Cardiac resynchronization therapy: a meta-analysis of randomized controlled trials

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ABSTRACT

Background: Studies of cardiac resynchronization therapy in addition to an implantable cardioverter defibrillator in patients with mild to moderate congestive heart failure had not been shown to reduce mortality until the recent RAFT trial (Resynchronization/Defibrillation for Ambulatory Heart Failure Trial). We performed a meta-analysis including the RAFT trial to determine the effect of cardiac resynchronization therapy with or without an implantable defibrillator on mortality.

Methods: We searched electronic databases and other sources for reports of randomized trials using a parallel or crossover design. We included studies involving patients with heart failure receiving optimal medical therapy that compared cardiac resynchronization therapy with optimal medical therapy alone, or cardiac resynchronization therapy plus an implantable defibrillator with a standard implantable defibrillator. The primary outcome was mortality. The optimum information size was considered to assess the minimum amount of information required in the literature to reach reliable conclusions about cardiac resynchronization therapy.

Results: Of 3071 reports identified, 12 studies (n = 7538) were included in our meta-analysis. Compared with optimal medical therapy alone, cardiac resynchronization therapy plus optimal medical therapy significantly reduced mortality (relative risk [RR] 0.73, 95% confidence interval [CI] 0.62–0.85). Compared with an implantable defibrillator alone, cardiac resynchronization therapy plus an implantable defibrillator significantly reduced mortality (RR 0.83, 95% CI 0.72–0.96). This last finding remained significant among patients with New York Heart Association (NYHA) class I or II disease (RR 0.80, 95% CI 0.67–0.96) but not among those with class III or IV disease (RR 0.84, 95% CI 0.69–1.07). Analysis of the optimum information size showed that the sequential monitoring boundary was crossed, which suggests no need for further clinical trials.

Interpretation: The cumulative evidence is now conclusive that the addition of cardiac resynchronization to optimal medical therapy or defibrillator therapy significantly reduces mortality among patients with heart failure.
plantable defibrillator among patients with mildly symptomatic and advanced heart failure.

Methods

We used the PICO (population, intervention, comparison and outcome) approach to develop the research question for our systematic review. The population of interest included patients with mildly symptomatic or advanced heart failure, with a QRS interval of more than 120 ms. The intervention of interest was cardiac resynchronization therapy with or without an implantable cardioverter defibrillator in patients receiving optimal medical therapy. Comparisons between the following interventions were made: cardiac resynchronization therapy versus optimal medical therapy alone; and cardiac resynchronization therapy with an implantable defibrillator versus a standard implantable defibrillator. Optimal medical therapy was defined as evidence-based use of angiotensin-converting-enzyme (ACE) inhibitors or angiotensin II receptor blockers, β-blockers, spironolactone (if indicated) and diuretics at a stable dose for at least one month. The primary outcome was all-cause mortality. Only studies that provided mortality data were included.

Literature search

We searched the MEDLINE (1980 to Dec. 31, 2010), EMBASE (1980 to Dec. 31, 2010) and Cochrane Library (1980 to Dec. 31, 2010) databases for literature on cardiac resynchronization therapy and implantable defibrillator in patients with heart failure. We also searched various sources of grey literature as well as the US Food and Drug Administration website. Bibliographies of relevant systematic reviews were manually searched. Details of our search strategies are available in Appendix 2 (www.cmaj.ca/cgi/content/full/cmaj.101685/DC1).

Eligible studies were randomized controlled trials evaluating the effects of cardiac resynchronization therapy compared with control in adults with symptomatic heart failure or arrhythmia. Patients may also have been receiving medical therapy or have an implantable defibrillator.

Data extraction

Two of us (R.P. and J.H.) independently screened each citation for inclusion. Two reviewers (G.W. and R.P.) independently reviewed the full-text version of relevant articles and extracted the following data from the included studies: baseline characteristics of the study population, interventions and comparison groups, features of the study design, and the outcome of mortality. If necessary, discrepancies between the two reviewers were resolved by discussion involving a third independent reviewer (A.T.) to achieve consensus.

Assessment of risk of bias

The Cochrane Risk of Bias Tool was used to assess the risk of bias in the included studies.15 With respect to trials evaluating cardiac resynchronization therapy, random allocation of patients after implantation of the device, rather than before implantation, is an important source of bias, because these trials likely overestimate the potential benefits of the intervention.

Statistical analysis

Data were pooled using the random-effects model, and treatment effect was expressed as a relative risk. Heterogeneity was evaluated using the $F$ statistic. Subgroup analysis was conducted for New York Heart Association (NYHA) class. The optimum information size was considered for assessing the minimum amount of information required in the literature to reach reliable conclusions about cardiac resynchronization therapy.16−18

Figure 1: Flow diagram of selection of studies for the meta-analysis.
Results

The literature search identified 3071 citations (Figure 1). Of these, the full-text versions of 140 articles were retrieved for further review. (The list of excluded studies is available in Appendix 3, at www.cmaj.ca/cgi/content/full/cmaj.101685/DC1.) If duplicate reports of the same study were found in preliminary abstracts and articles, the data from the most complete dataset were analyzed. In total, 12 trials met the selection criteria for inclusion in our meta-analysis.14,19−29

The characteristics of the 12 trials are summarized in Table 1 (additional details about the studies are available in Appendix 4, at www.cmaj.ca/cgi/content/full/cmaj.101685/DC1). A total of 7538 patients were enrolled in these trials (4244 in the cardiac resynchronization therapy groups and 3294 in the control groups). Five trials compared cardiac resynchronization therapy plus optimal therapy (n = 1342) with optimal medical therapy alone (n = 1013).20,21,24,26,27 Seven trials compared cardiac resynchronization therapy and an implantable defibrillator (n = 2902) with an implantable defibrillator (n = 2281).14,19,22,23,25,26,29

The length of follow-up ranged from 3 to 40 months. Five studies had a follow-up of 12 months or less.20,21 Male patients accounted for 63% to 89% of the study populations. The mean age varied from 62 to 66 years.

All of the 12 studies included patients with ischemic (38%–70% of patients) and non-ischemic cardiomyopathy. The mean left ventricular ejection fraction was consistent across the studies (21%–25%). The distribution by NYHA class was as follows: four studies enrolled only patients with NYHA class I or II heart failure; four other studies enrolled only patients with NYHA class III or IV disease; in the remaining four studies, 8%–80% of patients had NYHA class I or II disease (20%–92% had NYHA class III or IV disease). Although the minimum duration of QRS interval required for patient enrollment differed between the studies, the mean QRS interval was similar across the studies (153–176 ms).

The risk of bias was often low except for

### Table 1: Characteristics of 12 studies included in the meta-analysis of cardiac resynchronization therapy for congestive heart failure

| Study               | No. of patients in intervention/control groups,* study design | Mean length of follow-up, mo | Age, yr, mean (SD) | Male, % | Ischemic cardiomyopathy, % | Mean ejection fraction, % (SD) | QRS interval, ms, mean (SD) | NYHA class, % | AF, % | RBBB, % |
|---------------------|-------------------------------------------------------------|------------------------------|-------------------|---------|---------------------------|-------------------------------|-------------------------------|----------------|-------|--------|
| Lozano et al., 2000 | CRT-ICD/ICD (109/113); crossover                            | 3                            | 65 (10)            | 83      | 68                        | 22 (0.007)                    | NR                           | III: 35         | NR    | NR     |
| MUSTIC, 2001        | CRT/OMT (29/29); crossover                                  | 6                            | 63 (10)            | 75      | NR                        | NR                           | NR                           | 176 (19)       | NR    | NR     |
| MIRACLE, 2002       | CRT/OMT (228/225); parallel                                 | 6                            | 64 (11)            | 68      | 54                        | 21.7 (6.3)                   | 166 (20)                     | III/IV: 100    | 0     | NR     |
| MIRACLE ICD, 2003   | CRT-ICD (187/182); parallel                                 | 6                            | 67 (10)            | 77      | 70                        | 24 (6.2)                     | 163 (22)                     | III/IV: 100    | 0     | 13     |
| MIRACLE ICD II, 2004 | CRT-ICD (85/101); parallel                                  | 6                            | 63 (12)            | 89      | 57                        | 24.5 (6.7)                   | 165 (24)                     | III/IV: 100    | NR    | 16     |
| COMPANION 2004      | CRT-ICD/ICD (595/671/308); parallel                         | 14.8–16.5                    | 67 (67)            | 55      | 22                        | 160                          | III/IV: 100                 | NR              | 10    |        |
| RHYTHM-I CD, 2004   | CRT-ICD (119/59); parallel                                  | 12.1                         | NR                | NR      | NR                        | 24.8 (7.7)                   | 168                          | III/IV: 92     | 0     | NR     |
| CARE-HF, 2005       | CRT-ICD (409/404); parallel                                 | 29.4                         | 66 (74)            | 38      | 25                        | 160                          | III/IV: 100                 | 0               | NR    |        |
| VECTOR, 2005        | CRT/OMT (59/47); parallel                                   | 19.9                         | 67.1 (9.7)         | 63      | NR                        | NR                           | NR                           | 29 (71)        | NR    | NR     |
| REVERSE, 2008       | CRT-ICD (419/191); parallel                                 | 12                            | 62 (11)            | 79      | 55                        | 27 (7)                       | 153 (12)                    | III/IV: 100    | 0     | NR     |
| MADIT-CRT, 2009     | CRT-ICD (1089/731); parallel                                | 28.8                         | 65 (11)            | 75      | 55                        | 24 (5)                       | 65% > 150                   | III/IV: 100    | 12    | 13     |
| RAFT, 2010          | CRT-ICD (894/904); parallel                                 | 40                            | 66 (9)             | 83      | 67                        | 23 (5)                       | 158 (24)                    | III/IV: 20     | 13    | 9      |

Note: For complete study names, see Box 1. AF = atrial fibrillation, CRT = cardiac resynchronization therapy, ICD = implantable cardioverter defibrillator, NR = not reported, NYHA = New York Heart Association, OMT = optimal medical therapy, RBBB = right bundle branch block, SD = standard deviation.

*All patients received optimal medical therapy.
implantation of the cardiac resynchronization therapy device after randomization (Table 2). (For details see Appendix 5, at www.cmaj.ca/cgi/content/full/cmaj.101685/DC1).

Overall effect of cardiac resynchronization therapy
A summary of the overall effect of cardiac resynchronization therapy on mortality is provided in Figure 2. In general, a relative risk reduction of 22% in mortality was found when cardiac resynchronization therapy was added to treatment (relative risk [RR] 0.78, 95% confidence interval [CI] 0.70–0.87); there was no significant heterogeneity across the trials ($I^2 = 0$).

Cardiac resynchronization therapy versus optimal medical therapy alone
Five studies evaluated the effect on mortality of cardiac resynchronization therapy plus optimal medical therapy versus optimal medical therapy alone. All of these studies involved patients with NYHA class III or IV heart failure. A significant relative risk reduction of 27% in mortality was found (RR 0.73, 95% CI 0.62–0.85) (Figure 2). There was no significant heterogeneity across the studies ($I^2 = 0$); all studies indicated a relative risk reduction in mortality, but only the largest study (CARE-HF [Cardiac Resynchronization in Heart Failure]) reported a significant reduction (RR 0.65, 95% CI 0.53–0.80). Without the CARE-HF study, the reduction in mortality in the treatment group was not significant compared with optimal medical therapy alone. The CARE-HF study and the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) study were the principal studies that led to the change in guidelines recommending that cardiac resynchronization therapy be used in addition to optimal medical therapy in patients with NYHA class III heart failure and ambulatory patients with NYHA class IV disease.

Cardiac resynchronization therapy and implantable defibrillator versus implantable defibrillator
The intervention of cardiac resynchronization therapy and an implantable defibrillator, in addition to optimal medical therapy, was considered in seven studies that reported mortality. Patients with a spectrum of heart failure ranging from NYHA class I to IV were enrolled in these studies. A significant relative risk reduction of 17% was found (RR 0.83, 95% CI 0.72–0.96) (Figure 2). Although there was no significant heterogeneity across the studies ($I^2 = 0$), before the RAFT study, three studies indicated a relative risk reduction in mortality and three studies indicated a relative risk increase; none of these relative risks was significant. RAFT was the largest study, with a significant relative risk reduction of 20% (RR 0.80, 95% CI 0.67–0.94). Without the RAFT study, the reduction in mortality with the intervention of cardiac resynchronization therapy and an implantable defibrillator was not significant (RR 0.93, 95% CI 0.70–1.23).

Table 2: Methodologic quality of the 12 studies of cardiac resynchronization therapy included in the meta-analysis

| Study               | Adequate sequence generation | Concealment of allocation | Single or double blinding | Blinding to outcome* | Incomplete outcome data addressed | Free of selective reporting | Free of other bias | Implantation after randomization |
|---------------------|------------------------------|----------------------------|---------------------------|---------------------|----------------------------------|----------------------------|------------------|-------------------------------|
| Loranzo et al.      | ND                           | ND                         | ND                        | Yes                 | Yes                              | Yes                        | Yes              | No                            |
| MUSTIC              | Yes                          | ND                         | Yes                      | Yes                 | Yes                              | Yes                        | Yes              | No                            |
| MIRACLE             | Yes                          | Yes                        | Yes                      | Yes                 | Yes                              | Yes                        | Yes              | No                            |
| MIRACLE ICD         | Yes                          | Yes                        | Yes                      | Yes                 | Yes                              | Yes                        | Yes              | No                            |
| MIRACLE ICD II      | Yes                          | Yes                        | Yes                      | Yes                 | Yes                              | Yes                        | Yes              | No                            |
| COMPANION           | ND                           | ND                         | Yes                      | Yes                 | Yes                              | Yes                        | Yes              | Yes                            |
| RHYTHM ICD          | ND                           | ND                         | Yes                      | Yes                 | ND                               | Yes                        | Yes              | No                            |
| CARE-HF             | Yes                          | Yes                        | Yes                      | Yes                 | Yes                              | Yes                        | Yes              | Yes                            |
| VECtor              | ND                           | ND                         | Yes                      | Yes                 | ND                               | Yes                        | Yes              | No                            |
| REVERSE             | ND                           | ND                         | Yes                      | Yes                 | Yes                              | Yes                        | Yes              | No                            |
| MADCIT-CRT          | ND                           | ND                         | Yes                      | Yes                 | Yes                              | Yes                        | Yes              | Yes                            |
| RAFT                | Yes                          | Yes                        | Yes                      | Yes                 | Yes                              | Yes                        | Yes              | Yes                            |

Note: For complete study names, see Box 1. ND = insufficient detail provided.
* Refers to whether the outcome of mortality was adjudicated by a blinded events committee.
**Patients with NYHA class I or II disease**

The intervention of cardiac resynchronization therapy and an implantable defibrillator versus an implantable defibrillator in patients with NYHA class I or II heart failure was considered in four studies that reported mortality. A significant relative risk reduction of 20% in mortality was found (RR 0.80, 95% CI 0.67–0.96) \(^{13,23,28,29}\) (Figure 3). There was no significant heterogeneity across the studies \((I^2 = 0)\), with three studies having a non-significant reduction or increase in relative risk \(^{23,28,29}\) and only the RAFT study having a significant relative risk reduction of 26% (RR 0.74, 95% CI 0.59–0.92). \(^{24}\) Without the RAFT study, the reduction in mortality with cardiac resynchronization therapy and an implantable defibrillator was not significant (RR 0.97, 95% CI 0.70–1.34).

The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy) study was larger, but it reported a nonsignificant relative risk reduction of only 6% (RR 0.94, 95% CI 0.67–1.32). \(^{29}\)

**Patients with NYHA class III or IV disease**

Four studies considered the effect on mortality among patients with NYHA class III or IV heart failure when cardiac resynchronization therapy was combined with an implantable defibrillator. \(^{14,19,22,25}\) A nonsignificant relative risk reduction of 14% was found (RR 0.86, 95% CI 0.69–1.07) (Figure 3); there was no significant heterogeneity across the studies \((I^2 = 0)\). Without the inclusion of the RAFT study, the other three studies combined had a relative risk reduction of 17% (RR 0.83, 95% CI 0.48–1.43) with a wide confidence interval.

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### Table: Mortality; study group, n/N

| Study                  | CRT  | Control | RR (95% CI) |
|------------------------|------|---------|-------------|
| **CRT v. OMT**         |      |         |             |
| MUSTIC, 2001 \(^{1,20}\) | 1/29 | 2/29    | 0.50 (0.05–5.21) |
| MIRACLE, 2002 \(^{21}\) | 12/228 | 16/225 | 0.74 (0.36–1.53) |
| COMPANION, 2004 \(^{24}\) | 131/617 | 77/308 | 0.85 (0.66–1.09) |
| CARE-HF, 2005 \(^{26}\) | 101/409 | 154/404 | 0.65 (0.53–0.80) |
| VECTOR, 2005 \(^{27}\) | 1/59 | 1/47    | 0.80 (0.05–12.4) |
| **Subtotal**            | 246/1342 | 250/1013 | 0.73 (0.62–0.85) |
| \(p = 0\)              |      |         |             |
| **CRT-ICD v. ICD**     |      |         |             |
| Lozano et al., 2000 \(^{19}\) | 5/109 | 10/113  | 0.52 (0.18–1.47) |
| MIRACLE ICD, 2003 \(^{22}\) | 14/187 | 15/182 | 0.91 (0.45–1.83) |
| MIRACLE ICD II, 2004 \(^{23}\) | 2/85 | 2/101   | 1.19 (0.17–8.26) |
| RHYTHM ICD, 2004 \(^{25}\) | 6/119 | 2/60    | 1.51 (0.31–7.27) |
| REVERSE, 2008 \(^{28}\) | 9/419 | 3/191   | 1.37 (0.37–4.99) |
| MADIT-CRT, 2009 \(^{29}\) | 74/1089 | 53/731 | 0.94 (0.67–1.32) |
| RAFT, 2010 \(^{14}\) | 186/894 | 236/904 | 0.80 (0.67–0.94) |
| **Subtotal**            | 294/2902 | 321/2282 | 0.83 (0.72–0.96) |
| \(p = 0\)              |      |         |             |
| **Overall**             | 542/4244 | 571/3295 | 0.78 (0.70–0.87) |

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**Figure 2:** Results of random-effects meta-analysis of overall mortality among patients with heart failure given cardiac resynchronization therapy (CRT) in addition to optimal medical therapy (OMT) or implantable cardioverter defibrillator (ICD). Values less than 1.0 indicate a decreased risk of death with cardiac resynchronization therapy. Note CI = confidence interval, RR = relative risk. For complete study names, see Box 1. *All patients received optimal medical therapy.*
Optimal information size
With the recent addition of the RAFT study to the body of evidence on cardiac resynchronization therapy in patients with mildly symptomatic or advanced heart failure, the Lan–DeMets sequential monitoring boundary has now been crossed (Figure 4). The cumulative evidence is now conclusive that the addition of cardiac resynchronization therapy to optimal medical therapy or to implantable defibrillator significantly reduces mortality (for details see Appendix 6, available at www.cmaj.ca/cgi/content/full/cmaj.101685/DC1).

Interpretation
Our findings indicate an unequivocal benefit of cardiac resynchronization therapy in addition to optimal medical therapy or an implantable cardioverter defibrillator in reducing all-cause mortality. This effect was particularly evident among patients with NYHA class II heart failure, a group in which a significant reduction in mortality had not been shown before the RAFT study, even in the presence of an implantable defibrillator.

The overall beneficial incremental effect of cardiac resynchronization therapy is supported by findings from the analysis of optimal information size. With the recently reported RAFT study, the sequential monitoring boundary has now been crossed, which indicates that the cumulative evidence now conclusively shows that the addition of cardiac resynchronization therapy to optimal medical therapy or to implantable defibrillator significantly reduces mortality among patients with mildly symptomatic or advanced heart failure. This sequential monitoring boundary is designed to be restrictive so that, when crossed, there is clear evidence of benefit. The cumulative evidence available from the previous 11 studies was not sufficient for the boundary to be crossed.

Our findings add to those of prior meta-analyses examining the effects of cardiac resynchronization therapy among patients with heart failure. Previous meta-analyses showed observations similar to ours when comparing

| Study                          | Mortality; study group,* n/N | CRT-ICD | ICD | RR (95% CI) |
|-------------------------------|-------------------------------|---------|-----|-------------|
| **NYHA class I and II**       |                               |         |     |             |
| MIRACLE ICD II, 2004          | 2/85                          | 2/101   |     | 1.19 (0.17–8.26) |
| REVERSE, 2008                 | 9/419                         | 3/191   |     | 1.37 (0.37–4.99) |
| MADIT-CRT, 2009               | 74/1089                       | 53/731  |     | 0.94 (0.67–1.32) |
| RAFT (class II), 2010         | 110/708                       | 154/730 |     | 0.74 (0.59–0.92) |
| Subtotal                      | 195/2301                      | 212/1753|     | 0.80 (0.67–0.96) |
| \( I^2 = 0 \)                 |                               |         |     |             |
| **NYHA class III and IV**     |                               |         |     |             |
| Lozano et al., 2000           | 5/109                         | 10/113  |     | 0.52 (0.18–1.47) |
| MIRACLE ICD, 2003             | 14/187                        | 15/182  |     | 0.91 (0.45–1.83) |
| RHYTHM ICD, 2004              | 6/119                         | 2/60    |     | 1.51 (0.31–7.27) |
| RAFT (class III), 2010        | 76/186                        | 82/174  |     | 0.87 (0.69–1.10) |
| Subtotal                      | 101/601                       | 109/529 |     | 0.86 (0.69–1.07) |
| \( I^2 = 0 \)                 |                               |         |     |             |
| **Overall**                   | 296/2902                      | 321/2282|     | 0.83 (0.72–0.96) |

Figure 3: Results of random-effects meta-analysis of overall mortality among patients with heart failure given cardiac resynchronization therapy plus an implantable cardioverter defibrillator (CRT-ICD) versus an implantable defibrillator (ICD), by New York Heart Association (NYHA) class. Values less than 1.0 indicate a decreased risk of death with cardiac resynchronization therapy. Note CI = confidence interval, RR = relative risk. For complete study names, see Box 1. *All patients received optimal medical therapy.
cardiac resynchronization therapy with optimal medical therapy alone, but they did not show a mortality benefit when comparing cardiac resynchronization therapy plus an implantable defibrillator with an implantable defibrillator. The addition of the data from the RAFT study in our review substantially changed these findings, supporting cardiac resynchronization therapy over and above an implantable defibrillator in eligible patients with heart failure.

The lack of a significant relative risk reduction in mortality among patients with NYHA class III heart failure may be explained by several factors. Many studies had short follow-up, with a range of 3–12 months. In addition, the number of patients with NYHA class III disease (n = 1330) was significantly smaller than the group with NYHA class II disease (n = 3947). This difference is predominantly due to the publication of the CARE-HF study, which showed a significant reduction in mortality with cardiac resynchronization therapy over optimal medical therapy alone. That study’s findings resulted in the American College of Cardiology/American Heart Association Task Force on Practice Guidelines to issue a class I recommendation in 2008 for cardiac resynchronization therapy in patients with NYHA class III heart failure, a left ventricular ejection fraction of less than 35% and a QRS interval of more than 130 ms. The RAFT study, which originally enrolled patients with either NYHA class II or III heart failure, changed its inclusion criteria in 2006 to include only those with NYHA class II disease, thereby limiting the number of patients with NYHA class III disease available for analysis. No further studies have been done involving patients with NYHA class III heart failure to examine the effect of cardiac resynchronization therapy over a standard implantable defibrillator.

**Limitations**

There are some limitations to our meta-analysis that are inherent to the studies we included. First, the timing of randomization to cardiac resynchronization therapy was not uniform across the studies. In many studies, randomization was done after a successful implantation, instead of at study entry. Deaths that may have occurred before or during implantation were not counted in these instances.

Second, optimization of medical therapy was not accurately specified at baseline in the studies. This issue is of importance when examining the data by NYHA class.

Third, many studies did not report outcomes by NYHA class; therefore, the data used in the NYHA II and III classifications may not be completely accurate, because the raw data by NYHA class were not uniformly available.

Fourth, follow-up varied greatly, with a large number of studies not reporting follow-up beyond 6 months.

![Figure 4: Cumulative meta-analysis of the effect on overall mortality of cardiac resynchronization therapy in addition to optimal medical therapy or implantable defibrillator therapy among patients with mildly symptomatic or advanced heart failure. With the addition of the RAFT study, the cumulative Z score crosses the Lan-DeMets sequential monitoring boundary, which indicates that the cumulative evidence supporting cardiac resynchronization therapy in addition to optimal medical therapy or defibrillator therapy is now conclusive. For complete study names, see Box 1.](image-url)
These limitations may significantly underesti-
mate the true effect of cardiac resynchronization ther-
apy among patients with heart failure, particu-
larly when results of studies with prolonged fol-
low-up are compared with those of shorter dura-
tion. Finally, the mechanism by which cardiac 
resynchronization therapy prevents mortality in 
this patient population remains to be elucidated.

Conclusion

Our meta-analysis showed a significant reduc-
tion in mortality with cardiac resynchronization ther-
apy in addition to either optimal medical therapy 
or an implantable cardioverter defibrillator. Al-
though this benefit was evident across the spec-
trum of symptomatic heart failure, it was par-
sicularly evident among patients with mildly 
symptomatic heart failure (NYHA class II disease) 
who had a QRS interval of more than 120 ms, a 
finding not previously shown, even in the presence 
of an implantable defibrillator. The added risk of 
performing cardiac resynchronization in this patient 
population must be weighed against the 
benefit. Cardiac resynchronization therapy may 
now be extended to a much wider proportion of 
patients with heart failure, improving long-term 
outcomes in this growing population.

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