, 7</td>
<td>↓ Mortality High</td>
<td>-1 0 0 -1 0</td>
<td>+1 0 0</td>
<td>Moderate</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>3 RTC 2, 3, 4, 7</td>
<td>↓ Morbidity High</td>
<td>-1 0 0 -1 0</td>
<td>+1 0 0</td>
<td>Moderate</td>
<td>Moderate</td>
<td></td>
</tr>
</tbody>
</table>

2 Bristow et al., 2004  
3 Cleland et al., 2005  
4 Cleland et al., 2006  
7 Tang et al., 2010